Improving the assessment of exercise capacity and cardiorespiratory fitness in patients attending exercise-based cardiac rehabilitation

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Thesis Abstract

The aim of this thesis is *''Improving the Assessment of Exercise Capacity and Cardiorespiratory Fitness in Patients Attending Exercise-Based Cardiac Rehabilitation''*.

Cardiorespiratory capacity is an important predictor of morbidity and mortality in cardiac patients, due to the prognostic power, is an essential outcome to measure in cardiac patients in clinical practice. In cardiac rehabilitation programmes the assessment of cardiorespiratory capacity (by field tests or treadmill test) is an essential practice supported by U.K., European and U.S.A. guidelines, which gives support to patients risk evaluation and stratification, setting individual patients goals, exercise prescription, and evaluation of the same.

Overall, the findings of this thesis, which were generate by meta-analysis, cross-sectional studies and laboratory research, provide an insight into the factors associated with patients' initial performance, and oxygen cost in functional capacity tests. Together, this data may improve the application, interpretation and patient understanding of these test results. One aim of CR is to improve patients' functional capacity; we provide a standard value for ΔFitness, and information on factors which clinicians may need to consider when setting patient goals and interpreting changes in functional capacity, or ΔFitness due to CR.

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List of Publications

- Published articles

-Sandercock GRH, Cardoso F and Hurtado, V. *Changes in cardiorespiratory fitness in cardiac rehabilitation patients: a meta-analysis*. Int J Cardiol. 2013 Aug 10; 167(3):894-902.; doi:10.1016/j.ijcard.2011.11.068

-Sandercock GRH, Cardoso F, Almodhy M, Pepera G. *Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study*. Heart. 2013 Jun; 99(11):785-90.;

- Almodhy, M, Taylor, M. Cardoso, F. Beneke, R and Sandercock, GRH. *Pilot investigation of the oxygen demands and metabolic cost of incremental shuttle-walking and treadmill-walking in patients with cardiovascular disease*. BMJ Open 2014;4:e005216 doi:10.1136/bmjopen-2014-005216

-Cardoso, FMF; Meshal, A.; Pepera, P.; Stasinopoulos, MD; Sandercock, GRG; *Reference values for the incremental shuttle walk test in patients with cardiovascular disease entering exercise-based cardiac rehabilitation.* J Sports Sci. 2016 Mar 11:1-6.

-Buckley, JP; Cardoso, FM; Birkett BT; Sandercock, GRH; *Oxygen Costs of the Incremental Shuttle Walk Test in Cardiac Rehabilitation Participants: An Historical and Contemporary Analysis*. Sports Medicine 2016, pp 1-10.

- Letters to Editor

Sandercock G, Cardoso F, Almodhy M; *Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study*. Heart, 99, 198-1299. doi:10.1136/heartjnl-2013-304085.

- Congress communications, and published abstracts

-F. Cardoso, M. Almodhy, G. Pepera & G.R.H. Sandercock; *Changes in aerobic capacity over 8 weeks of cardiac rehabilitation assessed using maximal treadmill exercise testing*; BASES/FC30. Journal of Sports Sciences Suppl. Dec 2011. DOI:10.1080/02640414.2011.609363

-M. Almodhy, F. Cardoso & G. Sandercock; *Oxygen consumption during full and abbreviated 10 m shuttle-walk test;* BASES/FC30. Journal of Sports Sciences Suppl. Dec 2011. DOI:10.1080/02640414.2011.609363

-F.Cardoso, V. Hurtado, G. Sandercock- *Meta-analysis of changes in cardiorespiratory fitness in cardiac rehabilitation*; 11th Annual Graduate Forum, University of Essex, September, 2012

-Cardoso, F., Almodhy, M., Sandercock, G. *Predictors of change in cardiorespiratory capacity in Cardiac rehabilitation assessed by 10 m incremental shuttle-walk test*; 34th Conference of Portuguese Society of Cardiology, Vilamoura, April 2013;

-Cardoso, FMF., Almodhy, M., Pepera, G*. and Sandercock, GRH. *Predictores of performance in the Incremental Shuttle walking test at entry to Cardiac rehabilitation*; 20th conference of BACPR, Solihull, October 2013;

-Bukcley, J., Birkett, S., Cardoso, F MF, Almodhy, M, Sandercock, GRH.; *The Incremental Shuttle walk test ''MET's'' revisited;* BACPR EPG, Study Day Report, Birmingham, 16th of May 2014;

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- Cardoso, FMF., Almodhy, M., Pepera, G. and Sandercock, GRH. *Helping interpretation and improving patient understanding of Incremental shuttle-walking test performance in pre-rehabilitation*. BACPR Exercise professionals Group Study Day 15th of May 2015, Birmingham;

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Δ	Change
6-MWT	Six minute walk test
12MWT	12 min walking test
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACPICR	The Association of Chartered Physiotherapists in Cardiac Rehabilitation
ACE	Angiotensin-Converting Enzyme
ACSM	American College of Sports Medicine
AF	Atrial Fibrillation
AHA	American Heart Association
BACR	British Association of Cardiac rehabilitation
BACPR	British Association of Cardiac & Pulmonary Rehabilitation
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
CABG	Coronary Artery Bypass Graft
Cardiorespiratory fitness	Cardiorespiratory capacity
Comprehensive-CR	Cardiac Rehabilitation based in exercise plus education in risk factor management
CHD	Coronary Heart Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
CI	Confidence Interval

CR	Cardiac Rehabilitation
CVD	Cardiac Vascular Disease
ECG	Electrocardiogram
Exercise-based CR	Exercise-only and Comprehensive-CR
Exercise Capacity	Capacity to exercise in an exercise test
Exercise only-CR	Cardiac rehabilitation only based in exercise
Fitness	Cardiorespiratory capacity
IIT	Interval Intensity Training
ISWT	10 meter Incremental Shuttle walk test
HDL	High Density Lipoprotein
HF	Heart Failure
HRQoL	Health-Related Quality of Life
METs	Metabolic Equivalents
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
NHS	Nation Health Service
NSF	National Service Framework
NYHA	New York Heart Association
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RCT's	randomized clinical trials
RPE	Borg Rating of Perceived Exertion
SD	Standard Deviation
S	Seconds

SEE	Standard Error of Estimation
SIGN	Scottish Intercollegiate Guidelines Network
UK	United Kingdom
USA	United States of America
VO2	Oxygen Uptake
$\dot{V}O_{2peak}$	Maximal Oxygen consumption
WHO	World Health Organisation

Improving the Assessment of Exercise Capacity and Cardiorespiratory Fitness in Patients Attending Exercise-Based Cardiac Rehabilitation

Chapter 1: Introduction and Thesis Overview

1.1. Motivation

Exercise-based CR is effective in reducing all-cause mortality, cardiac mortality, and risk factors for CHD (Oldridge, et al. 1988; O'Connor, et al. 1989; Jolliffe, et al. 2001; Taylor, et al. 2004; Taylor, et al. 2006; Clark, et al. 2005; Heran, et al. 2011). All the above analyses included exercise-based CR programmes but only clinical endpoints were included in the analysis of mortality, which didn't fully explain how exercise-based CR is effective in reducing cardiac and all-cause mortality. It was surprising that none of the past studies examined change in fitness as an outcome, which is dependent on the dose of exercise used (only outcome measured) and may be the explanation for the positive effect of exercise-base CR.

Gains in fitness achieved by patients in CR are closely, inversely, related to patient mortality and morbidity and the evidence for this is strong and abundant (Ades, et al. 2006; Williams, et al. 2006; Balady, et al. 1996). These studies showed the cross-sectional associations between fitness and mortality, other studies have demonstrated the degree of impact that fitness gains had on mortality due to CR programmes (Myers, et al. 2002; Dorn, Naughton et al. 1999; Kavanagh, et al. 2003; Vanhees, et al. 1995). These studies did not give a standard reference for change in fitness to be used in CR programs and they do not fully explain the heterogeneity of changes in fitness reported in CR studies.

The outcome of the ISWT is meters, this absolute value is used in clinical practice to classify cardiac patient performance (exercise capacity) at entry to CR programmes. However, ISWT performance is not dependent solely on the patient's cardiorespiratory fitness. Fowler and Singh (2005) found that 63% of the variance in ISWT performance in cardiac patients was explained by cardiorespiratory fitness, but this univariate regression did not facilitate the assessment of alternative performance predictors identified elsewhere in cardiac patients such as height and BMI (Pepera, et al. 2013). The Incremental Shuttle Walk Test (ISWT) may be used to predict cardiorespiratory fitness (Fowler and Singh 2005), although the accuracy of any estimation of cardiorespiratory fitness is of some doubt (Woolf-May and Ferrett 2008 and Almodhy, et al. 2014).

1.2. Aim of the Thesis

The overall aim of this thesis was ''Improving the assessment of exercise capacity and cardiorespiratory fitness in patients attending exercise-based Cardiac Rehabilitation''. The tests included in the analysis were the Exercise Treadmill Test (ETT), and the 10 m Incremental Shuttle Walk Test (ISWT) applied in the assessment of patients with coronary heart disease (CHD).

The data reported in this thesis is of clinical importance and applicability. It improves the interpretation of changes in performance in tests due to CR. It has enabled the creation of a reference value for expected change in cardiorespiratory fitness due to CR programmes and has helped interpret predictors of change. The results also improve the interpretation of performance in the field test ISWT, creating reference values for performance interpretation and oxygen consumption quantification of the levels in the ISWT.

1.3. Structure and Main Outcome of the Thesis

This thesis is divided into 6 chapters. **Chapter 1** is a general introduction that continues on to **Chapter 2**, including a general introduction of the evidence about the effectiveness of CR in reducing morbidity, mortality, and its ability to reduce risk factors and improve quality of life. The literature also summarizes the recent state of the ISWT assessment in cardiac patients, highlighting gaps and potential future research.

Chapter 3 provides the first meta-analysis to quantify the gains in cardiorespiratory fitness of patients attending exercise-based CR. The analysis also identifies some of the characteristics (service or patient) that can influence the cardiorespiratory fitness gains in patients involved in CR. Service variables, such as including >36 sessions in the CR programme of aerobic or mixed aerobic and resistance exercise with a programme length of 12 weeks. The treadmill protocol used to assess cardiorespiratory fitness in patients has a major impact on the estimate of fitness improvement. Patients variables such as being young and male cause bigger increases in fitness and this population may benefit more from CR than older, female patients, who have lower changes in fitness. It is recommended that there is provision of exercise sessions for same sex groups and that patients should be allocated according to their age. This would help practitioners to differentiate between who achieves optimal increases in cardiorespiratory fitness in CR and not, improving exercise prescription in CR and expected outcomes according to the individual differences of the CHD patients. This chapter was published in the International Journal of Cardiology**.**

In **Chapter 4** reference data for the incremental shuttle-walking test (ISWT) in patients at entry to CR is provided for the first time. Distance walked in the ISWT varied greatly due to non-modifiable patient characteristics; particularly age and sex. It is proposed that clinicians may better-interpret ISWT performance by comparing absolute (distance walked) values with the age- and sex-specific reference values presented here. This practice may provide a more meaningful and individualised assessment of patients' functional capacity, exercise prescription, and magnitude of change in cardiorespiratory fitness expected at entry to CR programmes. Consequently, this may help 'triage' patients by better interpreting ISWT performance, taking into account patient age and sex at entry to outpatient- hospital CR and potentially identifying individuals who can be 'fast tracked' or can be referred back to CR. Regression equations based on the healthy population had little or no clinical utility in cardiac patients (Accepted for Publication in Journal of Sports Sciences, Dec 2015.).

Following a Pilot Study (published in BMJ Open), in **Chapter 5** a larger study was completed combining data from Essex and Chester. We reviewed historical studies on the oxygen costs of walking and then compared and critiqued the current results and those of previous similar studies on the ISWT. This resulted in further confirmation of the curvilinear nature of $\dot{V}O_{2peak}$ $(ml \cdot kg^{-1} \cdot min^{-1})$ as a function of walking speed. During the ISWT, it appears that CR participants have a $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) up to 30% higher than age-matched controls. Together, these findings suggest studies may have underestimated the $\dot{V}O_{2peak}$ $(ml \cdot kg^{-1} \cdot min^{-1})$ of cardiac patients as well as improvements in $\dot{V}O_{2peak}$ $(ml \cdot kg^{-1} \cdot min^{-1})$ following a programme of exercise-based CR. In estimating $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) from the walking speeds of the ISWT in CR participants, the following median equation was derived: $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) = 4.5e0.37· walking speed (mph) (Accepted for Publication in British Journal of Sports Medicine, Dec 2015).

Following Chapter 3 were moderators of change in fitness were determined, **Chapter 6**, confirmed some findings from Chapter 3, and further identify and non-modifiable and modifiable predictors of change, in ISWT and treadmill exercise test performance at the end of CR (post-CR). Findings suggest that CR should be tailored according to sex/age group. Sex/age- tailored CR including patients with high waist circumference, who smoke, should have a higher dose of exercise than others. Patients with high baseline fitness can be fast-tracked to community CR programmes. Females and older patients exercising in mixed-CR, those who smoke and have a higher waist circumference should exercise in higher doses to benefit as much as young and male patients who don’t smoke and have a lower was circumference, in cardiorespiratory fitness changes due to CR programmes.

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Chapter 2. Literature Review: Efficacy of Cardiac Rehabilitation and the Role of Assessing Functional Capacity.

Abstract

Exercise-based CR programmes (exercise-only CR and comprehensive-CR) in CHD patients are an effective treatment for preventing cardiac mortality, morbidity, all cause of death and improved quality of life. Such evidence is strongly provided by randomized control trials and meta-analysis. It is thought that CR is an effective therapy due to the positive impact in reducing risk factors for CVD (strong evidence for hypertension, smoking and total cholesterol) and by the improvement in cardiorespiratory capacity due to exercise in cardiac patients.

Assessment of functional capacity is an important component of clinical care, enabling decisions on diagnosis, prognosis, treatment effect and exercise prescription of cardiac patients, based on objective measures. Field tests are practical and simple to use in clinical or community settings in the absence of laboratory tests in all phases of Cardiac Rehabilitation. The test when compared with golden test treadmill shows a reasonable validity in cardiorespiratory capacity assessment. The studies show that the test is reliable from the first assessment when used in Cardiac Rehabilitation to measure changes in functional capacity due to exercise. In a short period of time or when the effect to measure is of low magnitude as a therapy effect for more reliable results and less error in assessment the studies, a practice attempt is suggested. The test shows sensibility to measure ~ 100 m changes in performance due to Cardiac Rehabilitation in a period of 6 to 12 weeks. In heart failure patients the ISWT is able

to diagnose low functional capacity, showing the performance and prognosis of major cardiac events in one years' time. The ability of the test to quantify performance based on meters has been proved, but no real quantification of performance in METs have been included in the studies. As METs are a measure of functional capacity used in clinical setting given support to diagnose, prognoses and exercise prescription in cardiac rehabilitation, the test performance in METs is needed to quantify, specifically the stage and speed that 5 METs cut point is achieved. Achieving a value higher than 5 METs is used to upgrade cardiac patients from phase III to phase IV, and is the value which insurance companies ask for as a minimum to provide cover to patients recovering from cardiac events.

2.1. Evidence for the Efficacy of Cardiac Rehabilitation (CR)

2.1.1. Reducing Mortality

Oldridge, et al. (1988) produced the first meta-analysis to report the effect of CR in patients suffering from myocardial infarction (MI) on all cause of death, cardiovascular (CV) mortality and recurrent MI. This meta-analysis focused on 10 randomized clinical trials (RCT's) conducted from 1972 to 1985. A control group of 2,202 patients, and an intervention group undertaking comprehensive-CR (exercise plus education in risk factor management) made up of 2,145 randomized patients were assessed.

In those patients enrolled in Cardiac Rehabilitation all-cause mortality was reduced by 24% over a two year follow up (OR 0.76; 95%CI: 0.63 *to* 0.92); and a 25% reduction of cardiovascular (CV) death (OR 0.75; 95%CI: 0.62 *to* 0.93) compared with the control group. There were no significant differences between groups in the rate of non-fatal re-infarction, (OR 1.15; 95%CI: 0.93 to 1.42). Sub-group analyses demonstrated a benefit for all-cause mortality in longer CR programmes (>36 months), producing significant reductions of around 35% (OR 0.65; 95%CI: 0.45 *to* 0.94); whereas no such effect was seen in shorter CR programmes (<12 weeks or 12 to 52 weeks) or in CV mortality in longer comprehensive CR programmes (Oldridge, et al. 1988).

This review included mainly studies of low risk, male patients who had suffered an MI. This meta-analysis makes it difficult to conclude the effects of CR in rates of mortality in different coronary heart disease (CHD) patients, in high risk patients, in women and elderly patients, as RCT's commonly excluded patients >65 years. Due to the heterogeneity in results in the RCT's included, it is difficult to conclude what the optimal duration of a CR programme is, and what is the mechanism by which CR has a positive influence in decreasing mortality, as not all trials show a decrease in risk factors and improvements in cardiorespiratory fitness.

O'Connor, et al. (1989) one year later, published a second meta-analysis trying to determine the benefit of CR in MI Patients. This study contained data from 22 RCT's including *n*=4554 patients that had suffered a myocardial infarction between 1960 and 1989, the entire intervention group took part in comprehensive-CR (exercise plus education in risk factor management). This meta-analysis, including 11 new RCT's not included by Oldridge, et al. (1988). End points included: overall and CV mortality, sudden death, fatal and non-fatal re-infarction identified and measured in one year intervals, with a three year mean follow-up.

The results were largely in accordance with those of Oldridge et al. (1988). Over a period of 3 years in the comprehensive-CR group compared with the control group there was a 20% decrease in all-cause mortality (OR= 0.80; 95%CI: 0.66 *to* 0.96), a 22% decrease in CV mortality (OR= 0.78; 95%CI: 0.63 *to* 0.96) and a 25% decrease in fatal re-infarction (OR=0.75; 95%CI: 0.59 *to* 0.95). Sudden death was reduced by 37% up to one year follow-up (OR= 0.63; 95%CI: 0.41 *to* 0.97), and this effect continued over two to three years although to a not significant extent. The rate of non-fatal re-infarction was not different to that in the control group, although was more common in the comprehensive-CR group than in the comparison group, 10.2 % *vs.* 9.5%.

Women comprised only 3% of the total sample in the 22 RCT's included by O'Connor, et al. (1989) and only four RCT's included any women at all. The main age range analysed was 50 to 60 years old, and RCT's commonly excluded patients >65 years, and some large RCT's included patients age from 40 to 55 years old. All the studies included exercise-based CR (exercise-only CR and comprehensive-CR), only 6 RCT's based on exercise-only CR as an intervention were included in the 22 RCT's analysed (O'Connor et al, 1989), making it impossible to understand the added benefit of the risk factor management component in to exercise component of CR. The studies showed that exercise with a risk factor component had a better effect in decreasing CV death and sudden death. The odds (OR) ratios for cardiovascular-related mortality and for sudden death were substantially lower in the comprehensive-CR RCT's than in the exercise-only CR RCT's. However, the relatively small number of exercise only-CR RCT's compared with comprehensive CR trials did not allow for definitive conclusions of which type of exercise-based CR is more effective to use in CHD patients. The lack of female patients, lack of different CHD patients and lack of inclusion of patients older than 65 years, made it difficult to conclude about the effectiveness of CR in this group of patients.

The two reviews (Oldrige, et al. 1988; O' Connor, et al. 1999) both suggested a 22-25% lower rate of CV mortality over 3 years in patients attending comprehensive CR, compared with patients receiving standard medical care (at that time, rest, health education and medication such as β-blockers). There is no evidence for the reduction of risk of no-fatal MI between the comprehensive-CR group and control group in both meta-analyses. The tendency for higher rates of non-fatal MI in O' Connor's review may be explained by higher survival capacity of fatal events, the exercise group may be protected against fatal events, due to the positive effects of the exercise in CV function, such as: Improved myocardial revascularization, better protection against dysrhythmias, better cardiovascular risk factor profile, improvement in cardiorespiratory capacity adopting healthy behaviours (modification of diet and smoking habits) and better surveillance by clinicians. These factors can also explain the positive effect of comprehensive-CR in reducing mortality (Oldridge, et al. 1988; O' Connor, et al. 1999).

Oldridge, et al. (1988) argued that the explanation for reduction in total and cardiac mortality may due to better cardiac function as improvements in cardiorespiratory capacity, although improvements were not consistently reported. O'Connor, et al. (1999), supported the view that the lower mortality rates reported in comprehensive-CR could be due to improvements in functional work capacity, a quantification of improvement in cardiorespiratory capacity, which, surprisingly, was not done in is study.

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There are some limitations to consider in the meta-analyses of Oldridge, et al. (1988); and O' Connor, et al. (1999) in regards to the results. The RCT's included in both studies had poor methodological quality and most of them were composed of a small number of patients, furthermore the RCT's mainly included only low risk MI male patients with a mean age of 52 years old, included in World Health Organization trials published in 1984 (Oldridge, et al. 1988; O' Connor, et al. 1999). The RCT's results revealed a great deal of heterogeneity, although this reflects the reality of different studies in CHD populations from different parts of the world, having differences in the RCT's variables such as: criteria for patient selection, baseline variability of patients included, the time to randomization, initiation of CR after MI, type and length of exercise interventions, and time of follow up.

The results make it impossible to conclude the impact of exercise only-based CR programmes in women, elderly patients and other forms of CHD than MI patients. The effectiveness of exercise-only CR (CR programme only based around the exercise component, without education on risk factors and behavioural change) in rehabilitation was impossible to determine, as most of the RCT's were based in comprehensive-CR programmes (Oldridge, et al. 1988; O' Connor, et al. 1999).

Twelve years after O' Connor, et al. (1999), Jollife et al. (2001) produced a systematic review of the available evidence assessing the effectiveness of CR. This review compared comprehensive CR (programmes including exercise and educational/ psycho-social interventions) with exercise-only CR. for reducing patient mortality and morbidity. As discussed, previous reviews had not been able to compare the effectiveness of these distinct types of CR interventions. Data from *n*=8440 patients (*n*=2845 patients in exercise-only group; *n*=5595 in the comprehensive CR), *n*=7,683 patients from 32 RCT's published from 1972 until the end of 1998 were included. Patient numbers were double those included in previous meta-analyses as data from n=27 new RCT's were included.

The patient inclusion criteria were broader than previous meta-analyses that only included MI patients. Joliffe, et al. (2001) included men and women of all ages attending programmes offered in both hospital and community settings. They also included a greater variety of CHD patients such as: MI, CHD patients who've had revascularization surgery (Percutaneous Transluminal Coronary Angioplasty -PTCA), and (Coronary Artery Bypass Grafting - CABG), angina pectoris and patients with known CHD defined by angiography.

Exercise-only CR reduced the risk of all-cause mortality by 27% (OR=0.73; 95%CI: 0.54 *to* 0.98) compared with only 13% in comprehensive-CR group (OR=0.87; 95%CI: 071 *to* 1.05), There was a 31% reduction in CV mortality in exercise-only CR (OR=0.69; 95%CI: 0.51 *to* 0.94) compared with a 26% reduction in studies of comprehensive-CR (OR=0.74; 95%CI: 0.57 *to* 0.96). The authors found no difference in the incidence of sudden death and non-fatal re-infarctions. No difference was found in the incidence of revascularization rate (PTCA, CABG) in both modes of CR programme, although CABG as an outcome was only reported in five RCT's and PTCA only reported in one RCT's, making it difficult to make conclusions about the CR effectiveness on these outcomes (Jollife, et al. 2001).

Jollife, et al. (2001) conducted a meta-analysis indicating a greater impact of CR programmes on all-cause mortality: 27% compared with a 20-24% reduction (Oldridge, et al. 1988; O'Connor, et al. 1989), and a 31% reduction in cardiac deaths, compare with 22-25% (Oldridge, et al. 1988; O'Connor, et al. 1989). There is no explanation for better CR outcomes reported in the exercise-only CR group compared with comprehensive-CR group intervention. Joliffe, et al. (2001) concluded that there was insufficient data to determine if exercise-only CR programmes were more effective than comprehensive programmes. Again, all end points used were of a clinical nature. Quantification of cardiorespiratory capacity gains may have helped to explain the differences between the two modes of CR. While all the studies reviewed were exercise-based, no such analysis was performed and there was no mention of patients' cardiorespiratory capacity or functional capacity.

This review (Jollife, et al. 2001) still had the limitations of previous meta-analyses (Oldridge, et al. 1988; O'Connor, et al. 1989). The individual trials overall were under-powered, and the quality of the earlier trials included was very poor (no randomization method reported or blinding assessment outcomes). One in three of the trials included had a 20% participant drop out to follow up. The number of women participants in trials was still low and was unequal in the different comparisons (4.4% in exercise-only an 11% in comprehensive CR) and the age of the patients included had a limit of 65 years old and a mean age of 53 years and 56 years in exercise-only CR and comprehensive-CR respectively. Patients involved in the study were of low risk, those excluded from the analyses included patients having undergone heart transplant, heart valve surgery or heart failure. Lastly, the studies didn’t report ethnic origin.

Use of exercise in exercise-based CR compared with standard medical care has proved to be more effective, although these early study limitations and the development of new drug therapies may reflect an overestimation of the benefit of exercise-base CR programmes in CHD patients compared with usual medical care patients. This review (Jollife, et al. 2001) included trials since 1972, the medication prescribed for CHD patients was β-blockers and calcium channel antagonists. In 1998 when the last studies were included in the analysis, patients were also medicated with statins, ACE inhibitors, aspirin, and thrombolytics prescribed more recently (Oldridge, et al. 1988; O’Connor, et al. 1989; Jollife, et al. 2001).

Since the last meta-analyses were published (Oldridge, et al. 1988; O’Connor, et al. 1989), five new RCT’s of exercise-only CR groups were included in the analysis. It was reported that patients were not receiving statins and 50% of them were just on β-blockers. In the comprehensive CR group fifteen new RCT’s were included in the analysis, all published after 1995, these studies reported more prescription of statins and β-blockers, but only three RCT’s reported the use of aspirin, and one RCT reported thrombolytic treatment. This review (Jollife, et al. 2001) concluded the benefits of CR programmes on mortality where all patients are medicated with aspirin, statins and ACE inhibitors, have not yet been studied.

Applicability of the evidence offered in previous meta-analyses (Oldridge, et al. 1988; O'Connor, et al. 1989; Jollife et al. 2001) of health policy change with the aim to provide better clinical practice is not yet clear. The past meta-analyses were under powered in testing the effectiveness of CR in several outcomes including mortality and morbidity of CHD patients. There was also a failure to consider a true representation of all diagnoses of CHD patients. There is a need to understand the effectiveness of CR programmes and how they complement the new variety of drug therapies, which were not available at the time of the last meta-analysis, this may have caused an overestimation of the effectiveness of the CR programmes on decreasing mortality and morbidity rates (Taylor, et al. 2004).

Three years later than Joliffe, et al. (2001), (Taylor, et al. 2004) performed yet another systematic review aiming to determine whether exercise-based CR could reduce mortality and morbidity in patients with CHD. They included data from trials of exercise-only CR, or in exercise in combination with psychosocial and educational interventions (Comprehensive CR). Outcomes of patients receiving both modes of CR programme were compared with those from control patients receiving normal care (prescribed medication but receiving no formal, structured exercise planning or education). Data from n=48 RCT's (18 exercise only trials, and 30 trials of comprehensive-CR) representing *n*=8940 patients and published from 1972 until

March of 2003. Taylor, et al. (2004) included 16 additional trials of a higher quality compared with the study of Jollife, et al. (2001).

Included studies had at least 6 months follow-up and included patients with several conditions CHD (MI, CABG, PTCA), angina pectoris and presence of CHD defined by angiography. All patients were involved in exercise programming including: supervised or unsupervised; different types of programmes: inpatient or outpatient; in community developed or home based (exercising independently). This is the first review to report what patients actually did during exercise-based CR sessions. Taylor, et al.'s (2001) review tested six hypotheses regarding CR's effects on patient mortality:

1. Different CHD diagnoses (MI-only trials vs others CHD trials);

2. Type of CR programme (Exercise-only CR vs Comprehensive CR);

3. Dose of exercise (duration in weeks x number of sessions x number of session per week x) (1000 < Units dose vs 1000 >Units dose);

4. Follow up period (≤12 months vs ≥12 months);

5. RCT's trial quality (jadad score ≤ 3 vs jadad score ≥3);

6. Year of publication of the trials (before 1995 vs 1995 or later).

The authors found a 20% decrease in all-cause mortality (OR=0.80; 95%CI: 0.68 *to* 0.93) and a 26% decrease in cardiac mortality (OR=0.74; 95%CI: 0.61 *to* 0.96) in patients attending CR. No significant differences were found for non-fatal MI, or the need for subsequent revascularization (Taylor, et al. 2004).

Exercise-only CR, (*n*=19 RCT's, n=2984 patients), decreased cardiac mortality by 28% (RR= 0.72; 95%CI: 0.55 *to* 0.95) (Taylor, et al. 2006). However, the authors found no differences in patient mortality according to patients' initial diagnosis, type of CR programme, dose of exercise, follow up period, trial quality or year of publication (Taylor, et al. 2004).

The results of this review are in accordance with the earliest reviews (Oldridge, et al. 1998; O'Connor, et al. 1999) in terms of CR's effectiveness in reducing mortality in CHD patients. Estimates are much lower than those in Jollife, et al.'s (2001) review, this decrease is probably due to the increase and development of new pharmaceutical therapies used in medical care of CHD patients in the new RCT's, such as acute thrombolytic therapy, beta-adrenergic blockers, aspirin and lipid management therapy. The last RCT's continue to reveal a positive effect on mortality due to exercise-based CR programmes (Taylor, et al. 2004).

This review was more representative of patients being treated for angina pectoris and revascularization procedures (CABG and PCTA). Overall, n=16 trials (37%) included revascularization patients compared with only *n*=6 trials of re-vascularized patients in the review by Jollife, et al. (2001). Trials of Post-MI patients still made up the majority of studies (n=32, 67% of all trials included). Women were represented in half of the

RCT’s (27 RCT’s) representing 54% of all RCT’s), women account for only 20% of the patients included, although the number increased compared with Jollife, et al. (2001), where women made up 4.4% of participants in exercise-only trials and 11% of those receiving comprehensive-CR.

Importantly, Taylor, et al. (2004) were the first authors who attempted to quantify the impact of exercise dose; where dose is defined as: duration in weeks * number of sessions * number of sessions per week. The analysis in exercise dose were completed based in cut-point between 1000 units vs. dose >1000 units. It would had been simpler to report the final effect in the outcome of all the variables, including the cardiorespiratory fitness of CHD patients, which also should be reported in these studies.

Taylor, et all’s (2004) review still possesses some of the limitations found in earlier reviews. The mean age was still only 55 years, data gained was from mainly low risk, male patients who had suffered an acute MI. The poor methodological quality of many trials, didn't provide details of the process of randomization, allocation concealment or blinding outcome assessment. Therefore, quality of the trials didn’t improve with time in this research field (Taylor, et al. 2004).

Just one year after Taylor, et al. (2004), a new review was published (Clark, et al. 2005). They produced an updated review aiming to determine the effectiveness of three modalities of secondary prevention programmes. These were classified as exercise-only CR, comprehensive CR, and secondary prevention without exercise;

including interventions based on education about CHD risk factors and/or psychosocial counselling. Again, the primary outcome measures were patient mortality and morbidity, only clinical outcomes were assessed in this review, there was no attempt of quantify the dose of exercise in exercise-based CR trials, as in previous review (Taylor, et al. 2004). Clark, et al. (2005) analysed data from *n*=21295 CHD patients included in n= 63 RCT's published between 1966 and 2004. With n=23 additional trials Clarke, et al.'s (2005) review included three times as many patients than the most recent review (Taylor, et al. 2004).

There was a 15% (RR= 0.85; 95% CI: .82 *to* 1.14) decrease in all-cause mortality (n=40 trials, *n*= 16142 patients). There were no statistical differences in effect in all-cause mortality in the three types of secondary prevention. Combining all RCT's including exercise in CR (n=27 trials, *n*= 6940 patients) a 17% (RR=.83; 95%CI: 0.72 *to* 0.96) decrease is reported compared with a 13% (RR=.87; 95%CI: 0.76 *to* 0.99) reduction in all cause of mortality by non-exercise CR programmes (n=14 trials, *n*= 9202 patients) (Clark, et al. 2005).

This study report for the first time that different secondary prevention programmes, including exercise-based CR, have a different effect in all-cause mortality in the long term, an overall 0.3% (RR= 0.97; 95%CI: 0.82 *to* 1.14) decrease at 12 months is reported. This is compared with a 47% (RR= 0.53; 95%CI: 0.35 *to* 0.81) decrease at 24 months of follow up, an effect of 23% (RR= 0.77; 95%CI: 0.63 *to* 0.93) is reported at a period of 5 years of follow up, being the limit in the trials being conducted. MI re-infarction was 17% lower (RR= 0.83; 95%CI: 0.74 *to* 0.94) after 12 months in CR including exercise, compared with group of usual care. The effects of the 3 types of CR didn't change during the time of follow up. Exercise-based CR produced a 27% (RR= 0.73; 95%CI: 0.6 *to* 0.89) reduction of re-infarction compared with only 14% (RR= 0.86; 95%CI: 0.72 *to* 1.03) in CR programmes without exercise (Clark, et al. 2005).

This review confirms the benefits of all modalities of CR for the secondary prevention of all-cause mortality over five years. The overall reduction in all-cause mortality (17%) is the smallest value reported in a systematic review. The value is low compared with the 20% to 27% reported previously (Oldridge, et al. 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al. 2004, 2006).

Mortality was 47% lower after two years, this high impact after 2 years follow up was never reported, this may be explained by the time taken for the effect of reduced risk factors in the reduction of atherosclerotic plaque instability or coronary artery diameter (Clark, et al. 2005). All meta-analyses published before (Oldridge, et al. 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al. 2004, 2006) never reported a significant lowering in the rate of re-infarction of CHD patients, as this study did for the first time. RCT's included in this meta-analysis had highly selected study samples. The higher benefit of usual care only as secondary prevention of CHD in this study, may be caused by the setting in which RCT's were performed, the fact that the management of the CHD patients was optimal. No attempt to report changes in cardiorespiratory capacity is made.

Clark's (2005) review is more superior than previous reviews (Oldridge, et al. 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al. 2004, 2006). Women represented less than 50% of the patients included in the analysis, although this was much higher than the 20% included in past meta-analysis (Taylor, et al. 2004). Only n=15 trials adequately described allocation of condition and method of concealment, all these factors are likely to effect the estimation of CR's effectiveness.

Heran, et al. (2011) updated the results for the effectiveness of exercise-based CR programmes (exercise-only and Comprehensive-CR) in reducing mortality, and morbidity in CHD patients using data from n=47 RCT's (n=17 exercise-only CR trials, and n=29 trials of comprehensive-CR). They included trials published until 2009 which included a follow-up of at least six months. This review included n=17 RCT's published between 2000 and 2009 updating the findings of the most recent review (Clark, et al. 2005). The authors included data from *n*=10794 patients (mean age of 56 years old) suffering from an MI, having received revascularization, having angina pectoris or coronary artery disease defined by angiography. Patients receiving valvuloplasty, patients with heart failure, heart transplants, implanted with cardiac-resynchronization therapy or implantable defibrillators were, however, were all excluded from the analysis. In this review exercise is quantified again as in Taylor, et al. (2004). The authors tested five hypotheses according to different variables presented in trials, concerning the effectiveness of CR in reducing mortality:

1. Different CHD diagnoses (MI-only trials vs others CHD trials);

2. Type of CR programme (Exercise-only CR vs Comprehensive CR);

3. Dose of exercise (duration in weeks x number of sessions x number of session per week x) (1000 < Units dose vs 1000 >Units dose);

4. Follow up period (≤12 months vs ≥12 months);

5. Year of publication of the trials (before 1995 *vs.* 1995 or later).

In studies (n= 30 trials, *n*=8971 patients) with a follow-up of at least 12 months, there was a 13% (RR= 0.87; 95%CI: 0.75 *to* 0.99) reduction in total mortality in patients attending exercise-based CR compared with the control group. No significant differences in total mortality were found in follow-ups less than 12 months. Cardiac mortality was reported in 19 RCT's (*n*=6583 patients), in studies with a follow-up longer than 12 months, there was a 24% (RR= 0.76; 95%CI: 0.63 *to* 0.87) reduction in cardiac mortality due to exercise-based CR. Not significant differences in cardiac mortality was found in just 12 months follow-up in both groups (Heran, et al. 2011).

There were no differences in rates of re-infarction or revascularization over 12 months or longer between patients receiving exercise-based CR and controls. When the hospitalizations were considered, a 31% (RR=0.69; 95%CI:0.51 *to* 0.93) reduction was reported in exercise-based CR compared with the control group at a follow up of 12 months, no significant changes were seen in follow-ups longer than 12 months. In this study no differences were reported in CR effectiveness on mortality between different CHD diagnoses, type of CR programme, dose of exercise, follow up period, trial quality, and between years of trial publication (Heran, et al. 2011).

Heran, et al.'s (2011) meta-analysis, assessing the effect of exercise based CR on mortality at a follow up longer than 12 months confirms the data from past meta-analysis (Clark, et al. 2005), although only half of the effect was reported. CV mortality was 24% compared with a 47% decrease in a past review (Clark, et al. 2005). Non significant differences in total mortality were found at just 12 months follow-up, confirming the little effect reported in past meta-analyses (Clark, et al. 2005). The effect on cardiac mortality was the same as reported in previous reviews (Oldridge, et al. 1988; O'Connor, et al. 1999; Taylor, et al. 2004).

The introduction of new drug therapies for CHD patients in trials that were not available in the earliest meta-analyses (Oldridge, et al. 1988; O'Connor, et al. 1999; Taylor, et al. 2004), may have contributed to the reduced effect of exercise-based CR on all-cause mortality. Analysis of this review showed no differences between the two types of exercise-based CR, confirming the conclusions of Taylor, et al. (2004) and Clark, et al. (2005). This was the second meta-analysis that attempted to quantify the impact of exercise dose. The analysis in exercise dose were completed based in cut-point between, 1000 units vs. dose >1000 units. It would have been simpler to report the final effect of the outcome of all these variables, what is the cardiorespiratory fitness of CHD patients, which also would be reported in studies.

Heran, et al. (2011) supported the view that exercise-based CR programmes had a more positive impact on reducing all-cause and cardiac mortality, more so than past analyses. Although this paper still possessed the same limitations as previous reviews (Oldridge, et al. 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al. 2004, 2006; and Clark, et al. 2005). The patients in the included RCT's analysed were of low risk; most of them post-MI men and with an average age of 55 years old and there were few patients included older than 70. This is not representative of the mean age of CHD patients which, in reality, is older. There was an under representation of cardiac groups (post-revascularization and angina pectoris), elderly women, and those from different ethnic origins, making it impossible to understand which groups benefit more from CR programmes. There was poor methodological quality in many of the trials, which failed to provide details of the process of randomization, allocation concealment or blinding outcome assessment. Losses to follow-up and drop out were relatively high, ranging from 21% to 48% in 12 trials. Follow-up of 80% or more was achieved in 33/47 (70%) studies. Further RCT's are needed to explain much of the variability presented in CHD and the implications of different clinical outcomes and mortality rates.

The literature on this topic is extensive (Oldridge, et al. 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al. 2004, 2006; and Clark, et al. 2005, Heran, et al. 2011). There is clear evidence of the effectiveness of exercise-based CR (exercise-only CR and comprehensive- CR) in reducing all-cause mortality and cardiac death, supporting strongly by the guidelines that now state the use of exercise-based CR as the core or central element in CR programmes of secondary prevention in CHD patients (NICE, 2007; Balady, et al. 2007). Because of the focus on mortality and clinical endpoint in the outcomes of the analyses, is it not known which mechanism is behind the positive effect reported on survival of CHD patients. The mechanism could be the positive effect of exercise in cardiac function, or the improvement in cardiorespiratory fitness (which was never quantified in the meta-analyses). The positive influence of exercise-base CR has in reversing endothelium dysfunction and inflammation of vascular wall, which leads the process of arteriosclerosis to CHD, can be also one of the causes that explain the efficacy of CR in reducing morbidity and mortality in cardiac patients.

Endothelial cell is the inner tissue in the structure of the entire vascular system, from the heart to the smallest capillaries. It is a thin layer that makes the interface between circulating blood and the rest of the vessel wall. Endothelial cells are involved in many aspects of biology vascular homeostasis, such as: allowing the continuous adjustment of vascular tone by vasoconstriction or vasodilation (controlling blood pressure), has a semi-selective barrier function between the vessel lumen and surrounding tissues, (performing physiological regulation of several materials and leukocyte traffic into and out of the bloodstream), is involved in inflammation process, prevents blood clotting (thrombosis & fibrinolysis), and induces formation of new blood vessels (angiogenesis). Endothelial dysfunction, or the loss of proper endothelial function, is expressed by an alteration in the basal endothelial phenotype (vasorelaxant, anticoagulant, antiplatelet and profibrinolytic), which is turn in vasoconstrictive, procoagulant, platelet-activating, and antifibrinolytic, characterizing the atherosclerosis process that leads to CHD. (Ribeiro, et al. 2010)

Exercise-base CR is effective in improving endothelium function and diminish the vascular inflammation and consequently reversing arteriosclerosis, although the mechanisms by which this work is not fully understood. Evidence suggest that the improvement of nitric oxide bioavailability that is diminish in endothelium dysfunction, is one of the mechanism by which exercise works. Nitric oxide is responsible for the inhibition of platelet aggregation, control of the cytokine adhesion to the vessel wall, and mostly important by the regulation of vascular tone, increasing the endothelium-dependent vasodilatation, each explains the reduction of myocardial ischemia due to exercise base CR. Antioxidant defences are also increase with exercise which reduces the nitric oxide degradation, formation of foam cells (fat-laden macrophages seen in the process of atherosclerosis) and vascular inflammation. Exercise can be also effective in reduction of endothelial adhesiveness of circulating leukocytes, increasing the number of circulating endothelial progenitor cells, which represents the capacity of the endothelium to regenerate after injury and angiogenesis, and also diminishes the level of inflammatory markers, that include the decrease in cytokine production by the adipose tissue, skeletal muscles, endothelial cells, and blood mononuclear cells namely proinflammatory cytokines and C-reactive protein (Ribeiro, et al. 2010; Ribeiro, et al. 2013). Furthermore, the exercise effect on the reduction of risk factors for atherosclerotic disease could be also an explanation for the positive effect of exercise based CR has on survival of CHD patients.

2.1.2. Risk factor reduction

Jollife, et al. (2001) produced the first systematic review to examine the effects of exercise-only and comprehensive-CR programmes on modifiable risk factors for CHD (total cholesterol, LDL, triglycerides, blood pressure, and smoking), they suggested some potential mechanisms explaining why CR is effective in reducing mortality. Total cholesterol (OR= -0.57 mml/l; 95% CI: -0.83 to -0.31) and LDL (-0.51mml/l; 95%CI: -0.82 to -0.19) and lipoproteins were significantly reduced with comprehensive CR. There is no explanation for differences seen between only-exercise CR and comprehensive CR. This can be explained due to different medication taken during the RCT's included, also exercise-only CR didn't show any reduction in risk factors, only five RCT's were available for analysis for risk factors in both groups. The risk factors analysed were limited to poor trials, reports in both groups were composed of a low number of trials that included the risk factor outcome, showing heterogeneity in the results.

Taylor, et al. (2004) three years later produced another systematic review focusing on the function of exercise-based CR in reducing risk factors specifically in CHD patients. Patients receiving exercise-only CR programmes, supervised or unsupervised, showed significant reductions in total cholesterol (RR= -0.37mml/l; 95%CI: -0.68 to -0.11), triglycerides (RR= -0.23; 95%CI: -0.39 to -0.07), systolic blood pressure (RR= -3.2mm Hg; 95%CI: -5.4 to -0.9) and likelihood of smoking cessation (OR=0.64; 95% CI: 0.50-.83). No significant changes in levels of LDL or HDL cholesterol were found.

This data (Taylor, et al. 2004) was used to examine how much of the 28% (RR= 0.72; 95%CI: 0.55 to 0.95) reduction in patient mortality could be attributed to the indirect effect of exercise-based CR on cardiac risk factors. Taylor et al. (2004) found that the 58% reduction in patient mortality due to exercise-based CR could be explained by risk factor modification; 24% due to smoking cessation, 19.7% from modification of plasma cholesterol and 15% due to reductions in systolic blood pressure.

The reduction of risk factors was an indirect positive outcome and disease related effect witnessed in exercise-base CR programmes in CHD patients, although other measures of the general state of health such the well-being of the patients should be taken in account in the overall assessment of the CHD patients. Health-related quality of life questionnaires are important tools, the outcome of which reflects the CHD patient performance in society and should be part of every CR programme design. World Health Organization, in 1997, mentioned in a document called: ‘’Measuring quality of life’’ that health related quality of life could be defined as:

‘’Quality of Life *is the individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment.’’*

2.1.3. Health-related quality of life

Jollife, et al. (2001) produced the first systematic review to understand the effectiveness of CR exercise based programmes and comprehensive programmes (Educational and psycho-social interventions) on health-related quality of life (HRQoL) in CHD patients. No clear changes in HRQoL were witnessed in the results. The difficulty in analysing the HRQoL is due to the heterogeneity of tools used to assess it between the RCT's. A total of 18 different tools used to assess HRQoL were identified in the RCT's, four of them were un-validated self-reported instruments and some of the psychological questionnaires used are not suitable in general CR practise.

Taylor, et al. (2004) concluded that the heterogeneity of trials and outcome measures used to assess HRQoL in the trials made it impossible to analyse the data. Many of the measures were generic, showing lack of sensitivity to detect changes and without inclusion of disease-specific measures. Although an improvement is seen in all RCT's that assessed HRQoL in CHD patients, the same improvements were seen in the control groups. Only 2 trials possessed 250 CHD patients, which had power enough to detect changes between groups, showing benefits over the control group.

Heran, et al. (2011), produced a review updating the results of the effectiveness of exercise-based CR programmes in improving health related quality of life of CHD patients compared to a control group receiving usual medical care in secondary prevention. A range of validated, disease-specific and generic tools for outcomes assessment were used, although the heterogeneity of how the results were assessed and presented makes it impossible to meta-analyse the data. In 7 RCT's of the 10 analysed, a significant improvement in HRQoL in exercise-base CR was reported, although an improvement was reported within control groups too.

2.1.4. Effectiveness of Cardiac Rehabilitation: A Critical Summary of the Evidence

Exercise-based CR is effective in reducing total and cardiac mortality, and risk factors for CHD. All the discussed analyses included exercise-based CR programmes but only clinical endpoints were included in the analysis of mortality, which don't explain fully how exercise-based CR is effective in reducing cardiac and total mortality. It was surprising that none of them examined change in fitness as an outcome, which is dependent on the dose of exercise used (only outcome measured), and may be the explanation for the positive effect of exercise-based CR (Oldridge et al, 1988; O'Connor, et al. 1999; Joliffe, et al. 2001; Taylor, et al, 2004, 2006; and Clark, et al., 2005, Heran, et al. 2011).

Gains in fitness achieved by patients in CR are closely, inversely, related to patient mortality and morbidity, and evidence is strong and abundant (Ades, et al. 2006 Williams, et al. 2006; Blair, et al. 1995; Balady, et al. 1996; Gulati, et al. 2003). These studies show us the cross-sectional associations between fitness and mortality, others studies have demonstrated the degree of impact that fitness gains have on mortality due to CR programmemes (Myers, et al. 2002; Dorn, et al. 1999; Kavanagh, et al.

2003; Vanhess, et al. 1995). Kavanagh et al. (2006) demonstrated that each increase of 1 ml·kg^{-1}·min^{-1} in $\dot{V}O_{2peak}$ was related with a 10% reduction in cardiac mortality. Vanhess, et al. (1995) demonstrated that each increase of 1% in $\dot{V}O_{2peak}$ was related with a 2% reduction in mortality. Myers, et al. (2002) showed that a 1 MET increase in fitness was related with 12% reduction in mortality, also Dorn, et al. (1999) showed that a 1 MET increase was related with 10% decrease in mortality in male MI patients. Levels of fitness gains are recognized to have clinical importance in cardiac patients, however only limited studies have tried to synthesise such information (Conn, et al. 2009; Swain, et al. 2006).

2.2. Incremental Shuttle Walk Test

2.2.1. Background of testing cardiorespiratory capacity

Assessment of functional capacity (an individual's ability to perform meaningful tasks on a safe and dependable basis in daily life) is an important component of clinical care, enabling decisions on diagnosis, prognosis, treatment effect and exercise prescription of patient's, based on objective measures (gas analysis). Laboratory tests such as incremental treadmill exercise or cycle ergometer tests with gas analysis are the 'Gold Standard' protocols for cardiorespiratory fitness (a health-related component of physical fitness, which is defined as, the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity) assessments in cardiac patients.

All the studies that show cross-sectional associations between fitness and mortality (Ades, et al. 2006 Williams, et al. 2006; Blair, et al. 1995; Balady, et al. 1996; Gulati, et al. 2003), and studies that have demonstrated the degree of impact that fitness gains have on mortality due to CR programmes (Myers, et al. 2002; Dorn, et al. 1999; Kavanagh, et al. 2003; Vanhess, et al. 1995) were based on the treadmill exercise test. Incremental treadmill exercise possess some limitations, they are not simple to use, there is a need for technical expertise, and involves expensive equipment, consequently it is not widely available in health care units (Bruce, et al. 1963; Ades, et al. 2006).

In the UK, the department of health recommends the use of exercise tests to evaluate patients at the beginning of Cardiac Rehabilitation, allowing risk stratification and prescribing exercise at the correct intensity, (SIGN, 2002; NICE, 2007). They also recommend summative assessment as an outcome measure or in Cardiac Rehabilitation to evaluate improvements due to attending the programme. European and UK guidance suggests that patients should achieve exercise intensity (sometimes referred to as functional capacity) equal to five Metabolic Equivalents (METS). One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O2 per kg body weight x min. There are a number of walking field tests available to assess CR patients' cardiorespiratory fitness when the treadmill exercise test is not available, such as the 10 m ISW test.

2.2.2. Walking field tests in cardiac patients

2.2.2.1. Development of walking tests

The large volume of expensive laboratory equipment used to test functional capacity in chronic bronchitis patients in many hospitals, meant that most of diagnostic decisions made at the level of patient disability were based on Spirometry testing. That is, assessing pulmonary function and using respiratory questionnaires with potential to assess the level of everyday disability. Unsatisfied with the subjective nature of self-reported symptoms; Mc Gavin (1976) developed a field test which was simple to apply and had no need of expensive equipment; the 12 min walking test (12MWT). It was designed to objectively measure functional capacity and define specifically the level of disability in these patients according to their test performance.

The distance achieved in 12 minutes, gives an estimation of functional capacity of the patient. This idea had been developed by Cooper, (1968) when he validated the 12 min run test (12 MRT) in 150 young healthy men with a highly validity of R=.897; significantly predicting $\dot{V}O_{2peak}$ with accuracy (+/1 3.5 $ml.kg^{-1}min^{-1}$) when correlated with $\dot{V}O_{2peak}$ measured during incremental treadmill testing. The length of 12 minutes of the test was supported by Katch (1973) as a good endurance time measure in his study done on cycle ergometer performance. The findings stated that the optimal duration for testing aerobic capacity during incremental testing was 8 to 12 minutes, and no further gains will be obtained in tests of longer duration.

Butland, et al. (1982) realised that for severely impaired pulmonary patients with a certain degree of disability performing the 12-minute length of the walk test required a high level of physical effort. Butland, et al. (1982) proposed that tests of shorter duration would be more suitable for functional assessment of these type of patients. The performance of different lengths of walk tests were analysed, 2 minutes, 6 minutes and 12-minute walk. Thirty patients with stable chronic pulmonary disease (61±12 years) performed the three distances of walking tests in a randomized design in different days, a high correlation was found between the tests length of 12 m *vs.* 6 m (r=.955), a high correlation between 12 m *vs.* 6 m walk test (r= .97) was found too by Bernstein, et al. (1994), suggesting the distance walked in six minutes was a suitable time length for functional capacity assessment. This was first applied as the 6 MWT in a study of heart failure patients by Guyatt, et al. (1985).

Tests that assess physical performance based on a walking distance covered in times such as 6 or 12 minutes present some limitations in the assessment of the clinical population's functional capacity. The test performance is self-paced in nature, which is highly influenced by patients' motivation and external encouragement (Guyatt, et al. 1984). Due to the constant work rate featured in the test it tends not to elicit a true maximal or symptom-limited performance in patients. This provides poor information about physiological responses to exercise, when the pace in performing of the test is analysed, it is seen that patients only push themselves in the first two minutes of the test, maintaining a comfortable pace in subsequent intervals of two minutes (Butland, et al.1982). This makes it difficult to objectively determinate the degree of disability and true functional capacity, not allowing for intra- or inter-patient comparison due to this lack of test standardization (Singh, et al. 1992).

The 12-MWT tends to show reliable results after the third attempt of the test (Mungall and Hainsworth, 1979; Butland, et al. 1982; Guyatt, et al. 1984) and in some studies only after four practice test walks (Swinburn, et al. 1985; Knox, et al. 1988). There is also only a low-to-moderate relationship between $V'O_2$ max directly measured on a cycle ergometer and distance walked in the test, (McGavin, et al. 1976; Allison and Anderson, 1981; Swinburn, et al. 1985; Bernstein, et al. 1994). Such low correlations between measures of functional capacity taken from the self-paced walk test, can be explained by the variables that the test is subjected to when used in a wide range of functional capacity levels.

2.2.2.2. 10 m Incremental shuttle walk test (ISWT)

Limitations of self-paced tests, inspired Singh, et al. (1992) to develop a new field test to be used in the clinical population in order to try and overcome the limitations of the past self-pace walk tests. The 10 m ISW test (ISWT) is a standard test, externally paced with a progressive, incremental walking speed protocol, able to elicit enough effort to provoke symptom limited maximal performance in patients. The ISWT was adapted from the 20 m shuttle run test developed by Leger and Lambert (1982).

Unlike the more commonly used 6 min walk test, the incremental shuttle walk test (Singh, et al. 1992, 1994; Fowler, et al. 2005) of functional capacity, is not a self-paced test, but is standardized to create an incremental, progressive structure of 12 speed levels. The test is paced externally by a CD, inducing the patient to exercise to a symptom limited maximal effort. The design of the test is a 10 m course, with a cone of 0.5 m before the 10m point at both extremes, allowing the patient to round the cones. The speed of the test increases by 0.17 $m \cdot s^{-1}$ every minute, starting at 0.50 $m \cdot s^{-1}$ at level one and finishing with a speed of 2.37 $m \cdot s^{-1}$ at level 12. The explanation of the test is pre-recorded, and is standardized for all patients before the test starts. At the start of the test, and every minute after, a triple bleep is heard (indicating a new level). The patient is paced during the level by a single bleep which, when heard, means they should be rounding the cone and turning round for the next lap. The test may be terminated volitionally by the patient if they feel unable to continue, or by the technician, when the patients fails to reach the cone by more than 0.5 m. The test is also terminated if the patient reaches 85% of maximal heart rate (Singh, et al. 1992) or reports their rating of perceived exertion (RPE) to be at 16 or more (SIGN, 2002).

The originally studied test was able to predict $\dot{V}O_{2peak}$ in a healthy population of 91 adults (32 females, mean age 25 years). There was a high correlation with $\dot{V}O_{2peak}$ direct measure and the 20 m shuttle run test (r=.84, SEE= 5.4 $ml \cdot kg^{-1} \cdot min^{-1}$). The same work load is applied to all patients due to the standard protocol design, allowing performance comparison between patients, what was not possible before with other field tests due to the variation in performance (distance achieved) during the test time. Due to the external pace, the test is less influenced by operator encouragement and patient motivation. The test overcomes problems found in previous self-paced tests, showing applicability in pulmonary chronic diseases in predicting functional capacity in a wide range of functional capacities. It is also capable of being used in other populations suffering disabilities from diseases such as cardiovascular disease (CVD).

To be clinically applicable the 10 m ISW test needs to meet certain criteria such as test-retest reliability, sensitivity and validity in the outcome measures.

2.2.2.3. Test-retest Reliability

Reproducibility of the results is an important characteristic to take into consideration when testing physical capacities. A test should be able to report reliable results when used at different times, in similar patient groups.

The reliability of the ISWT was first assessed by Singh, et al. (1992) when they developed the test. Three ISWT tests were conducted at same time of day at one week intervals, in 10 patients with chronic airway obstruction. The mean distance covered in three trials was: 345 m, 376 m and 378 m, there was a significant difference between 1st and 2nd trials, but no difference between 2nd and 3rd trials The mean difference in distance walked was -2.0, indicating very small systematic error. Confidence intervals indicated random error (95% CI -21.9 to 17.9) m. The larger difference found between 1st and 2nd attempts was interpreted by the test performance being influenced by learning effects. The authors concluded that the ISWT showed reproducibility after one walk practice.

Payne, et al. (1996) were the first to apply the ISWT in cardiac patients. These authors, assessed the reliability and the ability of the test to detect changes due to programming patients' rate-responsive pacemakers. Again, three ISWTs were performed by ten patients (4 female, aged 60 to 74 years,), with an interval between them of 20 minutes rest. The mean performance was reported in minutes, the differences between the three tests were not significant: 7.6 (1.7) min; 7.7 (1.6) min and 7.7 (1.7) minutes. The authors claim these results show good reproducibility of the test from the first attempt, suggesting that the learning effect was small and not as significant as it was previously (Singh, et al. 1992). Unfortunately, no acceptable measure of reliability was provided as a simple lack of statistically significant difference in means did not describe the systematic differences between pairs of test scores adequately.

In a more statistically rigorous analysis, Arnott (1997) assessed the reliability of the ISWT in patients who had undergone surgery (CABG) in the past 12 months. The study included n=30 patients (mean age 62, range 42 – 68 years) divided into group A, (n=20 patients that had not received CR) and group B, (n=10 patients who completed a CR programme). Patients were tested three times in one week, with at least 24 hours between tests. The results showed an improvement in final mean distance of 4.7% between test 1 and 2, and a 0.9% improvement between test 2 and test 3. The test performance is influenced by learning and training as showed by Singh, et al. (1992), although this influences were not significant in this study, suggesting a good reproducibility from the first attempt, even when assessing different levels of functional capacity.

Morales, et al. (1999) assessed the reliability of the ISWT and the 6 MWT in 17 heart failure patients (aged 53±10 years) who were clinically stable with an ejection fraction <40% (mean 23 ±8%) and a New York Heart Association Class of 2 to 4 (mean 2.8

±0.7). Patients performed trials of each test in a randomized order. No more than two tests were completed in a single day, with all tests being conducted within a two-week period. The mean distance walked during the three ISWT trials attempts was 445 m, 478 m and 485 m. The mean distance found in 6 MWT over three trials was 475 m, 496 m and 505 m. Significant differences in mean distance walked were found between trials one and two in both the ISWT and 6 MWT. There were no significant differences in distance walked between trials two and three in either test. The mean difference in the ISWT was -7m and the test-test correlation between trials 2 and 3 was (r=0.99). The tests show reliability after just one first practice attempt. The researchers explain this significance found between first and second attempt in both tests, as being due to training effect, as patients were subjected to six tests (three SWT and three 6 MWT) done in a short period of time of 12 weeks.

Lewis, et al. (2001) assessed the reliability of treadmill exercise test and ISWT in 25 heart failure patients (21 males, 53 [range 33-69] years). Patients performed three ISWT trials (1st test being a practice trial), and two trials of Naughton protocol treadmill tests with expired gas analysis to determine $\dot{V}O_{2peak}$. The performance achieved in treadmill trial 1 ($\dot{V}O_{2peak}$= 15.2 ±4.4 ml•kg^{-1}•min^{-1}) and 2 ($\dot{V}O_{2peak}$ =15.0 ±4.4 ml•kg^{-1}•min^{-1}) correlated well ($r=0.83$ $p<0.0001$) showing good reliability from the first attempt. After one practice attempt, mean distance walked during the second trial of the ISWT (400 ±146 m) was very similar to the third trials (401 ±129 m). Scores on these tests correlated very well (r=0 .90, $p<0.0001$), showing high repeatability after a first practise attempt. Results of the practice attempted were not reported so no comparison is possible with the second walk test to investigate if this test showed reliability from the first attempt. Furthermore, the study showed poor statistical description, no indication of random error in confidence intervals of distances measured between test 2 and test 3 were made.

Fowler, et al. (2005), investigated the reliability of the ISWT in predicting $\dot{V}O_{2peak}$ in 39 cardiac patients (34 males, mean age 61.2±8.5) years) who had been through CABG surgery in the previous 6 to 8 weeks. Patients performed 3 ISWT's in one week, one test on the first visit and on the second visit they performed two ISWT's separated by 45 minutes. The mean distances walked in the three tests were: 444.3 ±134 m; 485.3±147m and 478 ±141.1 m). A strong relationship was found between the three walk test distances and there were no statistically significant differences in means (p=.361). A small learning effect can explain an increase in mean distance achieved between performance in tests 1 and 2. The mean distance achieved between test 2 and 3 was 1.7 m (95%CI: -1.9 – 5.3) compared with mean distance achieved between test 1 and test 2 of 40.3 m (48.2) (95%CI: 24.4 – 56.1), this mean distance and systematic error found between attempt two and three of 1.7 m is smaller than 2 m as found previously (Singh, et al. 1992). No significant difference was found between attempt 1 and 2 of the ISWT, suggesting that the test is reliable from the first attempt, as suggested previously (Arnott, 1997). However, due to effect of learning seen in the coefficient of reliability between tests, 40.3 m is a large range of variance between tests, even if no significant differences were found between mean distance achieved in test 1 and test 2. Consequently, if the test is used for therapy or rehabilitation assessment effect, the results could be misleading.

Jolly, et al. (2008) investigated the reliability of the ISWT, questioning whether one practice walk of the test is really needed, or if the test shows reliability from the first attempt as showed by Arnott (1997). Significant differences between second and third attempt were not seen in all previous studies. The 353 patients (mean age 61.6 (SD 10.2) years; 282 (79%) male; 165 (46.7%) post-MI; 188 (53.3%) post-revascularisation; 68 (19.35) from a minority ethnic group) in the study were recruited from the Birmingham Rehabilitation Uptake Maximization (BRUM) trial of Cardiac rehabilitation. After the patients performed a practice walk of the ISWT, follow by another ISWT with only a 30 min interval. 1457 ISWTs were conducted, 353 pairs of ISWT were analysed for reliability between first and second attempt. There was a significant increase in mean distance achieved between the practice walk (358 ±152 m) and the second test *(*415 ±158 m P<.001). This significant increase was seen in all the sub-groups tested. There was a significant difference between mean distance in attempt 1 and 2. The test was deemed safe to apply to this large population of patients suffering from ischaemic symptoms, the heart rate recorded in both trials showed no significant difference. This suggests there was a similar effort applied throughout. The significant difference in distance achieved in ISWT was due to the learning effect of patients and not to motivational reasons. The study confirmed that a first practice attempt is needed to achieve reliability in the ISWT, supporting previous studies (Singh, et al. 1994; Morales, et al. 1999; Lewis, et al. 2001).

Based on the studies reviewed above, a practice walk is recommended in a clinical setting for more accurate, reliable results. The reliability in this study was assessed over a short term period (1 week) similar to previous studies of ISWT reliability, ranging from 3 days to 1 weeks' time. The results were under influence of learning and training effect due the amount of testing done in a short period of time (Singh, et al. 1992; Arnott, 1997; Morales, et al. 1999; Lewis, et al. 2001). It's important that studies in the future will test the reliability between first attempt and second with a better methodology design allowing enough rest time between tests. The long term reliability of the ISWT was not, however studied.

In comparison with the above-mentioned studies of short-term reliability, Pepera, et al. (2008) studied the long term reliability of the ISWT, which was never analysed before. All other reliability studies had included tests done in a short period of time (1-week time). This is important as the ISWT is supported by guidelines (SIGN, 2002; BACPR, 2012) to be used as a measure of changes in cardiorespiratory capacity due to Cardiac Rehabilitation and exercise prescription, in phase III and phase IV, varying the rehabilitation in a time of 6 to 8 in UK (Brodie, et al. 2006), so there is a need to understand the long term reliability of the test when used in real Cardiac Rehabilitation conditions.

Thirty stable cardiac patients (15 males; age 55 to 80 years), performed two ISWTs a minimum of eight weeks apart. There was no statistically significant difference in mean distance walked between test one (502 ± 101 m) and two (509 ±146 m). Total distance walked showed ICC of 0.80 (95% CI 0.62 + 0.90) and a test, re-test bias of only -7 m. Suggesting that there was no learning effect between the two trials of the ISWT. This suggests that a practice attempt of the ISWT may not be necessary if the test is applied over a longer interval such as 8 weeks. This is contrary to the results of studies assessing short reliability (Arnott, et al. 1997; Fowler, et al. 2005), although the limits of agreement found of -203 to 189 m were greater than those reported by previous studies done between the first and second test in a short time period (Singh, et al. 1992; Jolly, et al. 2008) and between pre and post Cardiac Rehabilitation (Fowler, et al. 2005; Arnold, et al. 2007).

Pepera, et al.'s (2008) study revealed low inter-individual test-retest reliability, the big range seen in the limits of agreement of -203 to 189 m showed a large inter-individual variance in performance between the tests. This random variation was bigger than the critical mean value of 100 m increase observed due to Cardiac Rehabilitation over a 6 to 12 week interval (Tobin and Thow, 1999; Fowler, et al. 2005). This study, due to the influence of biological variation, change in symptoms, patients' motivation, changes in exercise training frequency and capacity due to attendance; didn't measure changes in cardiorespiratory capacity due to Cardiac Rehabilitation. This study supported that no learning effect was present in long term reliability of 8 weeks, a practice walk of the ISWT was not deemed necessary if the aim is to assess the effects of the Cardiac Rehabilitation in clinically stable CVD patients, although further studies are needed to support this conclusion.

Woolf-May and Ferrett (2008) assessed oxygen consumption, expressed in metabolic equivalents (METs) achieved in two ISWTs performed by 31 men post myocardial infarction (mean age 63.5 range 53-77 years, involved in phase IV cardiac rehabilitation) and in 19 men not affected by cardiac disease (mean age 64.6 (7.5) range 51-76 years). There were no significant differences in performance between test 1 and test 2 in both populations assessed. Healthy adults walked 550 (93 m) vs 560

±110 m in trial one, and 430 ±100 m in trial two vs 424 ±116 shuttles in post myocardial infarction patients. This study suggests a practice attempt is not needed to achieve reliable results from the ISWT and is supported by previous studies on short term reliability (Arnott 1997; Fowler, et al 2005). However, the study reveals poor statistical description, no indication of random error in confidence intervals of distances measured between test 1 and test 2, make it difficult to compare with previous studies.

Short term reliability of the ISWT is good, with the suggestion of a practice walk. Longer term reliability of the ISWT, is reported as stronger than short term reliability, but possesses more systematic error in the final outcome of ISWT. There is a need for the ISWT to possess enough sensitivity to measure changes in ISWT performance due to exercise-based CR programmes.

2.2.2.4. Sensitivity

When measuring cardiorespiratory capacity, it is important that a test reports ability to discriminate changes in patients' functional capacity due to training, disease state variation or the effect of some change in pharmacotherapy. In general terms this characteristic of the test is termed sensitivity.

Payne, et al. (1996), for the first time, assessed the ability of the ISWT to discriminate between differences in functional capacity with or without rate responsive pacemakers. They tested ten patients (mean age 60 to 74 years, 4 women), one group to a fixed rate of 70 beats/min, and other group to a fixed rate response (as recommended by the manufacturer). The patients were tested twice in a randomized way, with 20 minutes between tests. In patients with a rate responsive pacemaker, the exercise time was significantly greater than the fixed rate pacemaker group: 8.8 (1.3) compared with 8.1 (1.3) minutes, $P<0.003$, and the diastolic volume/min was greater again in rate responsive group, 70 (24) volume/min compared with the non-responsive group, 52 (15), $P<0.009$). The test was therefore useful and sensitive enough to discriminate between different cardiac patients levels of exercise capacity with chronotropic incompetence, using a pacemaker.

Arnott (1997), applied the ISWT in CABG patients that had undergone surgery in past 12 months. The study was performed in 30 patients with a mean age of 62 years (range 42-68). Patients were divided into group A, 20 patients that had not gone to Cardiac Rehabilitation and group B, 10 patients that completed a Cardiac Rehabilitation programme. Before Cardiac Rehabilitation, Group A, patients achieved a mean distance of: 401,5m (SD 103.9); 421.5m (SD 115.4) and 425.5m (SD117.7); after Cardiac Rehabilitation, group B achieved a mean distance of: 523m (± 102.4); 549m (SD 115.6) and 554m (SD 114.6). The ISWT was able of differentiate between cardio respiratory capacity, in patients before Cardiac Rehabilitation and patients' after completed a 10 weeks of Cardiac Rehabilitation programme.

Tobin and Thow, (1999) assessed the ability of the ISWT to assess changes in cardiorespiratory capacity after 12 weeks of exercise based rehabilitation (2 sessions a week, one hour each) in 19 patients' (7 females, between 42-80 years, mean age

61 years) that went through CABG surgery (previous 6 months, with a mean of 10 weeks before rehabilitation). Pre and post rehabilitation cardiorespiratory capacity, showed an increase of 18% in test performance (mean distance increase of 117 meters), representing a mean increase of 0.71 METS, $p<0.01$. The results suggest that exercise interventions will improve patients' cardiorespiratory capacity, although due to ethical reasons no control group of CABG was able to be analysed for comparative measures.

Fowler, et al. (2005), investigated the sensitivity of the ISWT in detecting changes in performance due to 6 weeks of Cardiac Rehabilitation effect, in thirty-nine cardiac patients (age 61.2 ±8.5 years) who had undergone CABG surgery in the previous 6 to 8 weeks. After the 6 weeks a significant increase in mean distance of ISWT was seen ($p<.001$), showing a mean difference between the pre and post rehabilitation test of 81.8 m (95%CI; 53.2-110.4m). This change reported between pre and post rehabilitation was greater than the natural variability of test reliability [attempt 2 and 3 show a mean distance of 1.7 m (10.4) (95% interval of -1.9 – 5.3)], showing the test sensibility to detect changes in performance due to Cardiac Rehabilitation. Further studies are needed to quantify and understand the ISWT ability to measure change.

Arnold, et al. (2007) investigated the benefit of two sessions over one session a week of Cardiac Rehabilitation in a period of 6 weeks assessed by ISWT. The study was done in 206 post-myocardial infarction patients divided in two groups, one group did one session a week with 85 patients [65 men, mean age 61.8 (10.27) years] and a second group of 121 patients [94 men, mean age 59.24 (10.03) years] performing two sessions a week. There was a significant increase in mean distance achieved in ISWT in both groups. The bi-weekly group achieved a mean distance of 88.44 m (95% 70.3 to 106.59) ($p<.001$) and 100.71 m (95% confidence interval 80.81 to 120.60) ($p<.001$). In the group exercising once a week, there were no significant differences between the 2 groups in median distance achieved in the ISWT. The study concluded that no benefit comes after 6 weeks short term from adding one more lesson a week to the Cardiac Rehabilitation of patients, showing the ISWT sensibility to detect changes in both groups of this study. The magnitude of change in mean distance due to Cardiac Rehabilitation is supported by a previous study done by Fowler, et al. (2005).

2.2.2.5. Validity

Validity is a fundamental characteristic of testing; it is necessary that the test used is accurately measuring what it is supposed to measure. The 'Gold-Standard' measure of cardiorespiratory fitness is incremental treadmill test, so a high correlation should be reported to consider the ISWT a test of fitness.

2.2.2.5.1. Validity of ISWT in Chronic Obstructive Pulmonary Disease patients

Singh, et al. (1994) studied, for the first time, the validity of the ISWT in measuring cardiorespiratory capacity in pulmonary patients. He had previously demonstrated that the test is applicable for disability assessment in these patients. This proved useful in categorizing and comparing patients according to their functional capacity level, (Singh, et al. 1992). The relationship between the ISWT performance and the modified

Balke treadmill protocol with oxygen consumption measures, with the use of Douglas bag (golden test for functional capacity assessment) was compared. The study included 19 patients (17 males) suffering from stable chronic airflow, with a mean age of 61 (SD 7) years. They were tested during 3 visits to the hospital with one week apart. In the first visit a treadmill protocol was performed and a practice shuttle walk test, and in the second and third visit a randomized design of the patients was applied, i.e. a treadmill test followed one week later by an ISWT. The distance achieved in the second ISWT was used for the study proposal. A strong relationship (r=.88) was found between distance walked performing the ISWT and the direct measure of $\dot{V}O_{2peak}$ in treadmill test.

Singh, et al. (1994) after assessing the strong validity of the test to predict $\dot{V}O_{2peak}$, analysed the oxygen consumption during the ISWT by measuring the $\dot{V}O_{2peak}$ of the pulmonary patients with a portable oxygen consumption meter, during the test. 10 stable pulmonary patients (6 males, mean age 64 (7) years), performed two ISWTs on different visits to the hospital in a randomized balanced way, doing one test with portable gas analyses and one test without. A strong relationship (r=0.81) was found supporting the previous study focusing on ISWT distance achieved and $\dot{V}O_{2peak}$ direct measure. A linear increase in $\dot{V}O_{2peak}$ was seen as the test stages progressed suggesting the ISWT was able to provoke physical effort at symptom limited responses in patients, similar to a treadmill test. Heart rates of patients performing the treadmill test were higher than in ISWT at submaximal velocities. Singh, et al. (1994) also compared performance in the treadmill test and the ISWT with direct $\dot{V}O_{2peak}$ measured in both tests in 7 patients. The mean $\dot{V}O_{2peak}$ measure during the treadmill testing was

12.9 (±3.6) $ml.kg^{-1}min^{-1}$ compared with 11.1 (±4.2) $ml.kg^{-1}min^{-1}$ during the ISWT. No significant difference was found and the mean difference was small (1.8 95%CI -0.9 *to* 4.5 $ml.kg^{-1}min^{-1}$) with a correlation of r=.86.

The ability of the performance in ISWT to predict $\dot{V}O_{2peak}$ as analysed in this study confirms the ISWT as a valid tool to assess cardiorespiratory capacity in pulmonary patients. No other field test used before in these patients or in a limit disease population has been so strong in predicting $\dot{V}O_{2peak}$. The results support the safety of the test due to the gradual physiological response that provokes patients. The effort is similar to that produced in the treadmill protocol, due to the protocol design of incremental speed (1.7 m·s-1 increase) the ISWT is able of elicit maximum effort in patients, not seen before in other field tests (6 min walk test). Due to the standardized protocol the test is able a secure intra-inter subject comparison, also not possible before in other field tests. The test is easily applied to hospital conditions and is generally well accepted and preferred by patients compared to the treadmill test. The ISWT is an objective measure of cardiorespiratory capacity, although it doesn't replace the laboratory test. (Singh, et al. 1994)

2.2.2.5.2. Validity of ISWT in heart failure and heart transplant patients

Morales, et al. (1999) assessed the validity of the ISWT in heart failure patients compared to the cycle ergometer cardiopulmonary test (with a protocol design with a first stage 1 minute unloaded being followed by a 10 W/min stage increase). The study included the validity of the 6 minute test in predicting $\dot{V}O_{2peak}$ in these patients compared with the ISWT. The assessment was performed in 46 patients, aged 53 years (± 10 years) who were clinically stable and categorized with an ejection fraction <40% (mean 23%, ± 8%) also classified by the New York Heart Association as class 2 to 4 (mean 2.8 ±0.7). $\dot{V}O_{2peak}$ from the cycle ergometer test and distance walked in ISWT showed a high correlation (r=.83, p<.001), but the 6 minute test distance in this group of patients only showed a moderate correlation (r=.67, p<.001) with $\dot{V}O_{2peak}$ achieved in cycle ergometer test. The following formulae to predict $\dot{V}O_{2peak}$ were developed:

- $\dot{V}O_{2peak}$ = [0.023 x distance (m) SWT] + 5.9;

  r=0.83; r2=0.69; SEE= 2.55 p<.001.

- $\dot{V}O_{2peak}$ = [0.024 x distance (m) SWT] – [0.006 x weight (Kg)] + [0.06 x age (years)] + 6.44;

  r= 0.86; r2=0.74; SEE 2.37; P<.001.

Receiver operating characteristic curves (ROC) indicated that the ISWT had a significant diagnostic accuracy (ROC 0.97 and 0.83 p=.2) above the 6 min walk test. A distance <450 m in the ISWT was seen as a good predictor of peak $\dot{V}O_{2peak}$ < 14 $ml.kg^{-1}min^{-1}$, although larger studies are needed to support the prognostic power of ISWT to predict $\dot{V}O_{2peak}$ in cardiac patients, particularly heart failure patients (Morales, et al. 1999). In this study, a stepwise multivariate regression analysis showed that the distance walked in ISWT was the strongest independent predictor of peak $\dot{V}O_{2peak}$ (P<.0001), this was not the case for the 6 MWT (p=.64). The analysis took into account factors such as clinical and hemodynamic resting, echocardiographic and radionuclide-angiographic data.

Morales, et al. (1999) concluded that the ISWT is simple to apply, with the patients having no difficulty performing the test and coordinating their pace easily using the bleep sounds. The test was shown to be a valid diagnostic tool in predicting $\dot{V}O_{2peak}$ in moderate and severe heart failure patients, although this study possessed some limitations on the validation aspect. The validation process was based in cycle ergometer protocol which is known to underestimate $\dot{V}O_{2peak}$ by 5% to 10%, compared with golden test of cardiorespiratory capacity the treadmill test. So further studies are needed to support and fully understand the real capacity of the ISWT in predicting $\dot{V}O_{2peak}$, such as validating it against the treadmill protocol in this population and testing its' prognostic power.

The n= 46 heart failure patients involved in the study done by Morales, et al. (1999) were followed up in a mean time of 17 months (SD 8 months; range 8-28 months). After follow up, 15 of them (33%) had suffered a major cardiac event (5 cardiac deaths, 2 heart transplantations, and 8 of the patients had mechanical and inotropic hospital support. The best predictor of outcome at one year of follow up was the distance achieved in ISWT ($P<.03$), further demonstrating that distance in the 6 MWT had no predictive power ($p<.07$). A distance achieved of less than 450 m allowed identification of high risk patients having a major event in a short time period. This study suggested the ISWT predicts event free survival better them the 6 MWT in chronic heart failure patients over one year (Morales, et al. 2000).

Lewis, et al. (2001) included patients for heart transplantation, and was the first to assess the validity of ISWT in cardiac patients, by comparing it against the standard golden test for assessing cardiorespiratory capacity, the treadmill test. The study assessed 25 patients, 21 males, with a mean age 53 years (range: 33-69 years), who performed three ISWTs (1st test was practice), and two treadmill tests with gas ventilation assessment to determine $\dot{V}O_{2peak}$, using the modified Naughton protocol. The study results showed that the $\dot{V}O_{2peak}$ on the treadmill was highly correlated with the distance achieved in ISWT, $R=.73$, $p<.001$; a predictive equation was developed for estimating $\dot{V}O_{2peak}$ = 6.4 + (0.022 x Shuttle Walk Distance). They concluded that ISWT was easy to perform and had high applicability, was well tolerated and preferred by the patients in relation to the treadmill test. The ISWT was shown to be a valid test to assess patients with wide ranging functional capacity, and to predict $\dot{V}O_{2peak}$ in heart failure patients, being useful in clinical prognosis, prior to cardiac transplant surgery.

Lewis et al.'s (2001) study analysed the discriminative power of ISWT in 25 heart failure patients (21 males, mean age 53 years, range 33-69 years) before heart transplantation. From ROC curve analysis (Campbell, et al. 2007), a range between 370 and 430 m/s performance in ISWT, was identified with sensitivity and specificity to predict at 75%, a $\dot{V}O_{2peak}$ higher than 14 ml.kg^{-1}min^{-1} in this patients. The cut-off point of 450 m/s determined to predict a $\dot{V}O_{2peak}$ of 14 ml.kg^{-1}min^{-1} has high clinical importance in the prognosis of heart failure patients before transplantation, as levels of $\dot{V}O_{2peak}$ under this cut point have shown to be related to high short term mortality (Morales, et al. 2000). A clinical decision made on this cut point could help to prioritise which patients should take priority for heart transplantation. This cut point of 450 m had been detected before in a previous study in heart failure patients (Morales, et al. 1999) supporting the conclusions of this study.

2.2.2.5.3. Validity of ISWT in CHD patients

Fowler, et al. (2005), investigated the validity of ISWT in predicting $\dot{V}O_{2peak}$ in 39 cardiac patients (n=34 males, mean age 61.2 (SD 8.5) years) who had undergone CABG surgery in last 6 to 8 weeks. Until this, the test had only been validated in chronic, stable pulmonary patients (Singh, et al.1994), and in heart failure patients (Morales, et al. 1999; Lewis, et al. 2001). However, heart failure patients don't represent the major cardiac population, they are a population with low cardiorespiratory capacity levels and are representative of a final stage of cardiac disease. In a week's time three ISWT were performed one in the first visit to the hospital and two tests on the second visit with 45 minutes of interval between them. On the third visit a modified Balke treadmill protocol was performed with Oxygen uptake measures. A strong relationship was found between distances walked in the three ISWT performed and $\dot{V}O_{2peak}$ measured directly in treadmill test (r= .79; r= 86; r=.87), being an equation produced to predict $\dot{V}O_{2peak}$

- $\dot{V}O_{2peak}$= 7.81 + [0.03 x ISWT distance (meters)]. (no S.E.E was given)

A significant difference (p<.001) in mean maximal heart rate achieved in ISWT (133 bpm) compare with treadmill exercise (144 bpm), although a high correlation (r=.74) is seen between both maximal heart rates achieved in both tests. The ISWT is a valid tool to assess cardiorespiratory capacity in CABG patients after surgery, predicting strongly the $\dot{V}O_{2peak,}$ easy to apply and with good acceptability from the patients; The relation with the direct measure of $\dot{V}O_{2peak}$ in treadmill is as strong as Singh, et al. (1994) had reported on first validation of the test in chronic pulmonary patients, and stronger then studies done before in cardiac patients with heart failure (Morales, et al. 1999; Lewis, et al. 2001).

Woolf-May and Ferrett, (2008) assessed the oxygen consumption, expressed in metabolic equivalents (METs) achieved in the ISWT by n=31 men post myocardial infarction [mean age 63.5 (6.5), range 53-77 years, involved in cardiac rehabilitation Phase IV] and in 19 men no affected by cardiac disease [mean age 64.6 (7.5) range 51-76 years]. In their study it was analysed the effect of the turn performed by patients on the end and beginning of 10 m length in shuttle walk test against performing the walk test without turns walking uninterrupted, and if there were differences in METs achieved between both performances.

The METs values achieved in ISWT performance by Cardiac patients are used in clinical decisions and exercise prescription. Although the METs values are not specific for this population as they were achieved in by healthy people performing flat walk, what is not the specific performance done in the shuttle walk test effort as this one involves turns in the performance. Furthermore, the MET values in healthy adults have been seen to be stable, although influenced by factors such as age, body weight, cardiorespiratory capacity and comorbidities. Cardiac patients, on average, are of advanced age, with low cardiorespiratory capacity, overweight, and possessing several co morbidities. MET values are supposed to be different between cardiac patients and healthy adult people. In prescription, an inaccurate METs assessment of the patient my lead to a poor training effect or over exerting the patient which could lead to further cardiac events.

Patients and healthy adults performed two ISWT with direct measures of $\dot{V}O_{2peak}$ done by portable gas analyser. The tests were performed at different occasions, and the results were taken from the second test done due to the learning effect variance seen by previous studies between test one and test 2 as previously discussed. Due to ethical reasons healthy adults performed 2 treadmill tests using the same protocol as the ISWT, performing the test walking flat. Due to learning effect on performance witnessed in previous studies the second attempt was taken for results analyses.

The results of the study revealed that there were no significant differences on METs assessment between ISWT and the same incremental protocol (walking flat on the treadmill) performed by healthy adults. A limits of agreement analysis showed acceptability between both tests measured (mean difference -1.1 (8.8) (1.96 SD; 95% CI 7.7 to 9.9)). The variation between both measures was small and highly correlated ($r=.88$; $r^2=.48$, $p<.001$). These results are in accordance with previous studies of test validity (Singh, et al. 1994; Fowler, et al. 2005), and may show that the turning involved in the ISWT protocol has a small impact on $V'O_2$ max prediction or METs estimates.

This study supported the guidelines of ASCM (2007) regarding METS performed during flat walking in healthy people. When the performance in METs from the ISWT between cardiac patients and healthy adults, statistical differences were seen between both test's METs scores. The MET values achieved at maximal and submaximal walking speeds were significantly higher than those achieved by healthy adults ($p<.001$). Several factors may explain this difference in METS achieved by both populations, such as differences in body weight, fatigue, environmental (test venue), low cardiorespiratory capacity, medication and co-morbidities affecting cardiac patients.

This study supported the referenced METS given by the ACSM (2007) for healthy people performing the flat walk, and showed that the greater values in METS achieved by cardiac patients didn't allow a true comparison with estimated METs obtained in healthy people. They concluded that while further studies are needed to establish estimated METs at different stage speeds of the ISWT in cardiac patients, that the shuttle walk test is a valid test to be used in cardiac patients for cardiorespiratory capacity assessment.

2.3. Conclusion

Exercise-based CR programmes (exercise-only CR and comprehensive-CR) in CHD patients is an effective treatment for preventing cardiac mortality, morbidity, all cause of death and may improve quality of life. It is thought that CR is an effective therapy due to its positive impact on reducing risk factors for CVD (strong evidence for hypertension, smoking and total cholesterol) and due to the improvement in cardiorespiratory capacity due to exercise in cardiac patients.

Cardiorespiratory capacity is an important outcome in exercise-CR programmes. Measuring cardiorespiratory capacity enables decisions on diagnosis, prognosis, treatment effect and exercise prescription of cardiac patients, based on objective measures. Field tests are practical and simple to use in clinical or community settings in the absence of laboratories tests in all phases of Cardiac Rehabilitation.

The field test ISWT has shown high acceptability and practicability since the first time that it was applied in chronic stable pulmonary patients in a clinical setting. The first reliability studies measured in the short term (less than a week time) show that a practice walk is needed to achieve reliability as there is a learning effect caused by the performance between the first and second attempts. More recent studies have questioned the need for this first practice walk, due to its costly impact on clinical work. Furthermore, it could cause additional stress to the patients, showing no practicability, and no significant differences in the mean distance were witnessed. The long term reliability means there is no need for a practice walk, as demonstrated, the test is used in intervals of 6 to 8 weeks in the Cardiac Rehabilitation setting.

The ISWT showed sensitivity to measure change in cardiorespiratory capacity due to the effect of Cardiac Rehabilitation, an average range of 100 m of improvement between studies was reported.

The ISWT has demonstrated to have good validity in measuring cardiorespiratory capacity. An early study on chronic pulmonary patients compared mean distance achieved with $\dot{V}O_{2peak}$ performance during a treadmill protocol (r=.88) due to the high correlation between ISWT and treadmill performance established in recent studies. However, this correlation can be improved if patient characteristics like age or anthropometric measures (high, weight) and comorbidities are taken into account, as witnessed in previous multivariate analyses on the 6MWT (Ingle, et al. 2006).

When the performance in METs in the ISWT was compared in cardiac patients and healthy adults, statistical differences were seen between both group's METs scores. The METs achieved at maximal and submaximal speed were significant higher than the ones achieved by healthy adults. There is a need to further understand this very high oxygen consumption in CHD patients compared with healthy individuals.

The ISWT showed diagnostic accuracy in predicting $\dot{V}O_{2peak}$ in heart failure and heart transplant patients, the distance achieve in ISWT being the strongest independent predictor of $\dot{V}O_{2peak}$. From a distance achieved of less than <450 m/s it is possible to predict a peak $\dot{V}O_{2peak}$ of 14 $ml.kg^{-1}min^{-1}$. This distance has been supported as being the optimal cut point to prioritize patients for heart transplantation. The distance of >450 m/s achieved in ISWT had prognostic power in predicting event free survival after one year in heart failure patients. Despite this, more studies are needed to investigate the long term prognostic power of the ISWT in cardiac patients as studies done with treadmill protocol have worked towards (Joliffe, et al. 2002; Meyers, et al. 2002) including when focusing on the 6 MWT in cardiac patients (Sakir, et al. 2007).

Research questions and justification for addressing them within this thesis are, therefore, as follows.

Systematic reviews have concentrated on clinical outcomes to illustrate the efficacy of exercise based Cardiac Rehabilitation but none have examined whether CR results in changes in patients' cardiorespiratory fitness.

1. What evidence is there for changes in cardiorespiratory fitness of patients attending exercise-based Cardiac Rehabilitation? – the approach used to address this question will be a meta-analysis;

Only absolute performance in the ISWT is interpreted not accounting for individual differences of cardiac patients performing the test,

2. what are the predictors of performance in incremental shuttle walk test in cardiac patients? and base in this predictors will be possible to create percentile curves and normative values for the incremental shuttle walk test in cardiac patients?

There are clear disparities in current estimates of oxygen cost in ISWT,

3. What is the energy cost of the ISWT?

Little is known about what influences changes in fitness due to CR,

3. what are the predictors of change in fitness due to CR, assessed by treadmill exercise test, and ISWT in cardiac patients?

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Chapter 3. Changes in Cardiorespiratory Fitness in CR Patients: A Meta-Analysis

Abstract

Objective: The improvement of cardiorespiratory fitness in patients due to Cardiac Rehabilitation (CR) is an important therapeutic outcome. There is plenty of evidence included in several meta-analyses focusing on the effectiveness of CR in reducing morbidity and mortality. The magnitude of gains in cardiorespiratory fitness produced by CR is not well known, including the factors which influence such gains. This chapter aims to quantify the changes in cardiorespiratory fitness due to CR, and understand which variables affect this changes.

Methodology and results: A detailed literature search in changes in cardiorespiratory fitness in CR patients was made using electronic databases. The data collected was subjected to a random-effects meta-analysis, an effect size was produced to determine the aetiology of gains in cardiorespiratory fitness, and to determine potential sources of heterogeneity, analyses on subgroups were performed by Q statistics.

A total of n=31 studies, containing n=48 groups (n=3827 participants) showed a mean improvement in fitness of 1.55 (95%CI: 1.21-1.89) MET's, ($p<0.001$); equivalent to a standardised effect size of ES=0.97 (95% CI 0.80-1.13). Due to the high levels of heterogeneity shown by this value (Q=852, p<0,001), sub-group analyses on the effect size were performed. Improvements in fitness in patients were higher in cardiac programmes with more than 36 sessions and in studies where the Naughton Protocol

was used to assess patients, used as a modality of aerobic exercise or combined with resistance exercise. Age (young) and sex (males, and male-only exercise group) were some of the characteristics associated with the highest improvements in fitness. Programme (comprehensive or exercise-only), duration, study design, patients' primary diagnosis and patients' baseline fitness levels were unrelated to gains in fitness.

Conclusions: This is the first meta-analysis to quantify the gains in cardiorespiratory fitness of patients attending exercise-based CR. The analysis identifies some of the characteristics (service or patients) that can influence the cardiorespiratory fitness gains in patients involved in CR.

Service variables, such as including >36 sessions in the CR programme of aerobic or mixed aerobic and resistance exercise with a programme length of 12 weeks. The treadmill protocol used to assess cardiorespiratory fitness in patients had a major impact on the estimate of fitness improvement. Patient variables such as been young and male are shown to have greater impacts on fitness, those who may benefit more from CR are older, female patients, who have lower changes in fitness.

Provision of exercise sessions for same sex groups and patient allocation based on age is recommended. This would help practitioners to differentiate between who achieves optimal increases in cardiorespiratory capacity in CR and who doesn't, improving exercise prescription in CR.

Key words: Cardiorespiratory fitness; treadmill exercise test; predictors of change; cardiac patients; fitness improvements.

3.1. Introduction

CR is an effective therapeutic intervention for CHD patients, which reduces all cause mortality, cardiovascular mortality and morbidity (Oldridge, et al. 1988; O'Connor, et al. 1989; Jolliffe, et al. 2001; Taylor, et al. 2004; Conn, et al. 2009; Lee, et al. 1999). The effectiveness of CR in reducing patient mortality and morbidity can be explained in part by the positive effects that CR has in reducing modifiable risks factors for cardiovascular disease (Taylor, et al. 2006).

One proposal is that CR may not just add years to life, but also life to years (Thompson, 2009). Pharmacotherapy can effectively modify many CVD risk factors, rehabilitation based on exercise can also add to the improvement of functional capacity, mobility and patients independence, resulting in an increase in cardiorespiratory fitness (fitness from here in). The effectiveness of CR on the improvement in quality of life is independently associated with fitness improvements in cardiac patients (Lavie and Milani, 1997) and fitness levels are excellent tools with which to define prognostic cut points for future cardiovascular events (McAuley, et al. 2009; Sui, et al. 2007, Lyerly, et al. 2008). Gains in fitness achieved by patients in CR are closely, inversely, related to patient mortality and morbidity (Williams, et al. 2006; Blair, et al. 1995; Balady, et al. 1996; Gulati, et al. 2003; Myers, et al. 2002; Dorn, et al. 1999; Kavanagh, et al. 2003). Levels of fitness gains are recognized to have clinical importance in cardiac patients, however only limited studies have tried to synthesise such information (Conn, et al. 2009; Swain and Franklin, 2006).

A recent systematic review (Conn, et al. 2009) showed an increase in the physical activity levels of a wide variety of cardiac patients. Changes in fitness were also reviewed in this study as a secondary outcome. This analysis was based in randomized controlled trials, and largely concentrated on the quantification of standardized differences between post-test groups. This design was used to ensure data quality and the authors excluded cohort and observational design studies. Such studies normally represent a more naturalistic approach to clinical practice. It would be an unethical study design to exclude cardiac patients from CR, due to the effectiveness of this therapy (Dusseldorp, et al. 1999); the increase in cohort-design studies is, therefore, both necessary and common. Conn, et al.'s (2009) meta-analysis was restricted in studies used due to inclusion criteria. A Subgroup analysis could not be used by the authors to determine which components of exercise (frequency, intensity, duration, and modality) determined the gains in fitness in cardiac patients. Nevertheless the effect size representing the change in physical activity was converted to energy expenditure (1984 $Kcal \cdot week^{-1}$). It was difficult to translate the estimated gains in fitness to a common language used normally as $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) or metabolic equivalents (MET's).

3.2. Aims and hypothesis

The present chapter aimed to quantify the overall gains in fitness reported in studies of exercise-based CR. By expressing fitness in commonly-used units (MET's), results should have greater relevance for clinicians than those of previous studies reporting effect sizes. The secondary aim was to identify patient and programme characteristics associated with changes in fitness to provide guidance in designing CR programmes that maximize fitness gains for CR patients.

3.3. Methods

3.3.1. Search strategy

The search was made independently by three authors, using PubMed, Ovid, Web of Science and The NIH library. Broad terms were used for the search: exercise, cardiac (or cardiovascular) rehabilitation, training, functional capacity, fitness (cardiorespiratory fitness), $\dot{V}O_{2peak}$, $\dot{V}O_{2max}$. Initially the search allowed us to gather 7104 potential papers to include in the review. We aimed to include the most common ''core'' cardiovascular patient population in our analysis based on outpatient CR programmes. We produced a narrow search in terms of the paper's publish year and population age. Papers had a limit range (1970-2010) and population an age range (>18 years). The search included the Boolean operator ''NOT'' in the search terms used: heart failure, home-based and waking programme. These options used in the search refined it to 4321 abstracts that were manually analysed for eligibility. Meta-analyses referring to other CR aspects and clinical guidance documents had their references section analysed in our search for finding further references (O'Connor, et al. 1989, Oldridge, et al. 1988; Taylor, et al. 2004, 2006; Williams, et al. 2006; Conn, et al. 2009; Dusseldorp, et al. 1999; Swain 2005). Our analysis only included primary research studies according to the criteria established in Table 3.1.

The unsupervised or home-based intervention papers were excluded from analysis because of the great difficulty in assessing cardiac patients' adherence or quantifying exercise dosage variables used in such programme modality. The evidence of the effectiveness of home-based CR in the reduction of mortality and morbidity is lacking (Taylor, et al. 2007). The incremental load-bearing inclusion as the only kind of assessment used in the studies is justified by an attempt to standardize the method used for fitness assessment. Cycle ergometer tests produced lower assessment values of $\dot{V}O_{2peak}$. Field test are based in values estimation of MET's or $\dot{V}O_{2peak}$, which prediction equations used possess normally a large standard error of estimation (Morales, et al. 2000).

These criterions did not include home-based intervention papers and included only assessments of fitness made by incremental load-bearing in order to restrict the data analysis to a more commonly used model of CR. This criterion has been used in past meta-analyses to help prove the efficacy of CR in reducing mortality, morbidity and overall risk factor reduction (Taylor, et al. 2004; Conn, et al. 2009; Lee, et al. 1999; Taylor, et al. 2006). The criteria for exclusion gave the present meta-analysis different characteristics to the only other meta-analysis published on this topic (Conn, et al.

2009) which included a bigger variety of CR modalities and included all available methods of fitness estimation. Non-randomized trials were purposely included in the present analysis. There were small differences in values from comparison of distal post-test values in control group versus treatment group, and pre-test versus post-test values in treatment group shown in previous analyses (Conn, et al. 2009). The search results revealed many studies without control groups in their design. These tended to be more like ''service evaluation'' pieces of research done in natural settings and closer to the reality of health care (Blumenthal, et al. 1988; Dressendorfer, et al. 1995; Lavie and Milani, 1997). These trials had a high external validity, so were included in the study design and their characteristics included in the subgroup analysis.

Table 3.1. Study Inclusion exclusion criteria

Inclusion criteria

1. Published 1970–December 2010.
2. English language publication or translation available.
3. Participants with diagnosis of cardiovascular disease for whom exercise-based rehabilitation is internationally recommended: post-myocardial infarction, patients receiving revascularisation therapy, valvular replacement recipients and those suffering angina pectoris.
4. Intervention met our definition of cardiac rehabilitation. Supervised exercise training as a hospital outpatient or in a structured setting in the local community or at a residential centre.*
5. Experimental or quasi-experimental design (randomised controlled trial, non-randomised trial or cohort observation).
6. Fitness assessed by weight bearing incremental test pre- and post-rehabilitation and expressed as a unit which could be converted to Metabolic Equivalents (METs Vo_{2peak} or Vo_{2max} in $ml \cdot kg^{-1} \cdot min^{-1}$ or $l \cdot min^{-1}$).*
7. Necessary data to compute mean change in exercise capacity (mean, SD, t-value, F-value, p-value and sample size).

*Additional information: exclusion criteria.

4a - We excluded the following types of intervention; home-based exercise programmes (supervised or unsupervised); telephone, internet or email based programmes, home walking programmes, group walking programmes.

6a - We also excluded all non-weight bearing exercise tests (cycle ergometry) and did not include field tests of functional capacity such as timed walk tests, incremental shuttle-walking test, step tests and non-exercise estimates of fitness.

3.3.2. Data extraction and treatment

Means and standard deviations from the fitness assessment before and after CR were extracted from the studies that met the inclusion criteria. Most of the studies included METs as a measure of fitness, in studies that fitness results were given as oxygen consumption ($ml \cdot kg^{-1} \cdot min^{-1}$) this result was divided by 3.5 to calculate METs. The reported correlations between pre- and post-test data in CR studies were not reported in any studies, the magnitude of this relationship was estimated by using data from a CR programme at a local hospital. After ethical approval, we analysed 149 patient data records which included the use of the Bruce Treadmill protocol before and after a standard CR programme. Significant improvements in $\dot{V}O_{2peak}$ ($p<0.001$) were witnessed after using a repeated measures t-test, there was a correlation of r=0.535 between pre- and post-test values. In our meta-analysis we used this correlation coefficient to correct for the use of paired values. The final analysis included a total of n=31 studies, producing n=48 independent groups of patients. The overall change in fitness as the mean difference between pre- versus post-test was reported as METs, as this is a common way to report and analyse the oxygen consumption data by researchers and clinicians in every day work. Random effects modelling were also used to report the effect size (ES) for standardised mean difference in fitness and to enable comparisons with previous studies. To determine potential sources of heterogeneity, analyses on subgroups were performed by Q statistics (Berlin, 1995)

3.3.3. Data coding for subgroup analyses

Subgroup analyses were performed by the use of pre-selected moderator variables to understand the several causes of heterogeneity (Higgins, et al. 2002). From the analysis of subgroups it's possible to generate spurious findings, something strongly supported by previous papers (Higgins, et al. 2002; Davey Smith, et al. 1997). Therefore only a small number of subgroup analyses were performed by us, and the reason for being chosen was based potential causal mechanisms, magnitude of effects, and statistical significance shown within individual studies.

The data was coded by developing two broad categories. Data related to the study design and CR programme design was coded first, patients' characteristic data was coded afterwards. Length of programme was coded in weeks, total number of sessions included in each CR programme study, and exercise modality was coded as: aerobic, resistance or mixed. CR programmes were coded as comprehensive (including educational and/or behaviour change) or as being exercise-based only. The study design used in the analysis was coded as a cohort-study design or part of (randomised or non-randomised) trial including a control group. Treadmill protocols used for testing fitness pre- and post-test were coded by name and completed subgroup analysis in this category. The subgroup analysis of quantitative patient characteristics included age (Young, <50; Old 50-65 and Oldest, >65 years), baseline values of fitness (median split at >/<6.6 MET's), sex of patient group (Males, Females or Mixed). We coded the primary reason for CR attendance (Revascularization, Post-myocardial infarction or Mixed). The subgroups and the way they were coded and cut-offs can be seen in Table 3.2.

It was not possible to create subgroups based on all the variables identified. Intensity of exercise prescription was a variable that was impossible to analyse due to the broad and often overlapping categories (e.g. 60-85% heart rate maximum) or poor quantified terms used (e.g. 'symptom limited' or 'Borg scale'), which makes the data impossible to compare.

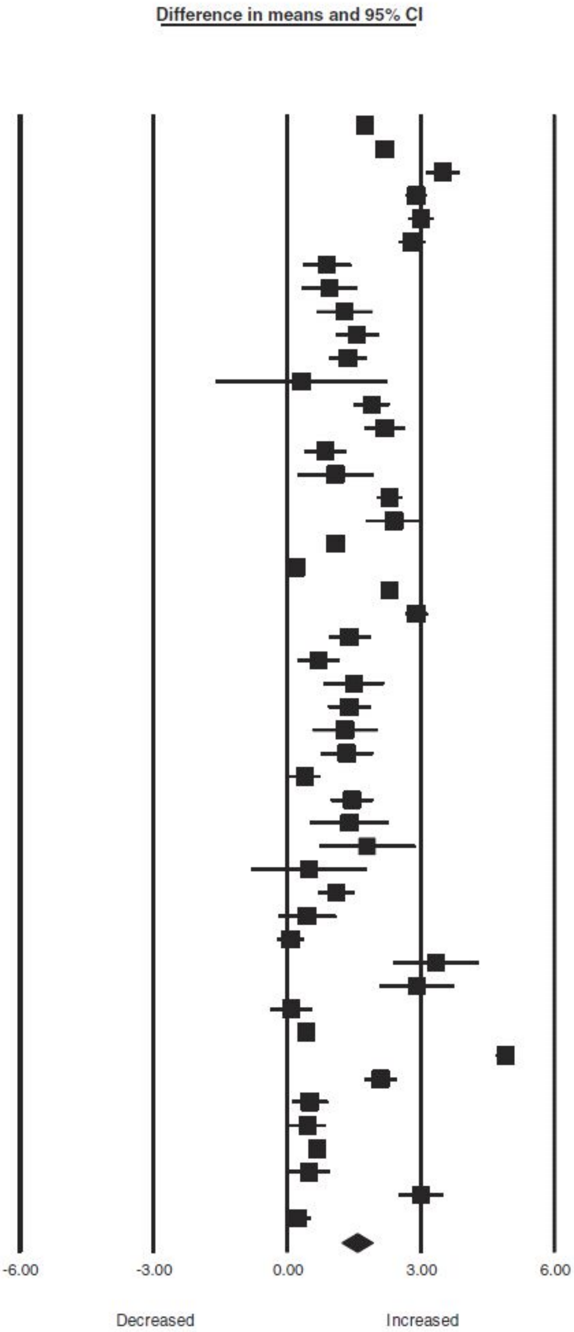
3.4. Results

The overall effect of CR on fitness levels was measured in metabolic equivalents (MET's) as shown in Fig. 3.1. A mean difference in fitness between Pre- vs. Post-test values of 1.55 (95%CI: 1.21 *to* 1.89) was calculated based on data from the (n=31) studies included in the analysis. An effect size (ES) =0.97 (95% CI 0.80 *to* 1.13) was calculated for the standardised mean difference between Pre- vs. Post-test using a random effects model. The difference was statistically significant ($p<0.001$), but also highly heterogeneous ($Q=852$, $p<0.001$). A forest plot visual analysis found that four groups representing four different studies (Miller, et al. 1984; Dressendorfer, et al. 1995; Brubaker, et al. 1996; Arya, et al. 2005) had mean effects larger than expected (>2SD higher). Removal of these groups somewhat lowered the mean standardized difference (ES=0.80 95% CI 0.63 *to* 0.94). The value obtained was still statistically significant ($p<0.001$) and the degree of statistical heterogeneity remained high ($Q=591$, $p<0.001$). These groups were reintroduced into the study prior to subgroup analysis, as they had no common nor distinguishing characteristics.

Fig. 3.1. Forest plot for mean point estimate of change in fitness due to CR.

Mean (95%CI) Change in Fitness (METs)

Study name	Difference in means	Standard error
Miller et al. (1984) a	1.750	0.081
Miller et al. (1984) b	2.200	0.083
Williams et al. (1985) a	3.500	0.199
Williams et al. (1985) b	2.900	0.122
Williams et al. (1985) c	3.000	0.156
Williams et al. (1985) d	2.800	0.156
Blumenthal et al. (1988) a	0.890	0.284
Blumenthal et al. (1988) b	0.950	0.322
Ades & Grunvald (1990) a	1.290	0.326
Ades & Grunvald (1990) b	1.570	0.252
Blumenthal et al. (1990) a	1.370	0.217
Blumenthal et al. (1990) b	0.320	0.991
Lavie (1993) a	1.900	0.206
Lavie (1993) b	2.200	0.235
Ades et al. (1995) a	0.860	0.244
Ades et al. (1995) b	1.090	0.443
Lavie & Milani (1995) a	2.300	0.153
Lavie & Milani (1995) b	2.400	0.318
Dressendorfer et al. (1995)	1.090	0.078
Brubaker et al. (1996) a	0.200	0.096
Brubaker et al. (1996) b	2.300	0.096
Balady et al. (1996)	2.900	0.133
Wosornu et al. (1996) (a)	1.400	0.244
Wosornu et al. (1996) (b)	0.700	0.242
Shiran et al. (1997)	1.500	0.347
Lavie & Milani (1997)	1.400	0.247
Nieuwland (1988) a	1.300	0.383
Nieuwland (1988) b	1.340	0.303
Carlson et al. (2000)	0.400	0.186
Belardinelli et al. (2001)	1.460	0.248
Hao et al. (2002) a	1.400	0.456
Hao et al. (2002) b	1.800	0.554
Hao et al. (2002) c	0.500	0.667
Vonder-Muhll et al. (2002)	1.100	0.213
Gordon et al. (2002)	0.450	0.336
Seki et al. (2003)	0.080	0.159
Hevey et al. (2003) a	3.340	0.499
Hevey et al. (2003) b	2.920	0.431
Lear et al. (2003)	0.100	0.243
Milani et al. (2004)	0.430	0.099
Arya et al. (2005)	4.900	0.111
Adams et al. (2008)	2.100	0.187
Seki et al. (2008)	0.510	0.211
Milani & Lavie (2010) a	0.460	0.218
Milani & Lavie (2010) b	0.680	0.073
Kosydar-Piechna et al. (2010)	0.500	0.239
Shabani et al. (2010)	3.000	0.260
Onishi et al. (2010)	0.250	0.143
	1.550	0.175



Legend: Points are mean points estimate (squares) with upper and lower 95% confidence intervals for the difference between pre-and post- CR measures of cardiorespiratory fitness (in metabolic equivalents). The overall mean point estimate (± 95%CI) is based on a random effects model. (Miller, et al. 1984, Williams, et al. 1985); (Blumenthal, et al. 1988, Blumenthal, et al. 1990);(Ades and Grunvald 1990); (Blumenthal, et al. 1990; Lavie, et al. 1993); (Ades, et al. 1995); (Dressendorfer, et al. 1995, Lavie and Milani 1995); (Brubaker, et al. 1996); (Balady, et al. 1996); (Wosornu, et al. 1996); (Shiran, et al. 1997); (Lavie and Milani 1997); (Nieuwland, et al. 1998); (Carlson, et al. 2000); (Belardinelli, et al. 2001); (Hao, et al. 2002); (Vonder-Muhll, et al. 2002); (Gordon, et al. 2002); (Seki, et al. 2003); (Hevey, et al. 2003); (Lear, et al. 2003); (Milani, et al. 2004); (Arya, et al. 2005); (Adams, et al. 2008); (Seki, et al. 2008); (Milani and Lavie 2009); (Kosydar-Piechna, et al. 2010); (Shabani, et al. 2010); (Onishi, et al. 2010).

3.4.1. Subgroup analyses: test for heterogeneity

Significant differences in between-group heterogeneity were seen in some subgroup analysis of programme design characteristics (Table 3.2). However, the overall programme length of the studies (>/< 12 weeks) didn't influenced changes in fitness. The number of exercise sessions didn't show statistically significant differences. Although programmes that included more than 36> (small number of studies k=5) sessions showed greater fitness gains than the studies that included 36 or <36 sessions. The two last groups showed a similar effect size for change in fitness. The use of aerobic or mixed exercise modalities had a similar effect in influencing fitness changes, both showing significance (p=0.024), prescribed resistance exercise only programme (few studies k=2) didn't have any effect on fitness. There were no statistical differences between comprehensive and exercise-only based CR programmes in improving fitness; however, it was possible to observe a tendency in effectiveness towards exercise-only CR. Study design (cohort or trial studies) had no significant effect in influencing fitness changes in our analysis. Programmes that used the Naughton protocol for fitness assessment had bigger improvements in fitness than in studies using Bruce, Balke or own reported protocol used in the studies. The studies that did not report the incremental design used in the assessment showed the small changes in fitness. Larger gains were seen in male groups and in the youngest age group, compared with women or mixed-sex groups and with the other age groups in the analysis. Analysis of the primary diagnosis subgroup showed no significant differences in between-group heterogeneity, although patients that suffered an MI possessed higher fitness gains when compared with other diagnoses. This subgroup analysis produced no significant results due to the small number of studies in the group that had only post MI patients (k=5). When analysing the groups possessing low or high baseline fitness measures no significant differences were found relating to influence on fitness gains.

Table 3.2. Subgroup analysis for moderators of fitness gains expressed as standardised mean difference.

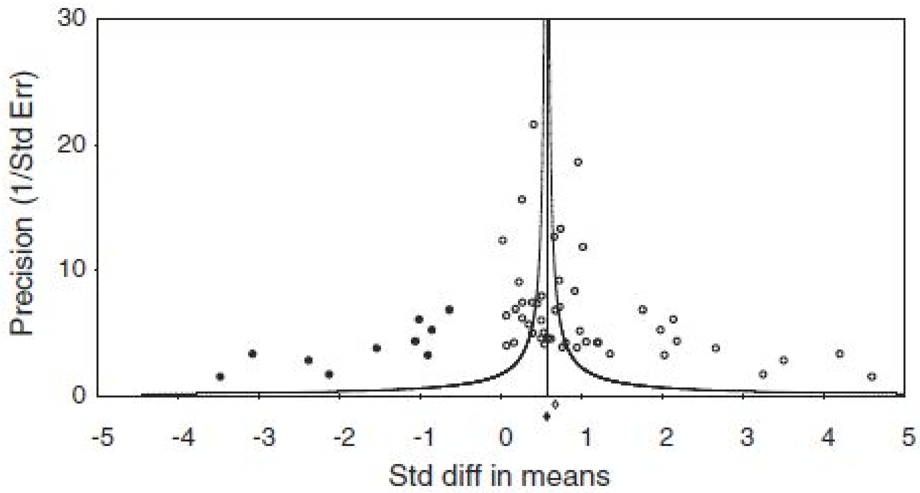
Moderator	Groups	k	Standardised mean difference	95% CI	P	Between group Q	P-value (between)	Within group Q	P-value (within)
Study characteristic subgroups									
Duration of programme	≤12 weeks	37	1.00	0.81–1.18	<0.001			204	<0.001
	>12 weeks	11	0.89	0.51–1.27	<0.001			630	<0.001
						0.2	.640		
Number of exercise sessions	<36	14	0.81	0.47–1.14	<0.001			158	<0.001
	=36	26	0.98	0.77–1.20	<0.001			520	<0.001
	>36	5	1.74	0.78–2.69	<0.001			116	<0.001
						3.4	.183		
Exercise modality	Aerobic	19	1.04	0.67–1.40	<0.001			375	<0.001
	Mixed	26	0.98	0.79–1.18	<0.001			462	<0.001
	Resistance	2	0.33	0.11–0.78	0.140			2.1	0.152
						7.4	.024		
Programme type	Comprehensive	28	0.83	0.65–1.03	<0.001			453	<0.001
	Exercise-only	20	1.13	0.81–1.15	<0.001			328	<0.001
						2.5	.117		
Treadmill protocol	Balke	6	0.70	0.49–0.92	<0.001			9.4	<0.001
	Bruce	14	0.79	0.60–0.98	<0.001			114	<0.001
	Naughton	5	2.41	1.08–3.74	<0.001			96.1	<0.001
	Own	14	1.12	0.70–1.55	<0.001			330	<0.001
	Not specified	8	0.48	0.22–0.74	<0.001			96.4	<0.001
						12.1	<0.001		
Study design	Cohort	22	0.98	0.80–1.20	<0.001			260	<0.001
	Trial	26	0.96	0.71–1.19	<0.001			450	<0.001
						0.1	.740		
Patient characteristic subgroups									
Sex	Females	3	0.92	0.08–1.76	<0.001			23.7	<0.001
	Males	19	1.44	0.98–1.89	<0.001			429	<0.001
	Mixed	21	0.65	0.48–0.62	<0.001			219	<0.001
						10.1	.011		
Age	Young	17	1.45	1.00–1.90	<0.001			235	<0.001
	Old	16	0.90	0.63–1.17	<0.001			143	<0.001
	Oldest	15	0.64	0.42–0.79	<0.001			359	<0.001
						13.5	<0.001		
Primary diagnosis	Post MI	5	2.08	0.87–3.30	<0.001			98.1	<0.001
	Revascularisation	4	0.96	0.34–1.86	<0.001			33.2	<0.001
	Mixed	38	0.86	0.69–1.04	<0.001			637	<0.001
						3.8	.144		
Baseline fitness	≥6.6 METs	25	0.97	0.74–1.20	<0.001			403	<0.001
	<6.6 METs	23	0.97	0.74–1.21	<0.001			445	<0.001
						0.0	0.993		

Legend: Duration of programme: as reported in manuscript 3 months assumed to be equal to 12 weeks. Number of exercise sessions: total reported in study (not the number actually attended). Exercise modality: aerobic — described as continuous exercise e.g. cycle ergometer, treadmill walking (home walking programmes excluded). Treadmill protocol: as given except 'own' — where authors described a highly modified or bespoke protocol with enough detail to replicate; 'Not given' — authors described using progressive/incremental exercise but did not provide enough detail to replicate. Study design: all values calculated as within-group, pre- vs. most distal post-test value, cohort describes studies in which not control group was used. Trial describes studies in which a waiting list, volunteer (selective) or random group of patients acted as controls. Sex — the characteristics of the group in which exercise training took place. Primary diagnosis — the reason given for patients attending CR. MI — myocardial infarction, revascularisation included coronary angioplasty procedures and coronary artery bypass grafting. Where emergency revascularisation took place following MI patients are classed as MI. Mixed—includes patient groups with mixed revascularisation and MI classifications as well as valvuloplasty and angina patients. Baseline fitness is maximal capacity derived from pre- rehabilitation treadmill testing grouped according to median split. Note; k values may not always sum to 48 due to missing data in some study

3.4.2. Publication bias

Funnel plots of precision (standard error) against effect size (standard difference in mean) are shown in Figure 3.2. Studies used in the analysis are shown in open circles and closed circles represent imputed studies. The strong evidence for publication bias in pre- versus post- rehabilitation improvement in fitness is evident in the asymmetry of the plot and clustering of imputed points provided.

Figure 3.2. Funnel plot of precision by standard difference in means.



Legend: Open circles represent studies included in the meta-analysis. Closed circles are imputed values demonstrating the significant publication bias in studies analysed.

3.5. Discussion

CR (CR) is established as an effective therapy to reduce mortality and morbidity in patients suffering from several cardiovascular diseases (O'Connor, et al. 1989; Oldridge, et al. 1988; Jolliffe, et al. 2001; Taylor, et al. 2004; Conn, et al. 2009).

Exercise-only CR is the type of CR on which the early meta-analyses were based on, showing the effectiveness of the therapy. There has been, however, an increase in comprehensive CR programmes, but exercise training is a core component that remains a mainstay in overall CR programmes (NZGG 2002; BACR 2007; Thomas, et al. 2007; SIGN 2002; Balady, et al. 2007; Corra, et al. 2010; Corra, et al. 2007).

The increase of cardiorespiratory fitness should be an outcome of CR (Balady, et al. 2007; Corra, et al. 2010), and probably an explanation of the mechanism by which CR has a positive impact and influence on health status. The reduction of the risk factors for cardiovascular disease in patients, are also an explanation for the effectiveness of CR (Lee, et al. 1999; Taylor, et al. 2004, Taylor, et al. 2006).

CR programmes are effective in increasing patients' fitness levels, as discussed previously (Swain, 2005) and an estimate of effect size has been previously published (Conn, et al. 2009). A lack of detail in trials focusing on increased fitness due to CR, made it difficult until now to fully explore variables that potentially explain the large inter-individual and inter-study differences in changes in cardiorespiratory fitness. Conn et al.'s (2009) study design criteria (a controlled trial or quasi experimental study) was very restricted in studies included, showing a lack of depth of analysis. Due to the proven effectiveness of CR programmes, the authors noted that is not possible to randomly assign patients to a control condition (Dusseldorp, et al., 1999).

This chapter aimed to produce an estimate of the improvements in fitness that researchers and clinicians can expect to observe in patients that complete an exercise-based CR programme. It also aimed to identify the characteristics of CR programmes and patients that can influence the magnitude of fitness gains. To achieve these aims, it was necessary to specially modify the design of the analysis so it could be built on existing research and reviews in this field. The analysis was created using three criteria.

First, fitness data was presented in metabolic equivalents (MET's), as this measure is well-accepted and easily understood by researchers and clinicians. This metric is well used across all different exercise modalities and all groups of cardiac patients. Researchers and clinicians use it to describe cardiorespiratory capacity and work rate in everyday tasks such as risk stratification and exercise prescription (Balady, et al 1996; Balady, et al. 2007; Ades, et al. 2006).

Second, cohort-studies were included in the analysis which was not limited to randomised control trials. This option allowed for the analysis of more data from many more study groups (k=48) compred with previous meta-analyses (K=28) (Conn, et al. 2009). A limitation of our study may be the design used resulting in an overestimation of the mean point of CR effectiveness. So to control the inflation factor in the final data result, we took the step and calculated a within-group correlation coefficient from our own empirical data and included this correlation in the analysis.

Third, in all our analyses we used random effects models and performed nine mixed-effects subgroup analyses, in an attempt to define the source of the expected heterogeneity of improvements in fitness. When the data being analysed is supposed to be heterogeneous, as interventions by exercise have been in the past (Conn, et al. 2009; Swain 2005), the use of random effect models is recommended (Berlin, 1995).

Most meta-analyses have an expected product heterogeneity (Higgins, et al. 2002) and so, researchers, in their analysis, use a pre-planned subgroup analysis to define and understand the source of the data heterogeneity (Davey, et al. 1997). Conn et al. (2009) didn't include a subgroup analysis, this was due to what they described as ''scan data'' in the research area. Their stringent study inclusion criteria could explain this lack of inclusion. A CR programme design should have all the elements for exercise dose prescription (frequency, exercise, intensity and modality), and patient characteristics (sex, age and condition), understanding which may influence fitness improvements may be very valuable.

3.5.1. Discussion of results

In our analysis of studies on CR programmes, we included 3827 patients and we created 48 subgroups from 31 published studies. Our results showed an increase in fitness of more than one and a half metabolic equivalents (1.55 CI 1.21-1.89 MET's) due to CR programmes. This increase is impressive and clinically important, providing further evidence of the effectiveness of using CR as a therapeutic approach to achieve higher levels of fitness, lower mortality and morbidity, and also increase quality of life.

When the data was converted from MET's to $\dot{V}O_{2peak}$, it showed that patients taking part in a CR programme can expect increases in fitness of 5.4 (95%CI: 1.21-1.89) ml.kg-1min-1. This measure represents the body's ability to use oxygen, commonly known as functional capacity, aerobic capacity, cardiorespiratory fitness or simply fitness, these measures are predictive of mortality and morbidity in the general population (Sui, et al. 2007; Gulati, et al. 2003; Myers, et al. 2002) and also in cardiac patients (Myers, et al. 2002; Dorn, et al. 1999; Kavanagh, et al. 2003; Vanhees, et al. 1995).

These studies show us the cross-sectional associations between fitness and mortality, others studies have demonstrated the degree of impact that fitness gains have on mortality due to CR programmes. Kavanagh, et al. (2006) demonstrated that each increase of 1 $ml \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_{2peak}$ was related to a 10% reduction in cardiac mortality. Vanhess et al. (1995) demonstrated that each increase of 1% in $\dot{V}O_{2peak}$ was related to a 2% reduction in mortality. Myers et al., (2002) showed that a 1 MET increase in fitness was related to a 12% reduction in mortality, also Dorn, et al. (1999) showed that a 1 MET increase was related to a 10% reduction in mortality in male MI patients. In our present analysis the improvement in fitness shown (1.55 CI 1.21-1.89 MET's) could represent a reduction in mortality ranging from 16% (Myers, et al. 2002) to 54% (Kavanagh, et al. 2003). By estimating the average in the four studies mentioned (Myers et al., 2002; Dorn et al., 1999; Kavanagh, et al. 2003; Vanhess, et al. 1995) we witnessed an average lowering of mortality of 32%. This reality demonstrated that our study was similar in values to what was shown in previous meta-analyses on CR programmes' effect on patient mortality rates (O'Connor, et al. 1999; Oldridge, et al. 1998; Jolliffe, et al 2001; Taylor, et al. 2004; Conn, et al. 2009).

Conn et al. (2009) meta-analysed various intervention effects of physical activity in cardiac patients, with an estimate effect size calculated for gains in fitness. It's important to highlight differences between this study and ours. Primarily Conn et al., (2009) studied physical activity. The comparable effect size for their primary outcome; gains in fitness due to physical activity was ES=0.49 (random effect models; pre- vs post-test values). When physical activity was converted to energy expenditure, the study found there was an increase of 1984 Kcal per week expenditure due to CR programmes. However, their effect size shown for fitness was not converted for any other metric.

This meta-analysis (Conn et al, 2009), had very restrictive inclusion criteria for the studies used in their analyses. Only randomised control trials were included, which limited their analysis and may have biased their results away from more realistic CR studies as those conducted were part of service evaluations, audits or as staff-led research in existing CR programmes. In these studies, it wouldn't be possible or ethical to withhold or delay CR to patients by recruiting them to be part of a control group. Conn et al, (2009) in their study showed a very restricted criterion concerning the studies included although the patient criteria was broad in terms of definition, with very diverse patients included those at risk of cardiovascular disease (CVD), intermittent claudication patients, angina patients, hypertensive patients and patients suffering from advanced heart failure phases. In the international studies used in the analysis only few groups of cardiac patients were offered outpatient CR programmes unlike those included in our study (NZCC, 2002; BACR, 2007; Thomas et al., 2007; SIGN, 2002; Balady et al., 2007; Corra et al., 2010; Corra et al., 2007). Our meta-analysis had a more broad criteria for study design, and patients included were only core CR patients including: MI-suffers, elective and emergency revascularization recipients and valvuloplasty patients. Our criterion of having fitness as our primary outcome and the inclusion of a subgroup analysis makes both meta-analyses very different from each other.

There are two generalized models of CR programmes that have been investigated referenced in the literature, both including a component of exercise training. A comprehensive CR programme includes, in addition to the exercise element, a component of patient education or behaviour change (such as smoking), when compared with exercise-only CR programmes. This kind of CR approach seems to be less effective in lowering cardiac and all-cause of mortality (Joliffe, et al. 2001; Thompson, et al. 2003).

The existence of different models of CR programmes (comprehensive or exercise only) is just one of many examples of differences seen in delivery of CR programmes that reflects the heterogeneity seen between CR programmes. Existing guidelines for CR programmes are available across much of the developed world such as the U.S. (Thomas, et al. 2007) and Europe (Piepoli, et al. 2010). However, some variation in written guidance, local understanding of such guidance and financial restrictions shows us that CR programmes could be more heterogeneous than first thought, when compared for instance with pharmacological intervention. Understanding this reality of difference between CR programmes, we assumed and expected heterogeneity in our data (which was confirm Q=852, $p < 0.001$) this being the reason why a sub-group analysis was performed.

3.5.2. Subgroup analyses: exploring the heterogeneity in response to CR

The large variation in individual response to exercise training, when submitted to a standardized and controlled exercise training programme is well known. The main cause of this heterogeneity in results is the pre-training initial values of the individual that are taken in account, such as risk factors or $\dot{V}O_{2peak}$. Increases ranging from no gain to 100% in $\dot{V}O_{2peak}$ in large groups of sedentary subjects is reported. The more sedentary an individual is, the more impact and response they will have to the exercise programme, showing increased fitness levels (Bouchard and Rankinen 2001; Swain, 2005). The prescription of exercise is also based on the variability of factors that define the dose of exercise applied to the individual (Intensity, Volume, Frequency and Modality used in sessions, as Length of exercise programme). This variability in exercise prescription and the effect that has on individuals response, is also a cause of heterogeneity in results. To our knowledge the causes of heterogeneity in results had never been investigated previously, only an estimate of CR impact on fitness had been completed until now (Conn, et al. 2009).

Exercise programmes should aim to improve the $\dot{V}O_{2peak}$ of subjects as much as possible, as high levels of fitness are protective of mortality and morbidity in primary and secondary prevention. A 2005 study manipulated the intensity at different levels and the duration (volume) of the activity was controlled to ensure the same energy expenditure was achieved. It was reported that high levels of intensity at vigorous intensity exercise, above 60%>$\dot{V}O_{2peak}$ when compared with moderate exercise intensity or lower intensities, were more effective in improving individual aerobic fitness (Swain, 2005).

A minimal threshold of 45% of $\dot{V}O_{2peak}$ exercise training is defined as effective in improving fitness in subjects with very low fitness levels (Swain and Franklin 2002). In a more recent review (Swain and Franklin, 2006) it is suggested that vigorous exercise at intensity of 6> METS is more cardio-protective than lower intensities, resulting in a higher impact on diastolic blood pressure, glucose control, $\dot{V}O_{2peak}$ levels and lowering the risk of CHD events in the subject. The high intensity had no influence on systolic blood pressure and blood lipid profile or body fat loss. This cut point of vigorous exercise Intensity of 6 METs had been associated before with lower risk of all-cause mortality in the Harvard Alumni Health study (Sesso, et al. 2000) as vigorous exercise has been related with reduced risk of death by CVD (Yu, et al. 2003) and future risk of CHD events. Intensity influence is independent of the hours spent on activity (Tanasescu, et al. 2002).

In exercise prescription of intensity, the exercise principle of overload (stress greater than normally encountered) applied as progression of intensity over time is fundamental for the patients to be able to achieve high levels of exercise work and intensity. Exercising at high intensities is important for subjects who are already relatively fit. Subjects with very low levels of fitness will need to progress from low, moderate to high intensities over time. The minimum suggested achievement during the exercise programme, is an effort of 6 > METS (Swain and Franklin, 2006).

Exercise performed at a higher intensity produced greater gains in $\dot{V}O_{2peak}$, even when the volume is increased to match the energy cost performed at lower intensity exercise or is maintained at a constant. Intensity is more determinant than volume in exercise prescription for obtaining optimal gains in V'o$_{2peak}$ (Swain, 2005; Gormely, et al. 2008). In a review (Swain, 2005) studies using interval exercise training of 3-5 minute bouts at $\dot{V}O_{2peak}$ in exercise sessions, seemed to be more effective in improving $\dot{V}O_{2peak}$ than continuous exercise training. Interval training has also been shown to be effective in increasing fitness and cardiac function in lower functioning patients suffering from heart failure (Tomczak, et al. 2011).

In cardiac patients in general, continuous exercise has proven to be effective in lowering all cause and cardiac causes death (O'Connor, et al. 1999; Oldridge, et al. 1998; Jolliffe, et al. 2001), although high interval intensity training tends to be used more often in patients submitted to CR. A low risk cardiac group with high levels of fitness (>9 MET's) were submitted to high intensity interval training (2min 40% $\dot{V}O_{2peak}$, 2 min 90% $\dot{V}O_{2peak}$) in comparison with a continuous exercise (65% $\dot{V}O_{2peak}$) training design. Both types of exercise training had similar effects on $\dot{V}O_{2peak}$ gains, although interval training increased greater tolerance to anaerobic exercise or anaerobic tolerance. Strenuous activities are presented in everyday life, with the authors suggesting that this will have additional health benefits, without increasing the risk of hazards occurring in exercise sessions, something well tolerated in CHD stable patients. Using high intensity interval training, it is suggested that in CR short exercise/ recovery is well tolerated, enabling increased exercise adherence by patients than exercise at moderate intensity in continuous mode. It’s suggested that passive recovery is preferred by the patients when exercising. The high interval intensity training (IIT) compared with continuous training produced a higher % of $\dot{V}O_{2peak}$ achieved and maintained during exercise and had beneficial effects in ventricular function and endothelial function and quality of life. Consequently, it is suggested by the authors that IIT has a greater benefit compared to the continuous normal mode used. It's suggested some caution is taken when utilising this type of exercise after an acute coronary syndrome, it is recommended to start with moderate intensity intervals and then progress in intensity (Warburton, et al. 2005; Guiraud, et al. 2009, 2011). In the analysis of the studies included in our study it was impossible to investigate the design of exercise aerobic intensity used, as this was not reported, therefore proving difficult to assess the impact of this variable in gains in fitness due to CR.

The differences seen in intensity exercise prescription may influence to a large degree the heterogeneity seen in our analysis. This variance in intensity of training reported in various studies (%$\dot{V}O_{2max}$, % $\dot{V}O_{2peak}$, %HRmax, RPE scores or being ‘’symptom limited’’) was associated with a wide range and overlapping reported training intensity sometimes (50-85% $\dot{V}O_{2peak}$), this turned subgroup analyses of this exercise variable impossible to determine the effect in changes fitness of subjects.

Intensity is known to be the principal determinant of the ability of exercise prescription to increase $\dot{V}O_{2peak}$ and improve health outcomes in healthy individuals (Swain and Franklin, 2006; Swain, 2005; Gormeley, 2008; Tanasesco, et al. 2002; Lee and Paffenbarger, 2000; Yu, 2003) and CHD patients (Swain and Franklin, 2002; Warburton et al., 2005; Tomczak, et al. 2011; Warburton, et al. 2005; Guiraud, et al. 2009, 2011), although there are other variables capable of influencing fitness gains in patients due to CR. The next section in the chapter discusses all of our subgroup analyses systematically, based on our choice for subgroup selection, results explanation and potential explanations for the findings and limitations.

3.5.2.1. Programme duration

In the studies included in the analysis, the duration of programmes was from four weeks to twelve months. Exercise programme duration normally shows a positive relationship with increases in fitness, although in unfit individuals such as CHD patients, most of the gains in fitness are observed in the first 4 to 12 weeks of a training programme. (Miller, et al. 1984; Soleimani, et al. 2009; Wright, et al. 2002). Twelve weeks, in our analysis, was both the median and modal value for the subgroup duration, making this the reference value for CR programme duration supported by guidelines in U.S. (Thomas, et al. 2007), U.K. (SIGN, 2002) or Europe (Piepoli, et al. 2010). Most programmes included in the analysis were ≤12 weeks, studies including more than 12> weeks (including 11 studies) showed a slight, non significant increase in cardiorespiratory fitness.

The heterogeneity was significant within-groups, and seen in both subgroups. The results agree with studies that have compared different lengths, 8 weeks to 12 months durations in CR programmes, showing just a slight increase or no increase following initial gains. (Ades, et al. 1995; Seki, et al. 2003). In a study when the fitness response was observed in a programme of CR with a 26 week duration (6 months) with a number of 64 exercise sessions, the significant change in fitness was seen between 3 and 11 weeks with 24 exercise sessions prescribed in training (Miller, et al. 1984).

A study by Heritage, et al. (2010) was performed to understand the effect of three months of comprehensive CR programme duration in community using patients' views and opinions. This included if the length of programme was enough and if it had a positive impact on their lifestyles. The assessment was made using questionnaires at end of CR programme and at a follow up of 3 to 6 months after. The results show that 90% of individuals rated the programme good to excellent with the same scores seen at 3 and 6 moths follow up. The authors suggested 3 months of CR programme was the correct duration, being sufficiently long as it was highly rated by the participants (Heritage, et al. 2010). In a study done by Reid, et al. (2005) the same number of sessions was maintained, and two different durations of CR programme were analysed. In a three months duration against 12 months, the analysis investigated the influence and impact of programme duration in physical capacity variables, risk factors, health-related quality of life, depressive symptoms, and cost of CR service to the cardiac health care system. There were no different outcomes at 12 or 24 months in the results and the cost of the two services was equal. The authors concluded that both types of duration had the same beneficial effects in CHD patients (Reid et al., 2005). The suggested 3 month duration of CR programme seems to be practical and effective but as a component of exercise prescription is a limiting variable to be analysed alone. The duration effect is influenced by the other components of exercise prescription that all define dose of exercise applied. For a better assessment of the effect of exercise dose on CHD patients' fitness a subgroup was created for the total number of exercise sessions prescribed in CR programmes.

3.5.2.2. Number of exercise sessions

The CR programmes in our analysis showed a wide range of exercise sessions prescribed (from 4 to 144). The total number of exercise sessions represent a good analyse of the exercise dose used in each programme, and we hypothesised that more sessions would result in higher fitness gains. This variable had a common mode and median value (n=36) for the number of exercise sessions prescribed. This represents the reality of CR programmes which generally consist of 3 weekly sessions over 12 weeks. In our analysis CR programmes of >36 sessions resulted in higher gains in patients' fitness than when prescribed a lower number of sessions. No differences were found between groups of patients exercising for 36 sessions or <36 sessions, although this last group shows the lower change in fitness due to CR in the analyses. Our analysis suggests that 36 sessions is enough to increase fitness levels in a CR programme close to the overall mean difference, but additional benefit could be seen if more sessions were added to the CR programme. In our analysis there was only a small number of studies with more than 36 sessions (n=5), this was probably due to potential cost implications and the burden placed on the patient. It's important to understand the potential benefit of exercise prescription in CR of more than 36 sessions in cardiac patients and their fitness levels.

The increased number of CR sessions in our analysis in general was associated with higher fitness gains in patients; this dose-response relationship is seen in several studies focusing on CR programmes. The fitness response to exercise is seen in a study in a programme of CR with a 26 week duration (6 months) with a total number of 64 exercise sessions. When patients have their fitness assessed at the end of the programme they have higher fitness levels compared with the first week and at the eleven week (24 exercise sessions prescribed for training) control test (Miller, et al. 1984). Another study investigated the impact of 5, 10 and 24 sessions of exercise prescription during 8 weeks of CR on the fitness of CHD patients. The study showed an improvement in exercise capacity correlated with the number of exercise sessions prescribed (Soleimani, et al. 2009). In a study (Reid, et al. 2005) with a total of 33 sessions and a duration of 3 months, there was a positive influence and impact on exercise variables, risk factors, health-related quality of life, depressive symptoms, and reasonable cost of CR service to cardiac health care system. This study supports the optimal number of CR sessions defined in our analysis.

We know that shorter CR programmes can also be effective in increasing fitness levels (Wright, et al. 2002). This study focused on shorter CR in CABG patients of 6 weeks in length, 1 session a week, circuit based with a low intensity progressive design and randomized for either CR or exercise alone. There were no differences relating to exercise capacity between groups, both significantly increasing in fitness levels, although the CR group had more benefits in terms of cardiac and pulmonary function (Wright, et al. 2002). There were limitations in our analysis, the group defined as <36 sessions presented a large variance (4-28 sessions), making it impossible to identify the minimum dose of exercise capable of stimulating change in fitness for those involved in CR programmes. This should be taken in account in future research as shorter programmes possess lower cost and may promote better adherence.

3.5.2.3. Exercise modality

The mode of exercise used in training sessions will influence physiological adaptations and physical capacity stimulated by exercise. In our analysis changes in cardiorespiratory capacity were analysed, representing changes in peak oxygen uptake. Aerobic endurance exercise is the modality of training specific to improvements in cardiorespiratory capacity. Most studies in to the effects of exercise training on CHD patients, use the aerobic exercise (O'Connor, et al. 1999; Oldridge, et al. 1998; Jolliffe, et al. 2001; Taylor, et al. 2004; Conn, et al. 2009; Swain and Franklin, 2006; Swain, 2005; Miller, et al. 1984; Swain and Franklin, 2002; Gormeley, et al. 2008; Tanasesco, et al. 2002; Lee and Paffenbarger, 2000; Warburton, et al. 2005; Guiraud; et al. 2009, 2010; Tomczak, et al. 2011; Carnethon, 2009; Soleimani, et al. 2009; Wright, et al. 2002; Reid, et al. 2005). It appears logical that this type of exercise training will be effective and produce large gains in fitness in patients due to CR programmes.

The results of our study support the assumption made in favour of aerobic exercise in its effectiveness in improving fitness levels. The resistance exercise group, showed no significant changes in fitness improvement. This group had only a small number of studies (n=2), therefore, some caution should be taken before drawing conclusions concerning the use of only resistance exercise training in CHD patients. Resistance exercise in combination with aerobic training has been used in different patients such as those with metabolic syndrome (Bateman, et al. 2011) or heart failure (Meyer, 2006; Maiorana, et al. 2000; Beckers, et al. 2008). The group of CR programmes that used aerobic endurance exercise in combination with resistance exercise (mixed group) had identical gains in fitness levels to the aerobic group. The results for gains in fitness produced by the combination of endurance and resistance exercise supports the idea that further improvements in fitness can be obtained by adding resistance exercise to prescribed aerobic exercise within the same exercise session.

Baum, et al. (2009) investigated strength capacity in cardiac patients and showed a natural decline in strength levels with increased age. This decline was observed in superior members as inferior body musculature. When compared with healthy controls, cardiac patients' leg strength was inferior, but no difference in arm strength existed. There was a qualitative difference between leg and arm strength in cardiac patients. Patients with low levels of fitness were related to lower levels of strength too (Baum, et al. 2009). These findings were supported by another study where low fitness levels in CHD patients was associated with decreased strength capacity and fatigability in two major leg muscles (quadriceps and hamstrings) (Ghroubia, et al. 2007). This decrease in leg strength in cardiac patients is not related to the disease and does not represent any pathological skeletal muscle metabolism. Instead, it is a consequence of inactivity and low issue of leg muscle strength. It's suggested that resistance exercise is used in CR programmes to improve leg muscle strength as they are essential to cope with everyday activities and to perform vigorous aerobic exercise (Ghroubi et al., 2007; Baum, et al. 2009). Resistance training alone has demonstrated its importance in cardiac patients. It has been shown to have a positive impact on some risk factors for CHD (Braith and Stewart 2006) and produces higher physical capacity levels, as it stimulates beyond other activities, such as aerobic endurance, balance, coordination and flexibility (Brochu, et al. 2002; Ades, et al. 2003; Ades, et al. 2005). The combination of aerobic endurance with resistance exercise has been supported in the guidelines for CHD patients (Thomas, et al. 2007; Piepoli, et al. 2010).

Our results show the importance of the use of combined aerobic with resistance exercise training in CR programmes. There is some evidence to support our findings. A study with randomized CHD patients (16 men) performing aerobic exercise or aerobic exercise combined with resistance exercise, measured the impact of both training programmes in the leg muscular fatigue and fitness levels. The authors concluded that combined aerobic with resistance exercise training was superior to aerobic training. The combination was more effective in improving exercise tolerance, decreasing fatigue in leg muscles and also correcting some neuromuscular alterations (Gayda, et al. 2009). A similar study was replicated in 92 women with CHD doing both types of exercise programme for 6 months. It showed similar gains in fitness for both programmes, although there was a significant difference in physical quality of life assessed at one year follow-up in favour of the combined endurance-resistance exercise training programme (Heather, at al. 2007). Another study included 70 male CHD patients doing a CR programme based on combined aerobic-resistance exercise for 12 weeks, resulting in a positive impact in fitness levels. There was no improvement seen in the leg muscle volume of patients principally in patients with low baseline leg muscle volume, although strength capacity was improved (Kida, et al. 2006, 2008).

It can be concluded that a combination of both modalities (aerobic endurance exercise combined with resistance exercise) can improve fitness levels and reverse the lack of strength in leg musculature seen in cardiac patients. Using both modalities is more appealing and showed more diversity in the CR exercise programme, resulting maybe in a better adherence to programmes compared with single modality CR programmes. Few studies showed results of adherence, making it impossible to comment on that point.

3.5.2.4. Comprehensive versus exercise-only CR programmes

Meta-analyses have shown differences between these two main types of CR programmes in patient survival (Jolliffe, et al. 2001; Taylor, et al. 2004), or no differences at all (Heran, et al. 2011; Clark, et al. 2005}. Our choice of subgroup analysis was determined by this fact. Survival data in both programmes was analysed due to the strong documented relationship between gains in fitness and mortality.

In our analysis we had as a hypothesis that exercise-only programmes would have a bigger effect on improvements in fitness. In our analysis no significant difference in between-group heterogeneity was found, although exercise-only programmes showed a trend towards larger gains than comprehensive-exercise programmes. Exercise only programmes were associated with lower mortality rates than comprehensive-exercise programmes. Exercise-only programmes have been found to reduce some behavioural risk factors like smoking; on which there is some rather counterintuitive evidence (Taylor, et al. 2004). A study showed that having a smoking habit assessed during hospitalization and being referred to CR 6 months later, is a good predictor of smoking cessation (Dawood, 2008). Psychological interventions may be less effective when used in CR programmes (Rees, et al. 2004).

The educational interventions in CHD patients showed no influence on all-cause mortality, cardiac morbidity, revascularization or hospitalization (Brown, et al. 2011; Whalley, et al. 2011; Rees, et al. 2004). Women were randomly assigned to a normal CR programme, exercising for three sessions/week for twelve weeks, combined with 10 educational sessions. The other group undertook the normal CR programme with the addition of a specific programme tailored for women based on motivational interviewing, guided by the trans-theoretical model (TTM) of behaviour change. This last intervention had significantly improved global quality of life (QOL), improved health perception, vitality, social function when compared to the normal CR control group, improving health behaviours may therefore increase adherence to exercise programmes (Beckie and Beckstead 2010, 2011; Rolfe, et al. 2010; Beckie, et al. 2011; Grace, et al. 2010)

Low fitness is an important risk factor for CHD and mortality. From the improvements in fitness and the relationship with lowering mortality in CHD patients and the result seen in our analysis of an obvious trend to higher fitness gains in exercise only-CR programmes, we recommend that the main aim of CR programmes should be focused on the delivery of the exercise sessions. Additional psychological or educational input into programmes had no or low benefit for patients. In our analyses the way the comprehensive-exercise CR was described in the literature was poor, limiting our analysis. Studies presented few details of the interventions done, it was not explained if educational sessions were in addition to the exercise component of CR or whether they displaced exercise sessions. Very little was reported on the length of sessions provided and there was no data on the attendance of the patients to these sessions.

3.5.2.5. Treadmill protocol

The modality of testing can affect the result of any fitness test, something that is well documented. This was the reason why our choice was limited to incremental treadmill test protocols. In our study analysis the reported protocols used to assess CHD patients fitness were varied. In most of the studies the authors gave enough information and description to replicate the protocol used, six studies reported that in their assessment an 'incremental test' was used. These studies formed a subgroup (not specified protocol) as they were a rather homogeneous subgroup of studies where the authors conceived and used their protocols (own protocol).

In our analysis the changes seen in patient fitness from studies where the treadmill protocol used was not described, the change in fitness measured was far lower than the overall mean (ES=0.48; 95% CI 0.22-0.74 METs). This made it difficult to comment on this due to the lack of information revealed by the studies.

The estimates made in other subgroups such as ''Balke'' and Bruce'' were similar, except for the studies using ''Naughton protocol'' this subgroup presented the highest effect size change over the all the others subgroups and the overall mean difference

(ES=2.4, 95% CI 1.08-3.74 MET's). It is recommended that caution is taken when gains in fitness are being compared and the studies use different protocols. Studies in the analysis that used Naughton protocol were normal in terms of duration, modality or patients factors which may have influenced increases in fitness, except including a large group of patients had larger increases (Arya, et al. 2005).

In relation to these studies we can only speculate as to why the increase in fitness levels were so high, but one explanation for this could be that the Naughton protocols is designed with short stages and soft transitions between workloads, making it highly suitable for cardiac patients in comparison to Bruce, that is by far the most commonly-reported protocol. In the studies using their own protocol (producing the second highest subgroup mean estimate) typically the design of the protocols had soft transitions and short stages, as seen in the Naughton protocol. These findings need further investigation to understand and define which protocol has the highest applicability, validity when assessing fitness levels in CHD patients involved in CR programmes.

3.5.2.6. Study design: cohort versus Trial

The study design cohort versus trial subgroup analysis was done with the intention of determining if trials of CR, being designed and implemented mainly by researchers, were able to produce different changes in fitness in comparison with other forms. Our analysis had the intention of discovering whether we were justified in combining data from a wide variety of study designs. It was hypothesised that trials might produce highest gains in fitness levels (pre- versus post-test) due to the influence of higher patient adherence to the study, the expertise of the researchers, selective nature of study participants, possibly having higher motivation to CR programmes due to their knowledge of being involved in a trial study.

No differences were found between the subgroup of two study designs. Effect sizes were almost identical and logically also very close to the overall mean value. These findings are similar to those of Conn, et al. (2009) who found that study funding status had no influence on changes in patients' physical activity levels. In our analysis we were confident of not introducing any bias into our results by using both study designs. A limitation of the analysis was the subjective nature of subgroup allocation. A number of cohorts were identified (with no control group) that had been supported with funding and other studies were not easy to classify due to the poor nature of study description of purpose and recruitment of patients.

3.5.2.7. Summary: programme-level moderators

Is it suggested that some heterogeneity in fitness gains seen can be justified by the choice of different treadmill protocols between studies. There was a moderate modifying effect of exercise modality, where programmes of mixed-modality appear to be more effective, and a total exercise dose define of 36 sessions as being optimal. Programme length, being exercise-only base CR or comprehensive-CR, and if the programme was part of a trial or cohort design of research, had no significant effect in fitness gains. However there are also differences at the level of the patient which may moderate changes in fitness observed.

3.5.3. Patient-level subgroups analysis

3.5.3.1. Sex

Epidemiological and clinical studies show that genders have differences in terms of CVD clinical profiles such as prevalence, presentation (symptoms and age of onset), and disease outcomes and disease management, although little information is available to explain how this happens, and why CVD affects different genders. CVD is prevalent in both genders and is the leading cause of death worldwide in both genders. Women possess a lower CVD mortality rate than men, although CVD is the biggest killer of adult women in most developed countries, with increased risk particularly in the over 50s age group. In last decade the CHD mortality in men has been declining in contrast with women's CHD mortality rate which has been stable. (Mikhail, et al. 2005; Pilote, et al. 2007).

Risk factors in women increases their risk of CVD events compared with men. CVD mortality rates are higher than men in women suffering from diabetes and hypertension. After an acute CVD event women with atrial fibrillation have greater risk of stroke than men with the same conditions (Pilote, et al. 2007).They are less likely to achieve optimal targets for blood pressure, glucose levels, and lipid values, and less likely to achieve good CVD management (Reibis, et al. 2009). Woman possess more co-morbidity factors such as diabetes mellitus, hypertension, hypercholesterolaemia, peripheral vascular disease, and heart failure (Mikhail, et al. 2005), and suffer more from depression which presents an additional independent risk for CVD (Möller-Leimkühler, 2007).

Woman also suffer more severe outcomes than men, and a higher mortality rate is seen in young women one year after an acute coronary event, which can be explained by the increased risk of death during the first days of hospitalization (Simon, et al. 2006). The mortality in woman undergoing revascularization is also higher than men with worse outcomes and more risks (Mikail, et al. 2005; Vaccarino and Koch, 2003). Beyond these unexplained sex related factors, differences in CVD outcomes in women remains largely unknown. There are other factors towards CVD behaviour between men and women that may help to explain and influence these differences in genders, such as cultural, psychosocial and socio-economic status (Pilote, et al. 2007).

Genders may also respond and benefit in different ways from CR programmes. Women's referral to CR is lower compared to men, despite being the same age and being submitted to the same clinical procedures. Women are less likely to be instructed on secondary prevention strategies and referred to CR by their clinicians or health carers. In CR women tend to be older with a greater cardiovascular burden, enrolling in CR at later stages of severity of their CHD disease, normally after valvular surgery or heart failure. Their rehabilitation process is also longer and more complicated (De Feo, et al. 2011; Caulin-Glaser, et al. 2001). Men tend to have better CR programme adherence, whilst women also participate less after being referred or dropping out (Tardivel, 1998; Ginzel, 1996; Yohannes, et al. 2007; Jackson, et al. 2005). Women have several barriers to CR, such as: less social support, transportation, family responsibilities, lack of CR awareness, seeing exercise as tiring and painful, and due to their co-morbidities. Psychosocial factors such as depression inhibition and anxiety are more prevalent in women as a barrier (Grace, et al. 2009; Cooper, et al. 2002; Barth, et al. 2009; Dunlay, et al. 2009). Some recent studies report that gender tailored CR programmes may improve attendance and adherence, such as the use of motivational interviews in combination with exercise CR programmes in women (Beckie, et al. 2009; Beckie and Beckstead 2009, 2010; Grace, et al. 2010).

There is a well-documented gender-bias in CR in favour of men, who are refereed to CR more than women, and there is and under representation of women in the research done in CVD (De Feo, et al. 2011; Caulin-Glaser, et al. 2001; Schuster and Waldron 1991). This bias towards men was confirmed in our study analysis. This bias maybe be explained historically due to CVD being more predominant in men, besides being the biggest killer in both genders. We had just three female-only groups versus 19 male-only groups. This small number of groups makes the analysis of the results more difficult and significant between-group heterogeneity was seen.

Higher gains in fitness were achieved by males compared with females although the difference in gains in fitness between men-only groups compared with mix-groups was even higher. These results were surprising as the mixed-groups were composed mainly by males. The analysis of group gender composition from previous reports found that in CR programmes 25% of the participants were women (Conn, et al. 2010;

Mikail et al., 2005). This tendency of higher gains in only one gender exercise group may cause difficulties in implementing CR exercise sessions composed of mixed-groups. Given the group-exercise nature of most CR exercise programmes the male behaviour toward mix-groups, show that men were not exercising at the same intensity and working less when exercising together with women. It's been hypothesised that men became overwhelmed in the presence of women, tending to feel shy and less confident to fully engage in CR exercise programmes (Yohannes, et al. 2007).

We hypothesised that male-only groups would provide a more competitive, ambient exercise session in which men engaged strongly with CR exercise sessions, working harder. A limitation in our analysis was that, whilst of interest, it had little clinical significance except to suggest that if possible, patients may benefit more by exercising in same sex CR exercise sessions. If this is of practical application in everyday clinical work, due to financial, special or temporal limitations are apparent.

3.5.3.2. Patient age

Like sex, patient age is a non-modifiable risk factor. Age has an impact on cardiac function and structure; the heart becomes more hypertrophic and hyporesponsive to sympathetic (but not parasympathetic) stimuli. Exercise induced cardiac responsiveness is also blunted in older patients. Age is associated with a decline in peak aerobic capacity ($\dot{V}O_{2peak}$, heart rate, ejection fraction and cardiac output responses to supine exercise in healthy men). These changes in cardiac function can be improved by long term exercise training adaptations and the effect they have on cardiac function. Lack of physical activity is a greater risk factor in older patients for chronic disease and disability, with exercise having potentially important implications on increasing health benefits in this population (Stratton, et al. 1994; Ferrari, et al. 2003; Fleg, et al. 2005; Heckman and McKelvie, 2008).

In patients older than 65 when submitted to CR programmes its shown that physical capacity, quality of life and body strength are increased, regardless of the presence co-morbidities. Older patients in response to aerobic exercise, have greater improvements in sub-maximal endurance capacity in comparison with more modest gains in $\dot{V}O_{2peak}$. It's known that older patients have lower adherence, and are less likely to be referred by physicians to CR exercise programmes (Ades, et al. 1993; Audelin, et al. 2008; Ståhle, et al. 1999; Simpson, et al. 2005, Lavie and Milani, 2004; Marchionni, et al. 2003; Williams, et al. 1985; Listerman, et al. 2011)

The present results show significantly greater fitness gains in younger patients compared with older or the oldest group of patients. These results are in agreement with the available literature (Williams, et al. 1985; Ades and Grunvald, 1990). The different significant results between age subgroups may be explained by a reduction in physiological adaptability in the oldest patients, in which the fitness gains were less than half those of younger patients. This may serve as a recommendation for practitioners in setting goals for patients, with lower expected gains in fitness in older patients, when fitness is shown in absolute terms, as in our analysis. If the gains in fitness levels were shown in relative percentage gains, the changes observed in older patients may be equal or even higher that of younger patients due to lower baseline fitness values.

3.5.3.3. Baseline fitness values

Individuals showed a different pattern of change in fitness which is related to their initial fitness values. Individuals with low initial values had greater increases in fitness, due to exercise training programmes; this is referred to in literature as the law of initial values. Statistically, this phenomena represents regression to the population mean and is well document in the exercise physiology literature (Bouchard and Rankinen, 2001) and has been seen in patients attending CR programmes (Sakuragi, et al. 2003). In this analysis patients were divided in two groups according to their baseline fitness values to test the hypothesis that those with lower baseline fitness would enjoy bigger gains in fitness. The results did not support this hypothesis however, as there was almost no between-group difference in fitness gains. The similarities seen, may be due to the fact that effective exercise prescription in CR programmes at individual level was reported in most studies. Exercising at individual level capacity, patients were able to exercise at similar relative exercise intensities thereby achieving similar improvements in fitness levels. While this result is encouraging, the subgroup analysis itself is limited as this one is focused on the arbitrary number of 6.6 MET's, determined simply by median split, which limited our findings to patients with more varied baseline fitness values

3.5.3.4. Primary diagnosis

The analysis was completed and showed a trend towards greater improvements in fitness in the post-MI patient subgroup in comparison with those being rehabilitated for revascularisation or other reasons. The between-group heterogeneity was not significant. The small number of studies in each specific subgroup made the interpretation difficult. This is a limitation of the analysis and is mostly due to the subgroup mixed-patient nature of studies that simply reflects the wide range of different patients referred and able to take part in CR programmes.

3.5.3.5. Summary: patient-level moderators

In summary of the results found, despite a big degree of heterogeneity between studies, increases in fitness levels were only significantly moderated differently by patients' sex (being male) and age (being younger). We recommend to practitioners to take note of these non-modifiable factors when implementing and designing CR programmes as it is suggested that younger male patients may particularly benefit from exercising in groups separated according to sex, enabling patients who can, to exercise in a more vigorous manner to promote optimal fitness levels.

3.6. Conclusions and limitations

Previous meta-analyses have confirmed the CR efficacy, used as a treatment to reduce patient mortality and morbidity. CR programmes possess this influence in mortality and morbidity due to modification, reduction of CHD risk factors and by the influence in improvement of cardiorespiratory fitness levels. High levels of cardiorespiratory fitness due to exercise training in CR programmes are associated with lower risk of cardiovascular mortality and morbidity. A previous meta-analysis (Conn, et al. 2009), including a wide range of interventions aimed at improving physical capacity in CHD patients, showed that programme variables such as more contact time with practitioners, more time exposed to exercise sessions and fitness testing were associated with higher levels of physical activity. Cardiorespiratory fitness is a more powerful predictor of health than physical activity, but Conn, et al.'s (2009), meta-analysis did not investigate factors that were related to fitness increases as they did for physical activity. Despite the inherent aim of CR to improve cardiorespiratory fitness and the direct relationship that cardiorespiratory fitness has with different outcomes (Lee et al., 1999; Myers et al., 2002; Dorn, et al. 1999; Vanhees, et al. 1995) no study has systematically analysed the factors that may modulate cardiorespiratory fitness improvements.

This is the first detailed evaluation of changes in cardiorespiratory fitness in patients undertaking exercise-based CR programmes and suggests patients may expect a 1.5 MET improvement in cardiorespiratory fitness. The increase seen in our analysis can represent a 16-54% reduction in cardiac mortality, depending on the estimation techniques used (Myers, et al. 2002; Kavanagh, et al. 2003). The studies included in our meta-analysis which were used to provide the mean estimate were, however, highly heterogeneous. It was observed in our analysis that CR programmes had variables able to promote optimal stimulus and higher changes in cardiorespiratory fitness, such as including >36 sessions in the CR programme of aerobic or mixed aerobic and resistance exercise with a programme length of 12 weeks period. No evidence was found suggesting that longer CR programmes had additional benefits to patients, and no evidence for combining exercise training with patient education (comprehensive CR) and improvements in cardiorespiratory fitness levels. Our results seen from a more scientific perspective, showed that a treadmill protocol used to assess cardiorespiratory fitness in patients had a major impact on the estimation of fitness improvement and, it is suggested that should be employed when comparing studies which have used different testing protocols.

Young patients and those who are male had bigger increases in fitness, and may benefit more from CR than older, female patients, who had lower changes in fitness. It is recommended that there is provision of exercise sessions for same sex groups and that patients should be allocated according to their age. This would help patients achieve optimal increases in cardiorespiratory capacity.

Our study found strong evidence of systematic publication bias, whereby significant findings from bigger studies were substantially more likely to have been published. The conclusions drawn from this meta-analysis are limited due to the inclusion of non-randomized and cohort-based study designs, although the inclusion of these studies allowed us to perform subgroup analyses which identified some moderators of the response of cardiorespiratory fitness to exercise-based CR.

3.7. References

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Chapter 4. Centile Curves and Normative Values for the Incremental Shuttle Walk Test at Entry to Outpatient Cardiac Rehabilitation.

Abstract

Objective: The Incremental Shuttle-Walk Test (ISWT) is used in Cardiac Rehabilitation (CR) to predict cardiorespiratory fitness. However, $\dot{V}O_{2peak}$ accounts for only 63% of the variance in test performance; and non-clinical variables (Height, BMI) may account for ~20% of variance in performance. The aim of this study was to identify additional predictors of ISWT performance, and produce centile curves and normative data of performance in ISWT in cardiac patients, as a cross-validation of the predictive power of the regression equation in the healthy population, to predict actual cardiac patients' performance in ISWT.

Methodology and results: 548 patients with clinically stable cardiovascular disease from four outpatient CR programmes completed the ISWT at entry to rehabilitation. We collected anthropometric and demographic data to identify predictors of test performance. Primary predictive variables were then used to produce normative values and centile curves of test performance.

Age and sex were the strongest predictors of performance. Men walked 113 m (β= 112.58 m; 95%CI 85.64 to 139.51) more than women. There was an age-related decline of 6.4 m (β=-6.36 m; 95%CI -7.78 to -4.95) and 5 m (β= -4.9; 95%CI -6.5 to -3.3) per year in males and females respectively. Male performance (m) was also influenced by height, BMI, presence of diabetes ~25% (R^2=.25), diabetes and height also predicted ~28% (R^2=.28) of female performance. Construction of centile curves confirmed a broadly linear reduction in expected ISWT values in males (25-85 years) but a more curvilinear trend in females. All prediction models correlated positively with actual cardiac patient data from the ISWT, although correlations were very low in strength (r<4).

Conclusions: These age and sex-stratified normative values may help practitioners to more accurately interpret individual performance at entry to CR. Improving exercise prescription and assessing change in cardiorespiratory capacity as patients fast track to community based CR. Regression equations based on a healthy population have little or no clinical utility in cardiac patients.

Key words: Cardiorespiratory fitness; Incremental shuttle walk test; Predictors; Cardiac patients, Centiles curves, Normative data.

4.1. Introduction

Functional capacity is an important outcome measure in primary and secondary prevention of coronary heart disease (CHD); it provides prognosis for future CHD events and mortality (Piepoli, et al. (2010). The Incremental Shuttle Walk Test (ISWT) may be used to predict cardiorespiratory capacity (Fowler and Singh, 2005), although the accuracy of any estimation of cardiorespiratory capacity is of some doubt (Woolf-May and Ferrett, 2008; Almodhy, et al. 2014). The test may also aid exercise prescription (Fowler, 2000; Woolf-May and Ferrett, 2008), and can be used to track changes in cardiorespiratory capacity and assess programme efficacy (Woolf-May and Ferrett 2008; Almodhy, et al. 2012; Sandercock,et al. 2012). The test is recommended for use in CR programmes in UK, by the department of health (SIGN 2002; BACPR 2012)

The ISWT is measured in meters, this absolute outcome value is used in clinical practice to classify cardiac patient performance (exercise capacity) at entry into CR programmes. ISWT performance is not dependent solely on the patient's cardiorespiratory capacity. Fowler and Singh (2005) found that 63% of the variance in ISWT performance in cardiac patients was explained by cardiorespiratory capacity, but this univariate regression did not facilitate the assessment of alternative performance predictors identified elsewhere in cardiac patients such as height and BMI (Pepera, et al. 2013).

Much of the variance in ISWT test performance may be due to non-modifiable factors such as a patient's sex and age (demographic characteristics) or anthropometric characteristics (such as height, weight, BMI), indicated by multivariate analysis of test performance in pulmonary-disease patients (Luxton, et al. 2008) and healthy individuals (Dourado, et al. 2011; Jurgensen, et al. 2011; Probst, et al. 2012; Dourado, et al. 2013; Harrison, et al. 2013).

Age, sex and weight, as predictors of ISWT were never identified in ISWT performance in cardiac patients. Understanding the variables that modify performance in patients (such as demographic and anthropometric), allows a more accurate interpretation of the absolute performance in the ISWT in cardiac patients according to their different individual characteristics. This can then improve clinical practice and decisions, e.g. physiological tests mediated significantly by age and sex, normative reference data may improve test interpretation (Cole, et al. 1995; WHO, 2006; Sandercock, et. al. 2012). In our study we attempted to quantify cardiac patients' ISWT absolute performance against centile curves and additionally we compare performance in meters in ISWT against the best predictors of ISWT.

Recent studies in the healthy population purport to provide normative ISWT data in healthy individuals. These authors also explored the applicability of such normative ISWT data in clinical populations (Dourado, et al. 2011, 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013). These studies actually provided equations which can predict ISWT performance in healthy individuals. Such predictions developed in healthy cohorts are useful, as they work as a standard reference against which performance of patients can be compared.

Such equations may be used to interpret CR patients' ISWT performance by estimating values as if the patient were healthy, and expressing actual performance as a percentage, as practised in the 6 min walk test (Enright and Sherrill 1998). These reference equations in healthy individuals (Dourado, et al. 2011, 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013) (Table 4.1) were never applied to clinical populations, such studies should ideally have validated their models by comparing predicted values with actual test performance in a clinical population. Unfortunately, no studies to date have attempted to do this.

In our study we intended to test the clinical utility of such equations. Any such equation must however be of clinical utility, and be practical to apply to cardiac patients in order to meet certain criteria for standard procedure of cross-validation:

- We expected differences as they were different populations, healthy individuals walk much further than cardiac patients, e.g. the healthy population walks on average 500 to 850 m in the ISWT (Jurgensen, et al. 2011; Probst, et al. 2011) compared to 350 m walked by cardiac patients (Pepera, et al. 2013);

- The equation should account for a credible amount of variance in the outcome measure of interest. However, as most of the variability in ISWT performance is dependent from cardiorespiratory fitness, we expected a low (<40%) proportion of variance to be accounted for;

- Any predictor variables used in these equations should be simple, objective measurements;

- There should be some similarities in the variables used in the prediction equation and those known to predict performance in the clinical population in which the equation will be used (in this case cardiac patients)

- When applied to a clinical population, the predicted values should correlate well with actual patient values (r>.5) – this process is called cross-validation.

The present chapter was not intended to predicted ISWT performance by developing yet another regression equation. Instead the primary aim was to quantify absolute ISWT performance in cardiac patients, and develop centile curves based on the strongest predictors of ISWT performance, and test the predictive power of regression equation in the healthy population to predict our actual cardiac patient data.

Table 4.1. Reference equation to predict performance in meters in Healthy

Studies	Reference equations for ISWT	S.E.E.	R^2
Jurgensen, et al. 2011	= 374.004 - (6.782 x Age) – (2.328 x Weight) + (3.865 x Height) + (115.937 x Gender)	114.7 m	50.3%
Probst, et al. 2011	= 1449.701 – (11.755 x Age) + (241.897 x Gender) – (5.686 x BMI)	167.8 m	71.0%
Dourado, et al. 2011	1. = 34.608 – (4.384 x Age) – (2.949 x Weight) + (553.336 x Height) + (114.387 x Gender) 2.= −243.867 − (2.833 x Age) − (3.259 x Weight) + (575.101 x Height) + (6.321 x Grip Strength)	79.4 m 74.6 m	64.9% 69.0%
Dourado, et al. 2013	1.= 347.7 - (7.2 x Age) – (3.0 x Weight) + (472.3 x Height) + (137.2 x Gender) 2.= 223.7 – (5.8 x Age) – (3.2 x Weight) + (421.3 x Height) + (62.1 x Gender) + (4.8 x Grip Strength) 3.= -54.6 – (5.8 x Age) + (-4.3 x Weight) + (666 x Height) + (75.3 x Gender) + (2.1 x Lean Body Mass) + (0.64 x Total Body Fat)	- - -	65.0% 73.0% 68%

Harrison, et al. 2013	= ISWT distance predicted = 603.35 + (61.87 × Forced expiratory volume in 1 second (FEV1) + (6.96 × Quadriceps maximal voluntary contraction) + (9.18 × Duke Activity Status Index) − (13.14 × BMI) − (4.01 × age)	220 m	50.4%

4.2. Aims and hypothesis

The primary aim of this chapter was to identify non-modifiable predictors of ISWT performance at entry to outpatient CR (pre-CR) and to produce reference values and centile curves based on actual performance. A secondary aim was to test the utility of published regression equations developed in healthy populations by cross-validating predicted values with actual ISWT performance in CR patients.

4.3. Methods

4.3.1. Participants

We accessed clinical records of n=547 (415 males) (76% male) patients (63.1 ± 11.3 years) who completed outpatient CR at four UK hospitals: (Greater London, Essex, Cumbria and Middlesex) and extracted clinical data and details of 10m ISWT performance at entry to rehabilitation. Table 4.2 gives the clinical characteristics and baseline measurements, diagnosis and reasons for attending CR.

Table 4.2. Descriptive Characteristics of Cohorts

Clinical Characteristics and Baseline Measurements	***Mean (SD)***
Number of patients	**547**
Age (years)	**63.1 (± 11.3)**
Gender	**M: 415 ; F:132**
Height (cm)	**170.6 (± 8.7)**
Weight (Kg)	**81.5 (± 17.3)**
Body mass Index (kg/m^2)	**27.8 (± 5.2)**
Diabetes	**153 (28%)**
Smoking	**140 (25.6%)**
Primary Diagnosis	
MI	**375 (68.6%)**
CHD	**119 (21.8%)**
Other	**53 (9.6%)**
Primary Treatment	
CABG	**263 (48.1%)**
PCI	**230 (42.1%)**
Valvuloplasty	**36 (6.6%)**
None	**18 (3.3%)**

CHD, coronary heart disease; MI, myocardial infarction; Others: valve, cardiac arrest, arrhythmia, ACS and even others; CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention.

4.3.2. Procedures and Data Collection

Data was collected at four hospitals that reported delivering comprehensive CR and routinely using the ISWT in accordance with the national guidance. The ethical approval for this study was obtained by Integrated Research Application Service (REC reference: 09/H0305/102) and approval to assess patient records by the National Information Governance Bureau (Request: ECC 1-04(e)/2010).

4.3.3. Statistical Analysis

We used a univariate linear regression to identify predictors of ISWT performance in the population as a whole, and used an independent t-test to describe the difference in male and female test performance. After differences were affirmed, we performed stepwise multiple regressions to determine significant predictors of ISWT performance in males and females. We assessed predictors for co linearity; defined as variance inflation factor >4.0 (Rogerson, 2001). Statistical significance was set at $p<0.05$ and all analyses were performed using SPSS 19.0 (SPSS, an IBM Company, Armon, NY).

We constructed centile curves for distance walked during the ISWT for males and females using the Generalized Additive Models for Location, Scale and Shape (GAMLSS) (Rigby and Stasinopoulos, 2006). GAMLSS models are part as a package included in the statistical software R (R Development Core Team 2011) and this statistic have been used by the World Health Organisation Multicentre Growth Reference Study Group (WHO, 2006).

We tested the power of the regression equations developed for healthy individuals, and one equation for cardiac patients (table1) to generate predicted values of performance in our cohort. We use a paired t-test to examine mean differences, and the Pearson Product Moment Correlation to examine the relationship between predicted and actual values of ISWT performance in cardiac patients.

4.4. Results

Overall ISWT performance ranged from 75 to 1145 m, (mean: 365 ± 164 m). Age was the strongest predictor (β=-5.95, 95%CI: -7.1 *to* -4.8) followed by sex (β=-112.6 m (95%CI -139.51 to -85.64)]. Independent t-tests verified that males (395±165 m) walked significantly further (t=8.081, $p<0.0001$) than females (269 ±118 m), so we performed all further analyses separately by sex.

Preliminary analysis of the whole data set confirmed sex was retained as a significant predictor of ISWT performance in all initial multivariate models. We therefore, analysed males and females separately. Results of multivariate regression models created for males and females are given in table 4.3. In these sex-specific regressions, age remained the best predictor of ISWT performance, explaining 16% and 17% in men and women respectively. Additional predictors were height, BMI and (Presence=1 or Absence=0 of) diabetes. None of these variables explained >5% additional variance in males but diabetes did explain an additional 7.9% variance in female performance. Overall variance explained in each model was 25% for men, and 28% in women; the majority of which was accounted for by patients' age.

Table 4.3. Predictors of ISWT in Males and Females

Predictors in males	***β***	***R^2***	***S.E.E (m)***
Age (years)	*β*= -5.9 m (95%CI -7.1 to -4.6)	.156	152
Height (cm)	*β*= 5.0 m (95%CI 3.1 to 6.8)	.208	148
BMI (kg/m^2)	*β*= -5.1 m (95%CI -7.9 to -2.2)	.235	145
Diabetes (Yes=1/No=0)	*β*= -48.7 m (95%CI -17.3 to -80.2)	.252	144
Model prediction	R^2= .25		
Predictors in females	***B***	***R^2***	***S.E.E (m)***
Age (years)	β= -4.8 m (95%CI -6.3 to -3.3)	.174	108
Diabetes (Yes=1/No=0)	β= -80 m (95%CI -39.5 to -120.5)	.253	103
Height (cm)	β= 2.8 m (95%CI 0.11 to 5.5)	.277	102
Model prediction	R^2= .28		

4.4.1. Normative Data and Centile Curves

Tables 4.4 and 4.5 give the normative values for ISWT performance at the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles in male and female CR patients. Figures 4.1 and 4.2 provide smoothed centile curves of the same data. There was a negative relationship between age and ISWT performance at all centile values in both sexes. The median expected value for the youngest patients was more than double that of the oldest in males and females. Male ISWT values were higher than female values across the age range (25-85 years). There was still, however, a two-fold difference in expected values between the 3rd and the 97th percentile in both sexes and at all ages. Distances walked (3rd – 97th percentile) varied on average by 628 (868 to 371) m in males and ~454 (634 to 300) m in females. The overall variance tended to decrease with age in both sexes.

In males, the relationship was broadly linear across the age range (25-85 years) for which centiles were constructed. The median ISWT performance of females was more curvilinear with a steeper decrease in younger women (25-60 years) followed by a gentler, more linear decrease from 60 years of age onwards.

Table 4.4. Centile Values for Total Shuttles Walked by Males Aged 25–85 Years

Age	*C3*	*C10*	*C25*	*C50*	*C75*	*C90*	*C97*	*Mean*	*SD*
25	277	413	413	609	699	860	1145	635	237
30	256	381	492	579	676	833	1092	603	221
35	236	351	458	549	651	803	1036	571	208
40	217	322	424	519	625	771	978	539	196
45	199	295	392	489	597	735	918	507	186
50	182	269	361	459	569	698	858	475	176
55	166	245	331	429	539	658	798	444	166
60	150	221	302	399	507	618	739	412	156
65	135	199	274	369	475	575	680	380	146
70	120	178	247	339	441	532	621	349	136
75	106	157	221	309	406	488	564	317	126
80	93	137	196	279	370	443	507	286	116
85	79	118	171	250	333	397	450	254	105

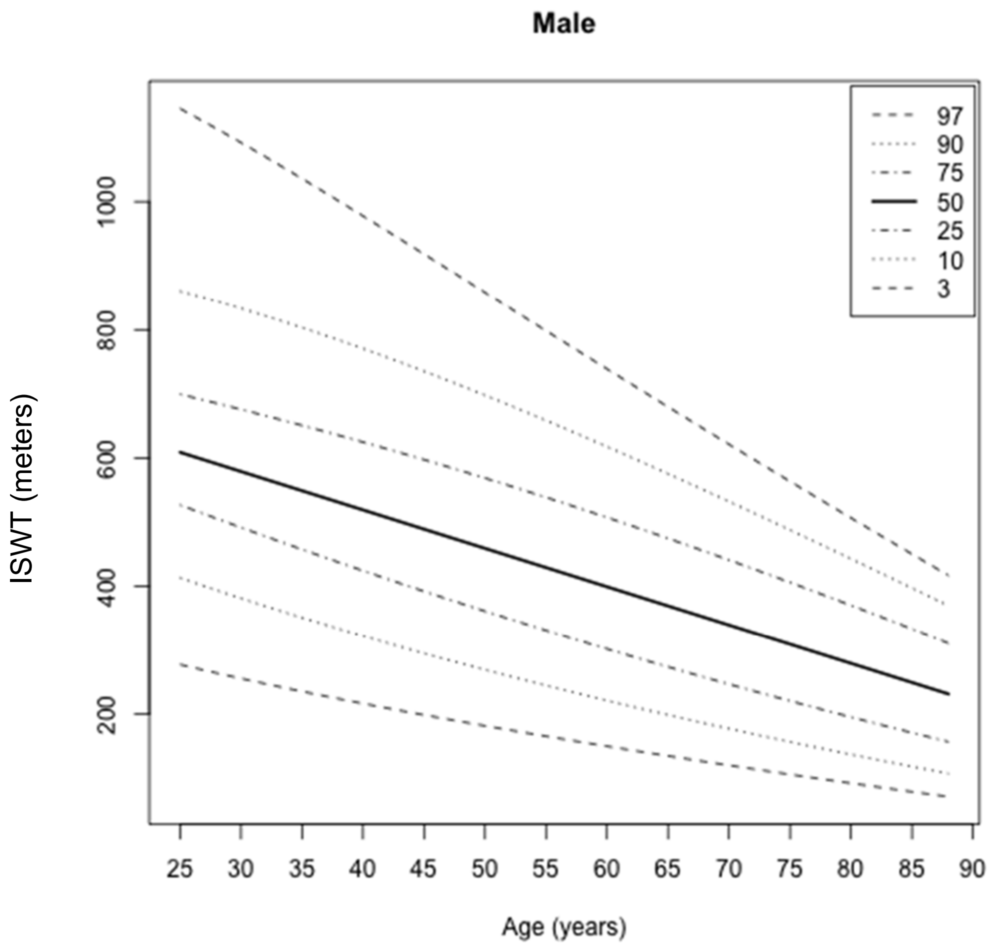


Figure 4.1. Centile Curves for Total Shuttles Walked by Males Aged 25–85 Years.

Table 4.5. Centile Values for Total Shuttles Walked for Females Aged 25–85 Years

Age	C3	C10	C25	C50	C75	C90	C97	Mean	SD
25	150	263	384	507	616	704	784	495	168
30	132	237	349	466	570	655	732	455	159
35	116	214	318	428	527	609	684	455	150
40	103	193	290	393	487	567	640	386	143
45	93	175	265	361	451	527	600	356	134
50	85	160	242	332	417	491	562	329	126
55	79	148	222	305	386	458	528	304	119
60	77	138	205	281	358	427	496	282	111
65	76	130	189	259	332	399	467	263	104
70	77	123	176	239	308	373	441	245	97
75	77	117	163	221	286	349	417	228	90
80	77	111	151	204	265	327	395	213	85
85	75	104	140	189	246	307	375	199	81

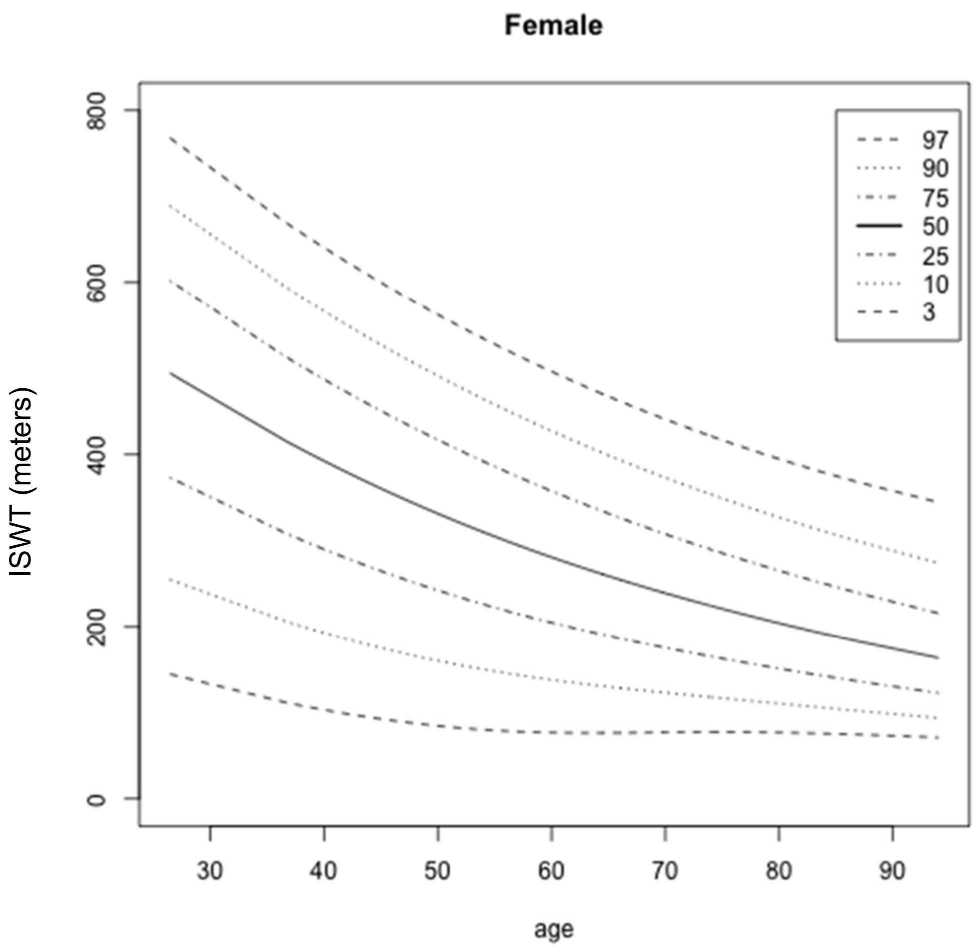


Figure 4.2. Centile Curves for Total Shuttles Walked in Females Aged 25–85 Years.

4.4.2. Cross-validation of Prediction Equations Developed in Healthy Populations

Paired t-tests verified that all equations developed in healthy individuals (Table1) significantly overestimated ISWT performance in CR patients. The only equation that produced an estimate of performance not significantly different from actual values was Pepera, et al. (2013) equation, in Table 1, and only when applied to women.

All prediction models correlated positively with our data. In men the highest correlation between predicted and actual values came from the equations featured in Jurgensen, et al. (2011) (r= .376), and Probst, et al. (2011) (r=.388) (Figure 3). The closest correlations between predicted and actual values in women were also those of Probst, et al. (2011) (r= .360) and Jurgensen, et al. (2011) (r= .324) (Figure 4). All the other models correlated under r= .3 with our data in men and women.

Figure 4.3. Predictive Values from Jurgensen vs Actual Data

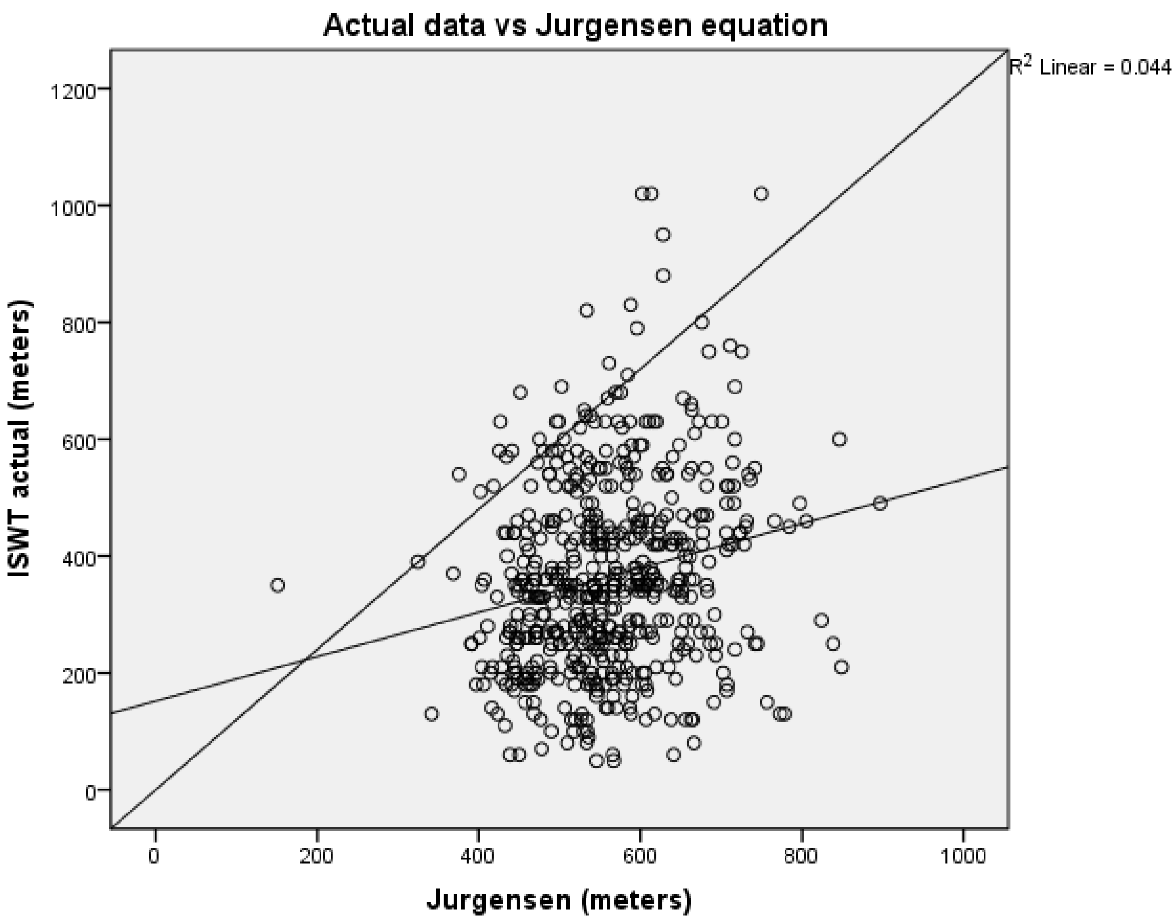
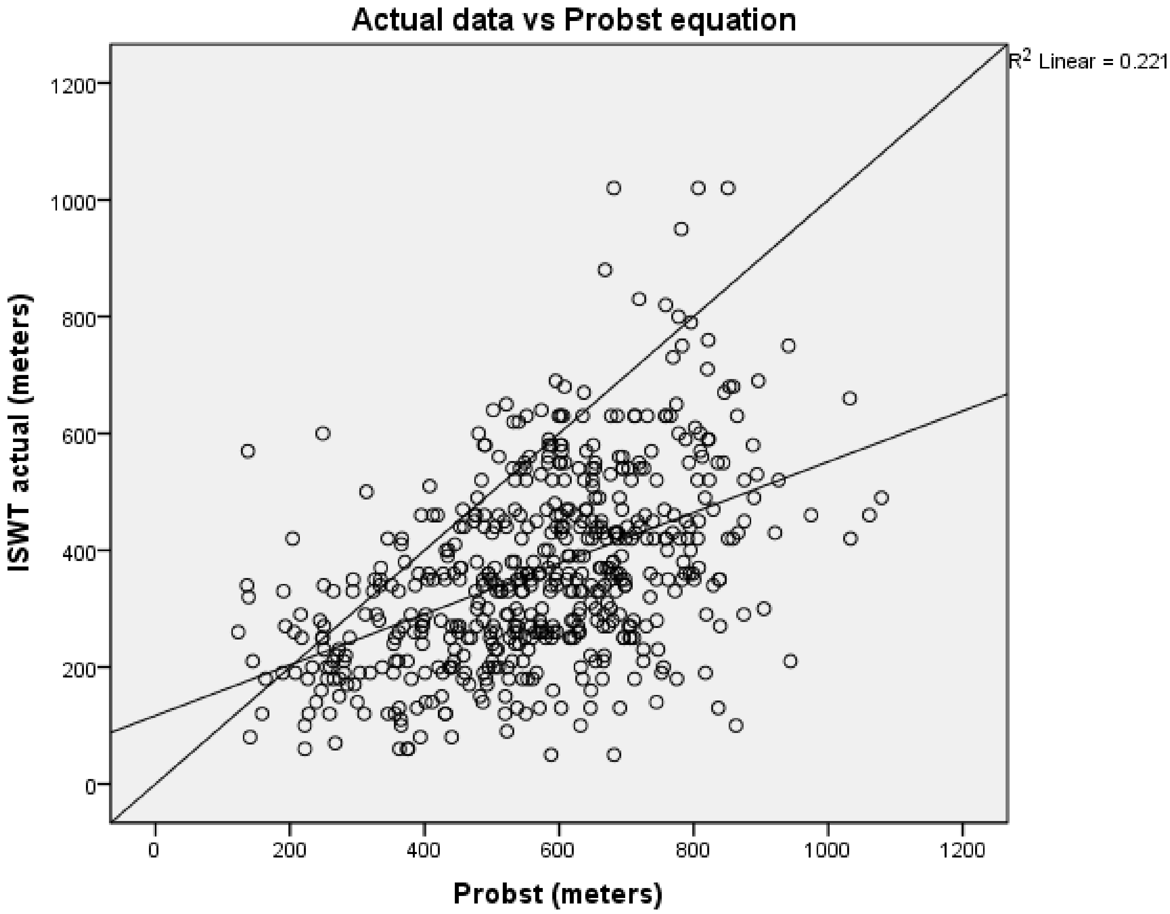


Figure 4.4 Predictive Values from Probst vs Actual Data



4.5. Discussion

The aim of this study was to aid the interpretation of functional capacity measurements made using the ISWT by considering the role of non-modifiable variables which may influence performance in cardiac patients. We presented reference values for the Incremental Shuttle-Walking Test (ISWT) in patients at entry to outpatient CR.

We confirmed that age and sex accounted for ~25% of variance in test performance and that males walked significantly further than females at all ages. In males, the median expected distance walked decreased by 59%; from 609 m at 25 years to 250 m at 85 years. The median distance female patients walked dropped by 62%; from 507 m at 25 years to 189 m at 85 years. Based on only the variance in test performance associated with age and sex – there was >300% variation in the distance walked between the youngest male and oldest female patients tested. While a large variation evident at each age in both sexes is likely due to differences in cardiorespiratory fitness (Fowler and Singh, 2005), such massive age- and sex-related variation suggests that reporting and interpreting ISWT performance simply as distance walked is problematic. These centile curves provide the first set of reference values in cardiac patients; which may allow practitioners to make meaningful age- and sex-referenced interpretation of ISWT performance at entry to outpatient CR.

The prediction models developed in the healthy population correlated poorly with our data (r<.4), and the predictors in regression equations reported are different than actual cardiac patients, they are of no use in clinical practice to predict ISWT performance in cardiac patients.

4.5.1. Predictors of ISWT Performance

Identification of age and sex as ISWT predictors was in agreement with studies on COPD patients (Luxton, et al. 2008) and healthy individuals (Dourado, et al. 2011; Jurgensen, et al. 2011; Probst, et al. 2012; Dourado, et al. 2013). The greater distance walked by males (126 m (95% CI: 100-151 m) further than females) was expected and of similar magnitude (110 m) to the mean of a previous study on cardiac patients

(Pepera, et al. 2013). In healthy individuals differences as great as 163 m (Jurgensen, et al. 2011), 183 m (Dourado, et al. 2011) and even 290 m (Probst, et al. 2012) have been reported, but it should be noted that these healthy individuals walked a much greater overall distance during the ISWT than the present sample of CR patients.

Sex-related differences in walking performance are likely due to higher absolute cardiorespiratory capacity, greater muscle strength and mass in males or also simply because they are taller than females on average and have greater stride length. Pepera et al. (2013) reported that stride length was the most powerful predictor of ISWT performance in cardiac patients; but that this dynamic measure was not routinely used in clinical practice. Pepera et al. (2013) found height (as a proxy for stride length) could predict 17% of variance in ISWT performance in a mixed-sex sample of cardiac patients. Conversely, height was only a very minor predictor of ISWT performance (2.4% in females and 5.2% in males) in the present study due probably to separate analyses by sex.

BMI predicted 2.7% of variance in male's ISWT performance and was negatively associated with test performance as has been reported in cardiac patients (Pepera, et al. 2013), as it has been in healthy individuals (Probst, et al. 2012). This is mostly because BMI is a measure of adiposity and greater body mass (especially fat mass) which increases the energy cost of walking.

Diabetes explained only 1.7% of the variance in test performance in males but was more important (7.9% variance) in females despite both a smaller sample size and lower incidence of diabetes in women (26%) compared to men (28%). Diagnostics showed no co linearity between diabetes and any of the potential predictors. This is a novel finding as diabetic status has been assessed in other studies. Diabetic women walked on average 80 m less than those without the condition. This suggests clinicians should take the presence of diabetes into consideration when interpreting ISWT performance, as the impact value of this magnitude is reported as 'mean change' in CR programs. Ideally we would like to create curves at least for females with and without diabetes, with more research needed.

We explained ~25 to 28% of the variance in sexes performing the ISWT by non-modifiable variables. The main source of variance in ISWT performance is cardiorespiratory capacity, explaining 63% of the variance (Fowler and Singh 2005). Diagnosis, treatment, medication and time from event to CR, waist circumference, blood pressure and smoking were not significantly related with ISWT performance in CHD patients as reported previously (Pepera, et al. 2010; Pepera, et al. 2013).

4.5.2. Cross-validation of Prediction Equations Developed in Healthy Populations.

The studies done in healthy participants with a similar mean population age (Dourado, et al. 2011, 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013) acknowledge the utility of ISWT in clinical practice, and claimed the utility of their prediction models in predicting performance in clinical populations, although they developed their studies only in healthy populations, reporting no justification for such claiming. Such studies should ideally have validated their models by comparing predicted values with actual test performance in a clinical population. Unfortunately, such analysis were not done in the available literature (Dourado, et al. 2011, 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013).

4.5.2.1. Mean Differences in Predicted and Actual Values

The application of all prediction equations developed in the healthy population (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013), reported in Table 4.1, in actual patient values, significantly overestimated their performance. All the studies (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013) reported higher mean ISWT performance than the patient values observed, e.g. the healthy participants walked on average 500 to 850 m in ISWT (Jurgensen, et al. 2011; Probst, et al. 2011) compared with a mean of 365 ± 164 m achieved in cardiac patients. Healthy population mean values of performance were higher than actual patients, this is expected as CHD patients have cardiorespiratory impairments and are more likely to have several co-morbidities. Overestimation of actual values does not necessarily invalidate any equation, as predicted values can be used as a health reference value point, and to express actual performance as a percentage, as practised in the 6 min walk test (Enright and Sherrill, 1998).

When we used both sexes of our cohort and predicted their performance using equations from past research (Jurgensen, et al. 2011) (Probst, et al. 2011) (table 4.6) there was a gross overestimation in predicted performance in cardiac patients. In Jurgensen, et al. (2011) and Probst, et al. (2011) equations for the prediction of performance in ISWT ranged in the men and women from 223 m (67%) to 465 m (140%) and 60 m (19%) to 181 m (50%) respectively.

Table 4.6 Prediction of ISWT Performance Using Patient Data as an Example

Actual patient	Age (years)	Weight (kg)	BMI (Kg/m²)	Height (cm)	ISWT (meters)	Jurgensen (m)	Probst (m)
Man	63	74	27.5	171.5	330	553 ± 115	795± 115
Female	63	80.5	29.6	173.2	360	429 ± 168	541± 168

4.5.2.2. Accounting for Variance in Equations Developed in the Healthy Population

Regression equations based on the healthy population performing the ISWT (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013) (table 1) explained 50% to 71% of the variance in performance. This is bad, as most of the variance in actual cardiac patient values is based on cardiorespiratory capacity. This compares favourably with the 25% to 28% of variance explained in our cohorts of male and female cardiac patients. The high proportion of variance explained by demographic and geographical variables in regression equations based on the healthy population is surprising as the most powerful predictor of ISWT performance should be the cardiorespiratory capacity of an individual or population. This suggests that either the ISWT is a poor measure of cardiorespiratory capacity in healthy individuals or that adding cardiorespiratory capacity would alter the predictors of ISWT performance.

4.5.2.3. Simplicity of Predictor Variables Used in Regression Equations.

Using complex, clinical variables to predict the relatively simple ISWT test outcome (distance walked) in actual patient values is of little use, even if a very powerful prediction equation was developed. This is because predictors should be simple measures that are easy to obtain in clinical practice. There are some simple applications of the regression equation used e.g. in healthy individuals. Adding more clinical measures (Hand grip, %Lean body mass, %Total body fat; or forced expiratory volume in 1 second, quadriceps maximal voluntary contraction, and Duke Activity Status Index) to their prediction models didn't increase predictive power in ISWT performance (Dourado, et al. 2011, 2013; Harrion, et al., 2013), as expected. Predictors used in regression equations should be simple and easy to obtain in clinical practise as reported in regression equations by Jurgensen, et al. (2011), Probst, et al. (2011) and equation one in Dourado, et al. (2011, 2013), Table 4.1.

Dourado, et al.'s (2011), equation two, equation two and three from Dourado, et al. (2013); and Harrion, et al.'s (2013) equations based on healthy individuals were excluded from the cross validation procedure as the predictors were too complex to use in clinical practice.

4.5.2.4. Similarity in Predictor Variables: Healthy Versus Cardiac Patients.

In order to be of useful, equations should include similar variables. In the case of predicting ISWT performance in CR patients, the presence of co-morbidities (such as diabetes) or clinical characteristics (size or site of MI) and low cardiorespiratory capacity would challenge the validity of equations based on development populations in which these characteristics are not present. Such systematic differences will simply produce gross overestimates of the performance in our cardiac patients.

No other regression equation (Jurgensen, et al. 2011; Probst, et al. 2011) differed in predictors reported in men and women, as actual cardiac patients:

Equation 4.x Predictors of ISWT in Male Cardiac Patients.

- ISWT = -45.154 - (5.9 x Age) + (5.0 x Height) - (5.1 x BMI) - [48.7 x Diabetes (1), no Diabetes (0)]; S.E.E. = 144.1 m;

Equation 4.x Predictors of ISWT in Female Cardiac Patients.

- ISWT = -11.924 - (4.8 x Age) - [80 x Diabetes (1), no Diabetes (0)] + (2.8 x Height); S.E.E. = 101.6 m.

Similar predictors were found between actual cardiac patients and healthy individuals. Sex and age were the primary predictors of ISWT performance in cardiac patients.

Age was also the most powerful variable in all regression equations based on healthy populations and to a lesser extent gender had also had a powerful effect (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011). Weight was not reported as a predictor in actual patients, as reported in regression equations based on healthy individuals (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011). BMI was a predictor in actual patients also reported by Probst, et al. (2011), and height too was a predictor, as reported by Dourado, et al. (2011; 2013); Jurgensen, et al. (2011)

In Jurgensen, et al.'s (2011) equation the predictors Age, Height, Gender, were the same reported in actual patients, they also accounted for the same magnitude and direction, than actual patients. The predictors were the same between genders which differs from actual cardiac patients.

In Probst, et al. (2011) proposed an equation that included Age, Sex and BMI as the same predictors as actual patients. The predictors were the same between genders which differs from actual cardiac patients. BMI was a predictor in male patients. BMI was not a predictor in female cardiac patients. Predictors also accounted for the same direction, although gender had double the magnitude than actual patients.

In Dourado et al. (2011, 2013) Age, Height, Gender were the same predictors as in actual patients. The predictors were the same between genders which differs from actual cardiac patients. Predictors also accounted for the same direction, although height was hugely increased in magnitude, compared with actual patients.

4.5.2.5. Correlation of Predicted Values in Actual Patients by Healthy Population Equations Versus Actual Patient Values

When examining the ability of the regression models based on healthy individuals (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011) (Table 4.1) in predicting patients' actual performance during the ISWT, the two equations that produced estimates that correlated best with actual patient values were Jurgensen, et al. (2011) and Probst, et al. (2011). Jurgensen's equation produced estimates that correlated weakly with actual values (Table 4.4) for men (r=.388), and women (r=.376). Broadly similar correlations were found between estimates based on Probst's equation and actual values (Table 4.5) in male (r=.324) and female (r=.360) CR patients.

These correlations were all weak and figures 4 and 5 showed that actual test values varied greatly for patients in any predicted performance (Jurgensen, et al. 2011; and Probst, et al. 2011). The low correlations (r<.4) between predicted and actual values suggest neither equations developed in healthy individuals holds the necessary predictive power for use in patients entering CR.

The numerous studies claiming to provide reference data for ISWT in cardiac patients are collectively flawed. None of these studies provided a justification for developing prediction equations in using healthy subjects. The studies claimed their predictions may be 'useful' in cardiac patients although none of them followed the standard procedure of cross-validation (Dourado, et al. 2011; 2013; Jurgensen, et al. 2011; Probst, et al. 2011; Harrison, et al. 2013), Table 4.7.

Predicting ISWT performance in cardiac patients from regression equations developed in healthy populations (Jurgensen, et al. 2011; Probst, et al. 2012) does not seem feasible. Their prediction of actual patient performance in ISWT correlated weakly ($r<4$) with actual patient performance. The predictors found are different in genders in actual cardiac patients whereas they were equal between genders in the healthy population. The same predictors in regression equations in the healthy population had different a magnitude and strength of prediction than in actual patients. Regression equations based on the healthy population had little or no clinical utility as claimed by the authors of such studies, so it is important to provide population-specific reference data.

Table 4.7. Comparison of Reference Equations in Healthy and Actual Cardiac Patients

Studies	Jurgensen, et al. 2011	Probst, et al. 2011	Dourado, et al. 2011	Dourado, et al. 2013	Harrison, et al. 2013
1- Explanation of amount of variation	-Very High, 50.3%	-Very High, 71.%	-Equation 1- Very High, 64.9% -Equation 2- Very High 69.0%	-Equation 1- Very High, 65.% -Equation 2- Very High, 65.% -Equation 3- Very High, 65.%	-Very High, 50.3%
2- Simplicity of predictors	-Yes	-Yes	-Equation 1- Yes -Equation 2- Complex	-Equation 1- Yes -Equation 2- Complex -Equation 3- No	-Complex
4- Similar Predictors (same magnitude and direction)	-Same direction and magnitude	-Same direction different magnitude	-Equation 1- Same direction different magnitude -Equation 2- No similar	-Equation 1- Same direction different magnitude -Equation 2- No similar -Equation 3- No similar	-No similar
5-Correlation, with actual patients	-r=.388	-r=.376	-Equation 1- r=.245	-Equation 1- r=.249	-----------

4.5.3. Current Clinical Application of ISWT Performance

The ISWT is sometimes used as an estimate of cardiorespiratory fitness, which explains ~62% of the variance in distance walked (Fowler and Singh, 2005). As stated above, we can assume cardiorespiratory fitness explains much of the variance in distance walked (3rd – 97th percentile) evident at all ages in both sexes. The ISWT is more commonly reported simply as distance walked (Fowler and Singh, 2005) which is clearly problematic given the expected variation in performance due to non-modifiable factors (figures 1 and 2).

The ISWT is also used to classify patients as either high or moderate/low risk based on achieving a criterion-related performance deemed equivalent to 5 METs (SIGN 2002) but there is some debate as to the distance walked during the ISWT which is equivalent to 5 METs (Fowler and Singh, 2005; Woolf-may and De Ferret, 2008; Almodhy, et al 2014). The significant age- and sex-related variance shown in our study suggests the use of a universal cut-point may be problematic. Regardless of cardiorespiratory fitness any single cut-off for all ages and both sexes will clearly favour younger, male patients and simply cannot account for the expected difference in patients' ISWT performance.

For example, to exceed the proposed 5 MET cut-off, all patients need to walk approximately 420 m (Fowler and Singh, 2005). Our data showed that this distance is within the lower part of the expected range for a 50 year old male (~25th percentile) but that an 80 year-old female would need to perform above the 90th percentile for age and sex to meet this criterion. The average 50 year old male is, therefore, more than seven times more likely to meet this criterion. Put simply, absolute (distance walked) cut-offs classify patients more by their age and sex than their cardiorespiratory fitness.

4.5.4. Clinical Application of ISWT Performance with Reference Values

The ISWT is used to provide information and feedback to patients on exercise capacity and improvements in fitness due to CR. Given the large variation in expected values (due to age and sex) we believe the centile curves presented here can provide a more meaningful and individualised interpretation of ISWT performance.

For example, at entry to CR, 80 year old female patients typically walk between 77 m and 395 m during initial assessment by ISWT. By comparison, 50 year old males typically walk much further (between 182 and 858 m). An absolute ISWT distance of 200 m would place a 50 year old male below the 5th percentile for age and sex; possibly indicating very low cardiorespiratory fitness, presence of significant co-morbidities or low test effort. Conversely, the same (200 m) absolute distance suggests an above-average performance for an 80 year old female patient. This above-average performance by the 80 year old female patient suggests that she might expect lesser improvement in ISWT performance due the law of initial values.

Conversely practitioners might expect much greater improvement in ISWT performance in the 50 year male patient.

The law of initial values suggests the largest improvements are seen in those with the lowest initial test scores. In the example male patient, the reference values may have aided goal-setting, such as aiming to attain a distance around the 50th percentile. In the female patient, however, a suitable goal might have been to maintain the same distance or to make a very small improvement. Test interpretation based on reference values may better-inform initial exercise prescription, improve application and individualization of exercise progression as well as inform practitioners and patients about the degree of improvement expected due to CR.

The ISWT has been successfully used to ‘triage’ patients more accurately at entry to outpatient CR; by identifying individuals to be ‘fast tracked’ to community rehabilitation (Robinson, 2011). The distances walked by the 60 year old patients in this study were 620 m which is equal to around the 90th percentile for men and well above the 97th for women in our population. The successfully fast-tracked patients are a minority and clearly not typical of patients entering CR. Interpretation of ISWT against an absolute distance will, however, create a preference for younger, male patients to meet any such potential fast-track criteria. The present data shows a 40 year old male is about 3 times more likely to meet this 620 m criterion cut-off than a 70 year old female.

We suggest practitioners could make more meaningful interpretation of test scores when combined with these reference data. Such a practice may aid clinical decision making, improve patient understanding, and goal setting for fast track at entry to outpatient CR or back referral to inpatient CR

4.5.5. Study Limitations

Our sample is typical of CR patients in England but may not be reflective of the intentional population. Given the potential clinical importance of diabetes in (particularly female's) ISWT test performance we would ideally have created curves separately for diabetic patients. Sample size prevented this but future research should assess the potential impact of diabetes on exercise test performance in cardiac patients.

The percentile values in each gender at all ages were disparate, representing the potential changes in ISWT performance is which are, most likely, dependent on cardiorespiratory fitness. Our present study goes some way to explaining the source of the remaining 35% of variance in CHD patients' test performance. Concurrent analysis of non-modifiable predictors identified here as well as cardiovascular fitness might explain a still greater proportion of test variance. To date, no large-scale multivariate analysis combining non-modifiable predictors and direct assessment of oxygen consumption has been performed in cardiac patients. If the ISWT is to remain in use as an estimate of cardiorespiratory fitness such a study is warranted to confirm the relative importance of all potential predictors.

These reference values provide only expected walking distances for patients entering CR and we cannot provide (or suggest) a clinical cut-off for ‘good’ or ‘poor’ test performance; such a threshold and factors which can predict changes in performance should be identified. Ultimately, differences in mortality and morbidity according to initial ISWT performance and improvements due to CR will be needed to produce valid clinical cut-offs of performance. Our data was gained from sequential patient records and while they are similar to other studies, they are lower than values from studies which recruited patients as volunteers and are, therefore, difficult to compare. To improve exercise prescription, predictors of change in ISWT performance should be identified.

4.6. Conclusion

We have provided the first reference data for the incremental shuttle-walking test (ISWT) in patients at entry to CR. Distance walked on the ISWT varied greatly due to non-modifiable patient characteristics; particularly age and sex. We propose that clinicians may better-interpret ISWT performance by comparing absolute (distance walked) values with the age- and sex-specific reference values presented here. This practice may provide a more meaningful and individualised assessment of patients’ functional capacity, exercise prescription, and magnitude of change in cardiorespiratory fitness expected at entry to CR programs. This may help 'triage' patients by better interpreting ISWT performance taking into account a patient's age and sex at entry to outpatient CR and potentially identifying individuals who can be 'fast tracked'. Regression equations based on the healthy population have little or no clinical utility in cardiac patients.

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Chapter 5. Oxygen costs of the Incremental Shuttle Walk Test in cardiac rehabilitation participants; an historical and contemporary analysis

Abstract

Objective: The Incremental Shuttle Walk Test (ISWT) has become a standardized assessment for cardiac rehabilitation (CR). Three studies have reported the oxygen costs (VO_2)/metabolic equivalents (METs) of the ISWT. In spite of classic representations from these studies graphically showing curvilinear VO_2 responses to incremented walking speeds, linear regression techniques (also used by the ACSM) have been used to estimate VO_2.

Two main aims: i. to resolve currently reported discrepancies in the ISWT VO_2-walking speed relationship and ii. to derive an appropriate VO_2 vs walking speed regression equation.

Methodology and results: VO_2 was measured continuously during an ISWT in 32 cardiac rehabilitation and 30 age-matched controls

Both the CR and control group VO_2 responses were curvilinear in nature. For the CR group $VO_2 = 4.5e^{0.37 \text{ x walking speed (mph)}}$.

Conclusions: CR vs control participants had a VO_2 up to 30% greater at the higher ISWT stages. The curvilinear nature of the VO_2 responses during the ISWT concur with classic studies performed for over 100 years. VO_2 estimates for walking, based

on linear regression techniques, are currently being incorrectly recommended and this study provides a resolve of this matter when the ISWT is used in CR populations.

5.1 Introduction

Direct measurements of maximal oxygen consumption ($\dot{V}O_{2max}$) and estimates of peak oxygen consumption ($\dot{V}O_{2peak}$) obtained from exercise tests provide valuable information for decision making in cardiac rehabilitation, including patient risk stratification (AACVPR 2013; ACSM 2013; BACPR 2014). The gold-standard measurement for assessing $\dot{V}O_{2max}$ is maximal incremental exercise testing by treadmill or cycle ergometry.

The Incremental Shuttle-Walking Test (ISWT) was originally developed to assess functional capacity of patients' chronic obstructive pulmonary disease (Singh, et al. 1992; Parreira, et al. 2014) but has been adopted to assess cardiorespiratory fitness in patients with cardiovascular disease attending exercise-based rehabilitation (Tobin 1999; Jolly, et al. 2008; BACPR 2014; NACR 2014). In the absence of Gold-Standard assessments, the ISWT has become widely used in cardiac rehabilitation (Brodie, et al. 2006).

The ISWT can provide practical valuable information for physical activity guidance and exercise prescription, along with more traditional information for evaluating changes in exercise capacity as an outcome measure for individual patients or whole service delivery (Sandercock, et al. 2013; Almodhy, et al. 2014). In the absence of direct measures of $\dot{V}O_2$ values during the ISWT, clinicians tend to rely on $\dot{V}O_2$ estimates, usually derived from a linear regression equation recommended by the American College of Sports Medicine (ACSM) (ACSM 2013).

To date, only three studies (summarized in Figure 1) have reported the oxygen cost ($\dot{V}O_2$ in [ml·kg^{-1}·min^{-1}] or metabolic equivalents [METs]) for individual stages of the ISWT in cardiac populations or age-matched controls (Woolf-May and Ferrett, 2008; Woolf-May and Meadows 2013; Almodhy, et al. 2014). The data from these studies make it possible to compare measured $\dot{V}O_2$ values with $\dot{V}O_2$ estimates from the ACSM equation (ACSM 2013). In all cases the values reported in both the healthy populations were greater than those estimated by the ACSM. Underestimation was even greater in cardiac patients'.

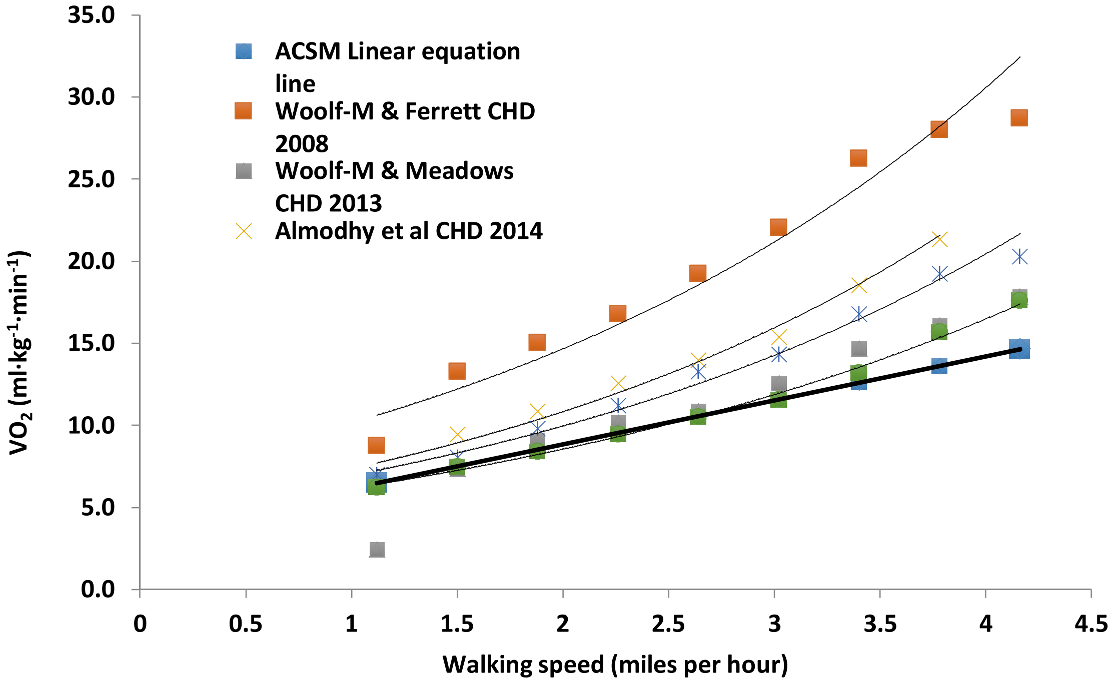
The first study (Woolf-May and Ferrett, 2008) reported $\dot{V}O_2$ values for cardiac patients up to 40% greater than estimated by ACSM during the initial test stages of the ISWT and up to 90% greater during the latter stages. In comparison to age-matched healthy individuals, the measured $\dot{V}O_2$ of cardiac patients was 26% and 47% greater at the lower and upper stages, respectively.

The second study from this same group (Woolf-May and Meadows 2013), reported recorded $\dot{V}O_2$ values during the ISWT similar to ACSM estimates at stages 1 to 5. The values then increased in a curvilinear fashion until being 20% greater than estimated by the ACSM equation at stage-9; far less than the 90% difference previously reported in a similar population. Also contrary to their former study, the $\dot{V}O_2$ values differed very little between cardiac rehabilitation participants and age-matched controls. Such inconsistencies without any comment from the same group of researchers means that cardiac rehabilitation professionals are currently faced with some confusion over estimating the oxygen costs of the ISWT whether for the purpose of exercise prescription or risk stratification.

An initial step towards resolving these inconsistencies was undertaken as pilot work during the early stages of this thesis; (Almodhy, et al. 2014). We undertook a small (n=8) pilot study in cardiac patients. We found $\dot{V}O_2$ that fell between those reported previously by Woolf-May, et al (2008) and those of Woolf-May, et al. (2013). The study also demonstrated that $\dot{V}O_2$ responses to the ISWT were fundamentally different to those of treadmill exercise; the gold standard method of assessing VO_2peak in cardiac patients and the reference standard for the ACSM equations.

Another area of concern with the extant descriptions of the ISWT's oxygen cost reported by Woolf-May et al., are the authors' interpretations of recorded data and the application of the ACSM estimation equations; both assume a linear relationship between increments in walking speed and $\dot{V}O_2$ (Woolf-May and Ferrett, 2008; Woolf-May and Meadows, 2013). This assumption is contrary to the accepted findings of numerous studies (Passmore and Durnin, 1955) (Margaria, et al. 1963, Menier and Pugh, 1968) dating as far back as 1912 (Douglas and Haldane, 1912), which consistently report a curvilinear increase in $\dot{V}O_2$ in response to increased walking speed.

Figure 5.1 Oxygen cost of the *Incremental Shuttle Walk Test* (ISWT) in cardiac rehabilitation participants and age-match healthy controls



Just as the historical data have shown, upon simple visual examination of the more recent ISWT data (Figure 5.1), there is clearly a curvilinear relationship between $\dot{V}O_2$ and walking speed. The curvilinearity of these values is made very apparent when the linear ACSM equation (ACSM 2013) is plotted as a reference line. The responses of heart rate (HR) and ratings of perceived exertion (RPE) reported by Woolf-May and Meadows (2013) (Woolf-May and Meadows, 2013) also demonstrated clear and corresponding curvilinear patterns, confirming the traditional assumption that these measures are strong correlates of measured $\dot{V}O_2$. The $\dot{V}O_2$ values in Figure 1 for the ISWT have been reported from stages 1 to 9. Stages 10 to 12 have not been included because these represent speeds for running (4.7 – 5.0 mi.h^{-1} or 7.5 – 8.0 km.h^{-1}), which traditionally have been shown to have a linear relationship with $\dot{V}O_2$ (Falls and Humphrey, 1976).

The disparity of findings between studies, the potentially flawed assumption of a linear relationship and the inadequacy of prediction equation to estimate the ISWT's oxygen cost are problematic. Further data are needed to promote confidence in cardiac rehabilitation professionals when wishing to apply assumptions of the $\dot{V}O_2$ values in patients who have been assessed with the ISWT.

5.2. Aims

The aims of this study have therefore been two-fold: i. to determine if $\dot{V}O_2$ responds in a linear or curvilinear manner to increases in walking speeds during the ISWT and ii: to resolve current discrepancies in reported values for the oxygen cost of commonly-completed stages of the ISWT in cardiac patients.

5.3. Methods

5.3.1. Participants

Following ethical approval from, cardiac rehabilitation participants from two community-based cardiac rehabilitation programs both of which adhered to national standards of service delivery (BACPR, Buckley et al. 2013) were recruited via open invitations to any patient diagnosed with and being treated for cardiac disease as per national guidelines (NICE 2013). Inclusion criteria were based on standard eligibility for a UK cardiac rehabilitation service (BACPR 2012). Patients were excluded from participating for the following reasons: an auditory impairment which did not allow them to hear the audio shuttle-pacing bleeps of the ISWT; cognitive impairment which prevented them from understanding how to perform the test or comprehend instructions to remain in independent control of their walking pace; a diagnosis of heart failure or chronic obstructive pulmonary disease which would affect normal pulmonary responses to exertion; or a significant neuro-musculoskeletal or vascular condition which impaired them from being able to safely perform and complete at least five stages of the ISWT whilst comfortably tolerating walking up to a steady vigorous pace. Age-matched controls were recruited, under the same exclusion criteria as the CHD patients, from people already attending the same community center either for personal health-promoting exercise or as participants from their local primary-care Exercise Referral program who had been referred for an elevated risk of cardiometabolic disease.

For 85% power, a $\dot{V}O_2$ of 1.75 $ml.kg^{-1}.min^{-1}$ was determined to represent a clinically important difference in oxygen cost, based on our pilot data (Almodhy, et al. 2014). In conjunction with this clinical significance and where participants were assumed to have enough fitness to complete five stages at an estimated $\dot{V}O_2$ of 14 $ml.kg^{-1}.min^{-1}$, 30 participants per group were deemed suitable for achieving the effect-size of at least 10% and an alpha of $p< 0.05$ and β=0.8.

5.3.2. Procedures

Prior to testing, all participants were health screened for clearance to perform moderate to vigorous exercise by way of standardized procedures (BACPR 2014, ACPICR 2015), which were employed by qualified cardiac rehabilitation staff. Measurements included resting heart rate, blood pressure, height, age and body mass, where all of these were also required for measuring the cardiopulmonary gas exchange.

All participants performed the recommended ISWT practice test (Singh, et al. 1992, Jolly, et al. 2008), which also included familiarization in wearing the respiratory face-mask though not connected to the gas analysis system. Participants then rested for the required 30 min before performing the actual data collection test. The test end-point, in keeping with current recommendations (SIGN 2002, ACPICR 2015) was the attainment of 75% of heart rate reserve (~80-85% HRmax) and/or an RPE of 14-15 on Borg's scale(Borg 1998). During the ISWT, cardiopulmonary gas exchange was measured continuously via a portable gas analysis system (K4b2 Mobile Breath by Breath Metabolic System, COSMED Rome, Italy). The expired air and gas concentrations were measured via a pneumotach connected to the face-mask (Hans Rudolph Ltd, USA.). The system was calibrated for each participant using known concentrations of oxygen and carbon dioxide and a three-liter syringe to calibrate for the volume of pulmonary air exchanged. Heart rate was measured using a Polar chest strap telemetry system (Polar Ltd., Kempele, Finland). For data analyses, the average $\dot{V}O_2$, heart rate and RPE captured in the last 15 seconds of each of the one-minute stages was recorded and entered into the statistical analyses computer software package (SPSS for Windows, version 20).

Ethical approval: “All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

5.3.3. Data analyses

Descriptive data are shown in table 5.1. Independent *t*-tests were performed to compare data between the cardiac group and the aged matched controls.

Using the curve estimation function in SPSS, we compared whether linear or exponential regression models explained more of the variance in $\dot{V}O_2$ according to ISWT stage. One-sample *t*-tests were used compare measured MET values with group-mean values from previous studies.

5.4. Results

Thirty-two cardiac rehabilitation participants and 30 age-matched controls completed the ISWT to Stage-5 or higher. Group comparisons are summarized in Tables 5.1 and 5.2.

Table 5.1 Descriptive characteristics of participants (mean ±SD)

	Cardiac group	**Age-matched controls**
N	32	30
Sex (male)	18 (56%)	11 (35%)
Age (years)	64.5 (±7.8)	63.4 (±8.6)
Height (cm)	173.1 (±8.2)	168.8 (±7.1)*
Mass (kg)	85.4 (±11.2)	78.7 (±16.9)
Body mass index (kg/m^2)	28.6 (±3.2)	27.6 (±5.2)
Walking distance - meters:		
Male	548 (±183)	687 (±158) **
Female	464 (±152)	650 (±192) **
Total	512 (±173)	664 (±179) **

Age-matched controls walked 152 m further (p<0.001) than cardiac patients (Table 2) and this difference remained when participants were divided into sub-groups of males and females.

Table 5.2. Participants' clinical characteristics and treatments.

Cardiac group	*N*	**Age-matched controls**	*N*
Angina	3	Hypertension	4
Myocardial infarction	7	Orthopedic	5
Angioplasty	8	Obese	3
Coronary bypass	9	Smoking	2
Others	5	Others	3
		Nothing reported	13

CHD others: atrial fibrillation; dilated cardiomyopathy; pacemaker; valve replacement. *Age-matched controls others:* stroke; chronic fatigue; diabetes control versus cardiac group **p* = .032 , ***p* ≤ .001

5.4.1. Oxygen cost of ISWT in cardiac patients and age-matched controls.

Within the control group, a subgroup analysis was performed between those with identified health conditions (n = 17) and those without (n = 13). There was no difference in the oxygen cost of walking in these two groups at any stage, which allowed the data to be pooled into one complete control group (*n*=30). Analyses of the data was capped at ISWT Stage-9 so as to focus on the evaluation just for walking; all participants who proceeded onto to Stage-10 or higher had to run, which is commensurate with a similar walk-run threshold reported in classic studies (Falls and Humphrey 1976).

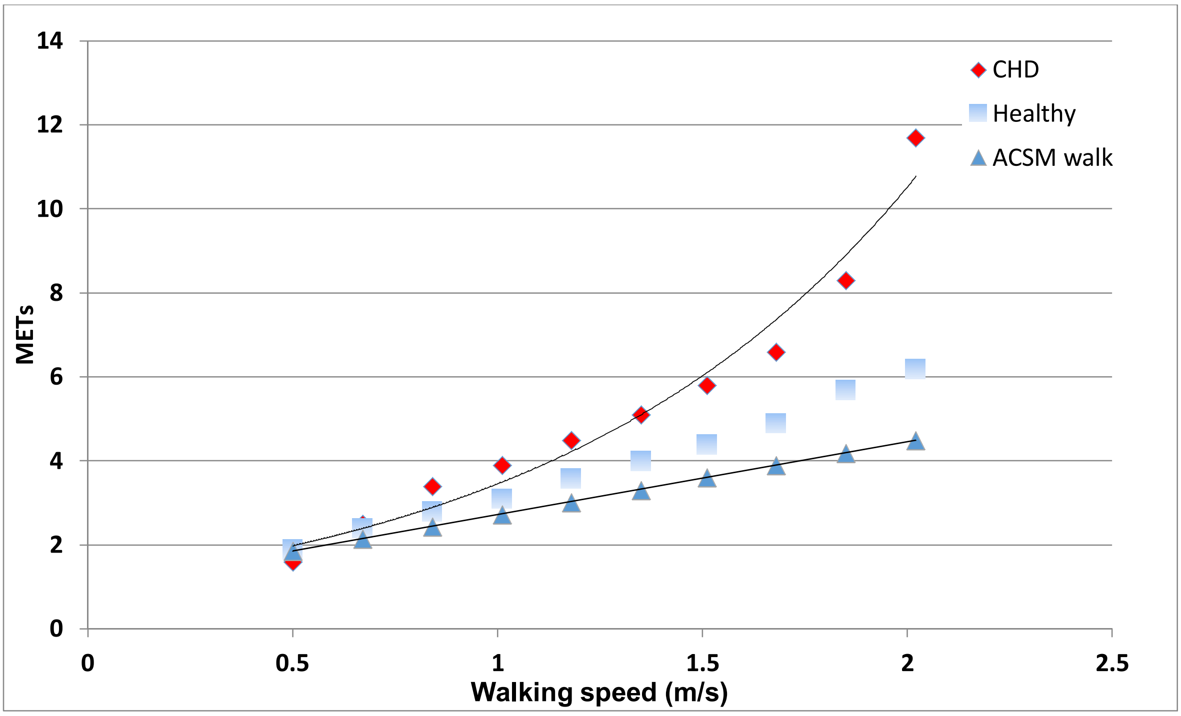
Table 5.3 Oxygen cost of ISWT in cardiac patients versus healthy, age-matched controls mean: difference in MET's

ISWT Stage	Walking Speed (mph)	Sample Size (Cardiac:Healthy)	Mean difference	95%CI
1	1.12	32:30	-0.2	-4.4 *to* -0.1
2	1.50	32:30	0.1	-1.5 *to* 0.4
3	1.88	32:30	0.4	0.1 *to* 0.7
4	2.26	32:30	0.6	0.2 *to* 0.9
5	2.64	32:30	0.6	0.2 *to* 1.0
6	3.02	27:30	0.7	0.2 *to* 1.2
7	3.40	21:30	1.0	0.4 *to* 1.5
8	3.78	17:30	1.3	0.6 *to* 2.1
9	4.16	11:30	1.9	0.9 *to* 3.0
10	4.54	0:30	5.5	4.2 *to* 6.8

5.4.2. Comparison of Linear versus Curvilinear Models to Describe Oxygen Cost of ISWT.

In healthy individuals the exponential and the linear model explain both at same level the oxygen consumption in performing the ISWT. The linear model (y= 0.47 + 2.75 x m/s) had an R^2=.989 and the exponential model (y=1.435e$^{.743 \text{ x m/s}}$) had an R^2=.988. In cardiac patients, linear regression did not adequately describe the response and the best model to describe the oxygen consumption when performing the ISWT was exponential (y= 1.138e$^{1.138 \text{ x m/s}}$) with a R^2= .962.

Figure 5.2. Comparison of oxygen cost of ISWT estimated from ACSM equation (linear) with measured values in cardiac patients (exponential) and age-matched controls (linear or exponential)



5.4.3. Conversion to metabolic equivalents (METs) for cardiac groups

For the purposes of practically applying this information in monitoring or guiding exercise intensity in cardiac rehabilitation, Table 5.4 summarizes the oxygen cost in units of METs at each ISWT stage. These values are based on the assumption that 1-MET equals a $\dot{V}O_2$ of 3.5 ml·kg^{-1}·min^{-1} (Ainsworth, Haskell et al. 2011). MET values from Almodhy et al. (2014) agree most closely with this current study where the mean difference for Stages 1 to 8 is 0.2 METs (range 0.1 – 0.4 METs). At Stage-9 the values differed by 0.7 METs.

Compared with this current study, Table 5.4 shows that the Woolf-May and Meadows (2013) cardiac participant values were lower at all stages; 0.6 METs lower at Stage-2, increasing to 1.7 METs lower at Stage-8 and 2.6 METs at Stage-9. In comparing this current study's values to the original study on METs by Woolf-May and Ferrett (2008), this range of differences was of a similar magnitude to Woolf-May and Ferrett (2008) but these values were systematically greater across the nine ISWT stages ranging in difference by 0.8 to 2.0 METs, respectively.

Table 5.4 Metabolic equivalents (METs) derived from the oxygen costs of the *Incremental Shuttle-Walking Test* in cardiac rehabilitation participants; current findings compared with previous studies.

ISWT Stage	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
ISWT walking speed mph (m·min^{-1})	1.1 (54.5)	1.5 (40.0)	1.9 (31.6)	2.3 (26.5)	2.6 (22.7)	3.0 (20.0)	3.4 (17.6)	3.8 (15.8)	4.2 (14.3)
METs Cardiac Groups Mean ± SD (n)	**1.7 ± 0.4** (n=32)	**2.5 ± 0.5** (n=32)	**3.2 ± 0.6** (n=32)	**3.7 ± 0.7** (n=32)	**4.2 ± 0.9** (n=32)	**4.8 ± 1.0** (n=27)	**5.5 ± 1.0** (n=21)	**6.3 ± 1.3** (n=17)	**7.6 ± 1.7** (n=11)
Almodhy et al (2014)	2.0	2.7	3.1	3.6	4.0	4.4	5.3	6.1	6.9
Woolf-May & Meadows (2013)	0.7	2.1	2.6	2.9	3.1	3.6	4.2	4.6	5.1
Woolf-May & Ferret (2008)	2.5	3.8	4.3	4.8	5.5	6.3	7.5	8	8.2

5.5. Discussion

The ISWT is widely used during patient assessment at entry to and exit from outpatient cardiac rehabilitation. This most recent study on the oxygen costs of walking during the ISWT in cardiac rehabilitation patients provides the first comprehensive comparison of a new data set with data from similar studies. We believe this is the first critique of such studies against the historical background of classic studies on the energy costs of walking.

The present data demonstrate that the oxygen cost of over-ground walking responds as a positively accelerating (curvilinear) function of speed which is independent of: testing protocol, participant age and clinical status. In light of this finding from our data alone or when combined with findings from extant studies which have reported this phenomenon for over a century, it is surprising that the ACSM continues to recommend the use of a linear regression equation to predict oxygen cost of walking (ACSM 2013). Such existing linear equations clearly and consistently underestimate VO_2 for walking speeds >2 $mi \cdot h^{-1}$ (>3 $km \cdot h^{-1}$)

From a clinically significant effect-size perspective, however, the values were close to those of the pilot study. (Almodhy, et al. 2014), which supports confidence in the recommended regression equation (Table 5.4) to be used by cardiac rehabilitation professionals.

The first study in this area (Woolf-May and Ferrett, 2008), reported much higher VO_2 values in cardiac participants when compared with data from all the other measures of cardiac groups (including this current study). It would now seem that their values appear systematically inflated from some potential anomaly in their measurements.

A general pattern now appearing from the four data sets of comparing the VO_2 in cardiac participants to age-matched controls during the ISWT is that most cardiac participants require an oxygen uptake of up to 30% more than age-matched controls, which is mainly found in the final three walking stages assessed (7, 8, 9).

The limitation in economy and higher oxygen consumption to exercise seen in CHD doesn't seem to be cause by any locomotion dysfunction, as motor pattern in ISWT performance was similar in age-match control, when performance was simply observed. The arteriosclerosis progression to CHD, promotes structural and metabolic dysfunction of the all cardiovascular system. Differences between CHD patients and age-matched control in the structure and metabolism of heart, peripheral circulation system and skeletal muscles, can be the cause and the explanation, for higher and less economical oxygen consumption in CHD patients when compared with age-match control, for same exercise intensity. CHD patients have limited endurance (aerobic) exercise performance. Heart is dysfunctional by the loss of the myocardial performance, resulting in poor increasing of cardiac output response to exercise intensity, leading to skeletal muscle hypoperfusion and lactic acidosis, causing fatigue and exercise intolerance. The limited response of the myocardial performance to the progressive oxygen demands in skeletal muscle exercising, seems to be the major limitation in CHD patients to exercise performance, still this lost in myocardial function doesn't fully explain the higher oxygen consumption by CHD patients compared with age-match control exercising at same intensity.

Skeletal muscle metabolism and structure dysfunction main explain further differences in oxygen consumption between cohorts in this study. Chronic diseases such as chronic pulmonary, renal disease, heart failure, have higher impact, and worsening of sarcopenia which is represented with loss of skeletal muscle strength and muscle mass with advancing age (decreased motor units, growth hormones, insulin-like growth factors, and impaired mitochondrial function) (Zizola and Schulz 2013). This is also seen in CHD patients (Ghroubi, et al. 2007). Chronic inflammation developed in heart failure, release inflammatory mediators into the circulation that further activate systemic inflammation, promoting muscle atrophy, fatty infiltration and decreased oxidative enzyme levels, what reduced oxidative metabolism with an earlier shift to glycolytic metabolism. Is also seen an alteration of fibre composition with an increased number of Type II fibers (anaerobic, glycolytic) as compared to Type I (aerobic, oxidative) (Zizola and Schulze 2013). Fibre shift has been found to happen also in COPD patients (Gosker, et al. 2007; Vogiatzis, et al. 2011; Maddocks, et al. 2014). This may be an explanation also for the abnormally low peripheral oxygen extraction during exercise seen in Heart failure patients. These peripheral mechanisms are also the cause of exercise endurance intolerance in heart failure (Dhakal, et al. 2015; Upadhya, et al. 2015). The explanation to the higher oxygen consumption, and the lake on oxygen economy by CHD patients compared with age-match control exercising at same intensity, can be due to skeletal muscles inefficiency in using oxygen, as described in heart failure and COPD patients. There is a need for further research in muscle dysfunction, as explaining the full extent changes in muscle structure, function, and metabolism, in CHD patients.

Chapter 4 and our previous work (Pepera, et al. 2013) explored anthropometric factors of height, body mass and body mass index, which can influence ISWT performance but they did not directly measure $\dot{V}O_2$. Taller individuals were found to perform better, and this relationship increased in strength at higher speeds. In this current study however, the cardiac group were significantly taller (Table 5.1) and yet were still less economical in $\dot{V}O_2$ than the control group; and there was no between-group differences in body mass index.

Another phenomenon, which is not accounted for in all the ISWT data sets thus far, is that the ISWT stages are only one-minute in duration. In healthy individuals exercising at a constant intensity, a duration of between 40 and 60 s is required for VO_2 to rise to a submaximal constant, where in patients with cardiovascular disease this can take up to 90 s (Koike, et al. 1998; Tajima, et al. 2009). Under beta-blockade, which is standard treatment for patients with ischemic heart disease or heart failure, the VO_2 kinetics are also slowed (Dodd, et al. 1988; Kowalchuk and Hughson, 1990). In all these cases affected by disease or medication, or both, the $\dot{V}O_2$values during the one-minute stages of the ISWT should theoretically be diminished in cardiac patients; therefore the differences in cardiac versus healthy controls could potentially be even greater than what is currently being reported. Future studies in comparing $\dot{V}O_2$between cardiac and healthy controls at a point after the $\dot{V}O_2$-slow component (Poole and Jones, 2012) are required to determine a possible correction factor if practitioners wish to transpose exercise intensity information from the ISWT in to steady-state exercise prescriptions.

5.5.1. Potential Impact of Findings on Use and Interpretation of the ISWT in Cardiac Rehabilitation Patients

It is clear that the ACSM equations should not be used to estimate oxygen cost of the ISWT and this recommendation also looks likely to be extended to walking speed in all adult populations. The acceptance of linear predictions of oxygen costs means the estimates of improvement in VO_2 in patients attending cardiac rehabilitation following an ISWT could be underestimated.

5.6. Conclusion

In light of historical studies on the oxygen costs of walking and then comparing and critiquing the current results and those of previous similar studies on the ISWT, there is further confirmation of the curvilinear nature of VO_2 as a function of walking speed. During the ISWT, it appears that cardiac rehabilitation participants have a VO_2 up to 30% higher than age-matched controls. Together, these findings suggest studies may have underestimated the VO_2 of cardiac patients as well as improvements in VO_2 following a program of exercise-based cardiac rehabilitation. In estimating VO_2 from the walking speeds of the ISWT in cardiac rehabilitation participants, the following median equation has been derived: $VO_2 = 4.5e^{0.37 \cdot \text{walking speed (mph)}}$.

Future work is required to make similar evaluations in other populations, which use the ISWT as an outcome measure and physical activity intensity guidance. In more accurately achieving the transposition of the relationship between walking speed and VO_2 (METs) during the ISWT to physical activity guidance, a correction factor may be required to accommodate the limited oxygen kinetics information that coincides with only one-minute stages of the ISWT.

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Chapter 6- Predictors of change in exercise capacity in ISWT and incremental treadmill test in cardiac patients

Abstract

Objective: Identifying characteristics of the exercise-based CR program itself which are associated with improved or worsened changes in fitness, as identifying both modifiable and non-modifiable individual characteristics which influence patients' fitness response to exercise training can aid goal setting, prescription and evaluating exercise prescriptions, as well as modifying and improving program delivery to maximise potential gains in fitness for patients.

Methodology and results: Five hundred and forty eight patients with clinically stable cardiovascular disease from four outpatient cardiac rehabilitation programs completed ISWT performance at entry to rehabilitation, and 53 MI patients where changes were assessed by treadmill.

There was a significant ISWT change in performance due to CR in male (111 m 95%CI: 100 to 122. M, t=19.9, p<0001) and female (80, 95%CI: 67 to 94 m, t=11.8 p<0001) patients. We analysed males and females separately. Young patients, those who are male and have a longer time between event and pre-test CR, had a lower performance in pre-CR test, have bigger increases in changes in performance in exercise tests, may benefit more from CR than older patients, those with a high pre-test performance, female patients with a high waist circumference and smoking habits, who have lower changes in exercise test performance.

Patients who were older, had a higher baseline ETT performance and those taking diuretics had smaller improvements in ETT performance. Attending more exercise sessions was associated with a larger change in ETT performance from baseline to retest at the end of their CR programmes.

Conclusion: It is recommended CR exercise should be provided in same sex and age sessions. The dose of exercise should be increased in women and elderly patients if exercising in mixed-CR groups. In sex/age-tailored CR groups, patients with low baseline fitness and a high waist circumference, who are smokers, should have a higher dose of exercise than others. Patients with high baseline fitness can be fast-tracked to CR community bases. Further investigation is needed to understand the right dose of exercise according to patients' individual characteristics and needs.

Key words: Exercise capacity; incremental shuttle walk test; treadmill exercise test; predictors of change; cardiac patients; fitness improvements.

6. Introduction

Cardiac Rehabilitation programs (CR) are effective in improving cardiorespiratory fitness (fitness), the meta-analysis in Chapter 3 (Sandercock, et al. 2011) demonstrated a gain of 1.55 (95% confidence intervals [CI]: 1.21–1.89) metabolic equivalent (MET) improvements in the cardiorespiratory fitness (CRF) assessed by Exercise Treadmill Test (ETT) of patients undertaking exercise-based CR programmes. A magnitude of change of ~ 100 metres in mean distance in performance of ISWT due to exercise-based CR programmes has been reported in several studies (Arnott, 1997; Tobin and Thow, 1999; Fowler and Singh, 2005; Arnold, et al. 2007; Sandercock, et al. 2007; Almodhy, et al. 2012; Sandercock, et al. 2012).

Gains in fitness achieved by patients in CR are closely, inversely, related to patient mortality and morbidity, and evidence is strong and abundant (Williams,et al. 2006; Blair, et al. 1995; Gulati, et al. 2003. These studies show us the cross-sectional associations between fitness and mortality, others studies have demonstrated the degree of impact that fitness gains have on mortality due to CR programmes (Myers, et al. 2002; Dorn, et al. 1999; Kavanagh, et al. 2003; Vanhees, et al. 1995, Keteyian, et al. 2008)

CR is effective in increasing changes in fitness (ΔFitness) in all patients (females and males), and in all age groups (young < 65 years, elderly-young 65-75 years or elderly >75), however changes in fitness are not of the same magnitude in all patients (Ades, 2001; Lavie and Milani, 2004; Audelin, et al. 2008). The degree of ΔFitness due to an exercise-based CR program depends on patients' individual non-modifiable characteristics such as age and gender, as reported in Chapter 3 (Sandercock, et al. 2011).

The impact of age on ΔFitness assessed by ETT, has been reported previously with abundance in literature, where some studies reveal no significant differences in age groups on ΔFitness (Balady, et al. 1996; Lavie, et al. 1993; Lavie, et al. 1995), others report that older patients have higher ΔFitness than younger patients (Ades and Grunvald, 1990; Ades, et al. 1993; Lavie and Milani, 1996; Lavie and Milani, 1995).

Higher ΔFitness in younger compared with elderly CHD patients have been fully reported in more recent studies, where they were assessed by ETT, (Williams, et al. 1985; Lavie and Milani, 2001; Sandercock, et al. 2011; McKee, et al. 2013, St. Clair, et al. 2014; Beckie, et al. 2013) by cycle ergometer test (Marchionni, et al. 2003); or 6 m walk test (Maniar, et al. 2009; Listerman, et al. 2011). In ISWT no predictors of change in performance have been assessed yet, only older age associated with less change in performance in cardiac patients (Almodhy, et al. 2012).

The same magnitude of ΔFitness between genders has been reported (Balady, et al. 1996); (Lavie and Milani, 1997), however differences according to genders have also been reported recently, females have less ΔFitness than males (Mckee, 2008; Sandercock, et al. 2011; Savage, et al. 2008; St. Clair, et al. 2014).

The degree of ΔFitness due to an exercise-based CR programme depends also on patients' individual modifiable characteristics. High baseline fitness with high patients' initial test score at entry at CR is negatively associated with ΔFitness. This fact has been shown (Beckie, et al. 2013; Mckee 2008; Lavie and Milani, 1994; Ballady, et al 1996; McKee, et al. 2008, 2013) and at 6 months follow-up from CR (Pierson, et al. 2004). A negative influence on ΔFitness was seen previously by waist circumference (Beckie, et al. 2013), BMI (Lavie and Milani, 1996) and the presence of diabetes (Milani and Lavie, 1994; Milani and Lavie, 1996; Savage, et al. 2008), low hand grip strength (Savage, et al. 2008), smoking (Weinberger, et al. 2014), BMI and smoking status at 6 month follow-up (Lee, et al. 2002).

Chapter 3 identified some of the characteristics of the clinical service that can also influence the ΔFitness in patients involved in CR. Programmes had variables able to promote optimal stimulus and higher ΔFitness, such as including n≥36 sessions in the cardiac rehabilitation programme of aerobic, or mixed aerobic, and resistance exercise with a programme length of 12 weeks. No evidence of additional benefits to patients was found for longer cardiac rehabilitation programmes, and no evidence for combining exercise training with patient education (comprehensive cardiac rehabilitation), and improvements in ΔFitness. ETT protocol used to assess ΔFitness in patients has a major impact on the estimate of ΔFitness and it is difficult to compare studies which use different testing protocols.

The ability to predict changes in exercise from performance in different types of testing of a (ISWT or Exercise Treadmill test) is a practical clinical necessity to better prescribe the dose of exercise and evaluate the exercise prescription, and to better tailor CR programmes according to patients' individual differences and needs.

6.1. Aims and hypothesis

Just as variables other than cardiorespiratory fitness are unlikely to account for the majority of variance observed in the ISWT performance, there is little value in attempting to create accurate predictive models of ΔFitness. The aim of this chapter is to identify non-modifiable and modifiable predictors of change in ISWT for the first time, and discriminate further predictors of change in performance assessed by Exercise Treadmill Test performance in post-outpatient CR patients (post-CR).

6.2. Methods

6.2.1. Participants

We accessed clinical records of n=547 (415 males) (76% male) patients (63.1 ± 11.3 years) who completed outpatient cardiac rehabilitation at four UK hospitals: (In Greater London, Essex, Cumbria and Middlesex) and extracted clinical data and details of 10 m ISWT performance at exit from rehabilitation. Table 4.2 gives the clinical characteristics and baseline measurements, diagnosis and reasons for attending CR of cohorts, presented in chapter 4.

We accessed clinical records of n=51 (44 males) (86% male) patients (63.1 ± 11.3 years) who completed outpatient cardiac rehabilitation (from May 2011 to November 2012 at the Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal), and extracted clinical data and details of Exercise Treadmill Test performance at exit from rehabilitation. Those aged ≥18 years, men and women, referred to the Hospital Cardiology Department after an acute MI. Exclusion criteria included the presence of uncontrolled cardiac arrhythmias, unstable angina pectoris, uncontrolled hypertension, significant valvular disease, diagnosis of heart failure, uncontrolled metabolic disease (e.g. uncontrolled diabetes and thyroid disease), presence of pulmonary and renal comorbidities, conditions limiting participation in exercise training (e.g. peripheral artery disease, orthopaedic limitations, and musculoskeletal disorder), abnormal hemodynamic responses, myocardial ischemia, and/or severe ventricular arrhythmias during baseline exercise testing. Table 6.2 gives the clinical characteristics and baseline measurements, diagnosis and reasons for attending CR of cohorts.

6.2.2. Procedures and data collection

Data collecting and ethical approval for this study was the same as presented in Chapter 4 for the ISWT cohort. The ISWT cohort had a core component of supervised exercise training and some aspect of formal patient education or counselling on lifestyle change. The services used mixed circuit-based (aerobic and resistance) exercise training sessions of 60 min duration, including a 15 min warm-up and cool-down performed at the beginning and end (SIGN 2002). The CR programmes were 6 to 8 weeks long, and based on one exercise session a week on average. Our median time from event to ISWT was 53 days.

Data for the ETT group was collected at one hospital which reported delivering comprehensive CR and routinely using the Exercise Treadmill Test in accordance with national guidance. The ethical approval for this study was obtained by the Hospital Ethics Committee (reference 627/2010). All procedures were conducted according to the Declaration of Helsinki, and the trial has been registered at ClinicalTrials.gov (NCT01432639).

Every patient who agreed to participate in the study provided a written informed consent. In brief, 4 weeks after an acute MI, consenting patients were assigned to an exercise-based CR exercise training, based on 3 supervised exercise sessions per week for 8 weeks (10 minutes of warm-up, 30 minutes of aerobic exercise on a cycle ergometer or treadmill at 70%-85% of maximal heart rate achieved in the exercise test and 10 minutes of cool-down). During the exercise sessions, the participant’s heart rate was continuously monitored by electrocardiogram, and levels of exertion were assessed with the Borg scale. In addition, these patients were also under the usual medical care and follow-up (e.g. regular appointments with a cardiologist and optimised medication).

6.2.3. Statistical analysis

Pearson Product Moment Correlation was used to examine the relationship of possible and logical predictors, with performance measured in both types of assessment, ISWT and Exercise Treadmill Test (ETT). Predictors of change in ISWT and ETT performance were identifed in the population as a whole, and an independent t-test was used to describe the difference in male and female test performance in the data from the cohort assessed by ISWT, as the data from the cohort assed by ETT did not have a sufficient number of females to discriminate between sexes.

After differences were affirmed, we performed enter multiple regressions to determine significant predictors of change in performance in the ETT group, and in the ISWT group by males and females. We assessed predictors for collinearity; defined as variance inflation factor >4.0 (Rogerson 2001). Statistical significance was set at $p<0.05$ and all analyses were performed using SPSS 19.0 (SPSS, an IBM Company, Armon, NY).

6.3. Results

6.3.1. Cohort performance assessed by ISWT

There was an overall ISWT change in performance due to CR, 365 ±164 m in pre-CR and 468 ±194 m in post-CR. Independent t-tests verified a significant difference of change in performance 104 ±107 m (95%CI 94.7 to 112.7, t=22.7, p<0001).

There was a significant ISWT change in performance due to CR in both sexes. Independent t-tests showed a significantly (t=19.9, p<0001) greater change in performance in males (111 95%CI 100 to 122 m), than females (80 ±79 95%CI 67 to 94 m).

We analysed males and females separately. Results of multivariate regression (Enter Method) are given in table 6.1 with predictors given in order of magnitude. Age was the best predictor of change in ISWT performance in males. Time from event to pre-test (days) predicted more changes, and higher pre-rehabilitation distance achieve in ISWT was a predictor of less change in ISWT performance. However, this model explained only 7.8% of variance for change in ISWT performance in men.

Age also predicted change in females but was less powerful than baseline ISWT performance. Waist circumference and smoking were both negatively associated with change in ISWT performance. This model explained 28% of the overall variance observed for change in ISWT performance in women.

Table 6.1. Predictors of change in ISWT performance due to CR

Predictors in males	***β***	***R^2***	***S.E.E (m)***
Age (years)	*β*= -2.91 m (95%CI -4.1 to -1.7)		
Event to CR (days)	*β*= 1.43 m (95%CI 3.1 to 6.8)	.078	111
Baseline ISWT (m)	*β*= -0.10 m (95%CI -1.72 to -0.25)		

Predictors in females	***B***	***R^2***	***S.E.E (m)***
Baseline ISWT (m)	β= -0.19 m (95%CI -0.30 to -0.10)		
Age (years)	β= -1.83 m (95%CI -2.9 to -.74)		
Waist circumference (cm)	β= -0.42 m (95%CI -0.7 to -.11)	.288	61
Smoking	β= -31.6 m (95%CI -61.3 to -1.8)		

6.3.2. Cohort performance assessed by ETT

Table 6.2. Descriptive characteristics of Cohort assessed by ETT

Clinical characteristics and baseline measurements	***Mean (SD)***
Number of patients	**51**
Age (years)	**55.4 (± 3.4)**
Gender (males)	**44 (86.3%)**
Height (cm)	**167.8 (± 8.6)**
Weight (Kg)	**76.7 (± 10.8)**
Body Mass Index (kg/m^2)	**27.3 (± 3.8)**
Diabetes	**11 (21.6%)**
Smoking	**24 (47.1%)**
MI	**51 (100%)**
CABG	**48 (94.1%)**

ETT performance improved from 514.5 ±148.8 s pre-CR to 600.5 ±160.3 s at post-CR. Paired t-test showed the mean difference in ETT performance 85.9 95%CI: 64.0 to 107.8) was statistically significant, (t=7.89, p<0001).

Results of the enter multivariate regression model is given in table 6.3. Patients who were older, had a higher baseline ETT performance and those taking diuretics had smaller improvements in ETT performance. Attending more exercise sessions was associated with a larger change in ETT performance from baseline to retest at the end of their CR programmes.

Table 6.3. Predictors of change in ETT performance due to CR

Predictors of change	*β*	R^2	*S.E.E (s)*
Age (years)	*β*= -3.29 (95%CI -5.4 to -1.1)		
Baseline ETT (s)	*β*= -.205 (95%CI -.36 to - .04)	0.31	67.2
Diuretics	*β*= -.73.1 (95%CI -137 to -8.4)		
Number of CR sessions	*β*= 6.82 (95%CI 7.4 to 12.9)		

Legend: ETT – exercise tolerance test. Diuretics (Y/N) Number of CR sessions (out of maximum value of 24)

6.4. Discussion

The National Audit of Cardiac Rehabilitation (NACR) shows UK programmes cater for a wide age-range of patients of both sexes who may present with numerous clinical diagnoses and any number of comorbidities (Doherty 2014). As would be expected in such a varied population, patients' ISWT performance is highly heterogeneous when assessed at the start of cardiac rehabilitation (Arnold, et al. 2007; Sandercock, et al. 2007; Sandercock, et al. 2012; Sandercock, et al. 2013) and the same is expected at exit of CR programmes. Despite evidence that performance differs by age and sex in healthy adults (Jurgensen, Antunes et al. 2011; Probst, Hernandes et al. 2012; Harrison, Greening et al. 2013), and supported by the findings of chapter 4 in predictors of performance in ISWT in cardiac patients, although there are no reference predictors to explain the heterogeneity seen in changes in performance in ISWT due to CR.

The aim of this study was to aid interpretation of changes in performance in CHD patients due to CR programmes, in exercise capacity measurements, in two different cohorts, one using the ISWT and other a Modified Bruce Treadmill Protocol Exercise Tolerance Test (ETT). Both cohorts analysed by us had significant improvements in exercise capacity in a post-CR test. The performance of Old patients and patients with higher baseline performance increases less due to CR. Age and Baseline performance are strong predictors of change in both genders in the ISWT cohort and ETT cohort. In ISWT cohort males who wait less than 12 weeks to start CR after an event, females with a bigger waist circumference and who smoke, were both negatively associated with change in ISWT performance. In the ETT cohort, those taking diuretics had smaller improvements in ETT performance, and those attending less exercise sessions.

6.4.1. Predictors of change in performance

6.4.1.1. Non-modifiable predictors

6.4.1.1.1. Gender

This study was able to discriminate predictors of change in performance of ISWT according to sexes. The performance of males changes more than that of women. This effect in sexes on the magnitude of changes assessed by ETT has been reported before by us in chapter 3 and elsewhere (St. Clair, et al. 2014; Mckee, 2008; Sandercock, et al. 2011; Savage, et al. 2008). Sex was not a predictor of change in performance assessed by ETT in our cohort, maybe due to the inclusion of only 7 women in the cohort of 51 patients assessed, not possessing enough power of analysis to discriminate differences between sexes.

There are no physiological reasons that justify males having more adaptation in exercise capacity due to CR than females, as seen in our findings in changes in performance assessed by ISWT. However, as discussed in chapter 3, more deep epidemiological and clinical studies report that women have worse CVD clinical profile as prevalence, worse presentation (symptoms and age of onset), worse disease outcomes, and worse disease management and rehabilitation, possessing more comorbidities, although not much is known why CVD affects genders differently (Mikhail 2005; Pilote, et al. 2007).

Women with CHD also have adverse psychosocial profiles, poor attendance at CR programmes, and specific gender biopsychosocial barriers to CR than men, as discussed in chapter 3 already and elsewhere (Beckie, et al. 2009). Randomised studies in females completing a tailored programme that included motivational interviewing guided by the Trans-theoretical Model (TTM) of behaviour change, and delivered with a motivational interviewing counselling style, compared with females in a mixed-gender CR programme under the same exercise prescription, revealed that the CR programme tailored for women significantly improved global QOL (Beckie and Beckstead, 2010), improved general health perceptions that contribute to healthy behaviours, social functioning, and mental health (Beckie and Beckstead, 2011), such as reduced depressive symptoms (Beckie, et al. 2011), increasing exercise attendance by 4 sessions and education sessions attendance by 31% (Beckie and

Beckstead, 2010). There are several reasons that may justify less responsiveness in ΔFitness due to CR in females then males.

Low level of baseline fitness is another factor associated with disability in females, reported in all studies that assessed changes in performance due to CR by ETT that discriminate genders in results (St. Clair, et al. 2014; Balady, et al. 1996; Lavie and Milani, 1997, Mckee, 2008; Sandercock, et al. 2011; Ades, et al. 2006) and in ISWT (Jurgensen, et al. 2011; Probst, et al. 2012; Harrison, et al. 2013), and supported by the findings of chapter 4 on predictors of performance in ISWT in cardiac patients.

When optimal clinical care and optimal conditions of a comprehensive-CR programme are established, similar changes in fitness in both genders due to the same CR programme have been reported (Balady, et al. 1996), and 1.4 and 1.6 METs change in fitness reported in females exercising in mixed-gender CR (Lavie and Milani, 1997; Beckie, et al. 2013), being of the same magnitude of what is expected in CHD patients responsiveness in fitness due to an exercise-based CR, as found in chapter 3 (Sandercock, et al. 2011). In chapter 3 (Sandercock, et al. 2011) women have higher ΔFitness when exercising in female-only CR compared with females exercising in mixed-gender CR.

Chapter 3 (Sandercock, et al. 2011) reports that males had higher gains in fitness exercising in gender-specific CR, than in mixed-gender CR, or female-only CR. Higher gains in fitness in male-only CR may be an effect of their competitive nature within the group session, making them exercise harder. When males exercise in a mixed-gender CR programme, they may feel distracted, and overwhelmed in the presence of females, or tending to feel shy and less confident, not fully engaging in CR exercise programme (Yohannes, et al. 2007). Females were more likely than males to describe that they limited activities to be “safe for their heart” (Audelin, et al. 2008).

Real CR programmes as in our study, presented in other literature (St. Clair, et al. 2014; Mckee, 2008; Savage, et al. 2008), or in a bigger view given by a meta-analysis done in chapter 3 (Sandercock, et al. 2011), reveal that CR in males increases more than females, which leads to the conclusion that tailoring exercise by gender will optimize ΔFitness outcomes in CR. These findings are important for practitioners in setting goals for patients, they should expect lower ΔFitness in female patients, and lower baseline fitness.

Based on the evidence, important implications for better service delivery (service design, better prescription of the dose of exercise, definition of CR goals, and evaluation of the exercise prescription) are concluded: that although CR should be tailored by sex, females exercising in mix-gender CR will benefit as much for CR as men in ΔFitness, if the dose of exercise (number of exercise sessions) is higher than males. Further research to determine the right dose of exercise is needed in both sexes as sexes also differ in baseline fitness.

Further research is needed to understand why differences in genders are seen in the magnitude of responsiveness to CR programmes. Analysis should focus also on other factors towards CVD behaviour between males and females that may help to explain the influence of differences in genders, such as cultural, psychosocial and socio-economic status (Pilote, et al. 2007). This will help to better design out-patient hospital CR programmes with the intention of optimising fitness changes.

6.4.1.1.2. Age

Like sex, patients' age is a non-modifiable predictor of ΔFitness. Age is a common predictor of change in performance in the ISWT cohort in both sexes, and also in the cohort assessed by ETT. The performance of old patients in exercise tests after CR changes less than that of younger patients, this finding was also reported in chapter 3 (Sandercock, et al. 2011) and elsewhere (Williams, et al. 1985; Lavie and Milani, 2001, Sandercock, et al. 2011; McKee, et al. 2013; St. Clair, et al. 2014; Beckie, et al. 2013), by cycle ergometer test (Marchionni, et al. 2003); or 6 m walk test (Maniar, et al. 2009; Listerman, et al. 2011).

Despite different findings elsewhere, where some studies reveal no significant differences in age groups' effect on ΔFitness (Balady, et al. 1996; Lavie, et al. 1993; Lavie, et al. 1995), others report that older patients have higher ΔFitness than younger patients (Ades and Grunvald, 1990; Ades, et al. 1993; Lavie and Milani, 1996; Lavie and Milani, 1995).

The fact that ageing has a negative effect on ΔFitness in CHD patients, as in our findings, can be also supported by previous literature which reports that elderly patients with CVD have very high rates of disability, as the consequence of CHD disease or pathology, higher recurrent coronary events, and higher health resources use, than people without coronary heart disease. More advanced age (middle age 65-75 years and older age patients 75> years), and especially female patients with clinical manifestations of angina pectoris or chronic heart failure are associated with the highest rates of disability. Older CHD patients suffer more from depression symptoms (Pinsky, et al. 1990, Ades, 2001, Rich, et al. 1992; Ades, et al. 2002; Lavie and Milani, 2004; Audelin, et al. 2008) age is also a predictor of death in CHD patients (Rich, et al. 1992).

Age has a negative impact on cardiac function (decline peak aerobic capacity), and structure as reported in chapter 3. Lack of physical activity is a higher risk factor in older patients for chronic disease and disability, and the cardiac responsiveness due to exercise based-CR is also blunted in older patients. (Stratton, et al. 1994, Heckman and McKelvie, 2008; Ferrari, et al. 2003; Fleg, et al. 2005). This may represent some reduction in physiological adaptability, particularly in the oldest patients, as a possible cause for less ΔFitness in elderly compared with younger patients in post-CR tests when submitted to the same exercise-based CR protocol. In chapter 3 (Sandercock, et al. 2011) the ΔFitness were less than half those of younger patients. Several factors can explain less ΔFitness in elderly patients.

Other factors associated with disability in elderly are a low level of baseline fitness, reported in all studies that assessed changes in performance due to CR by ETT (Williams, et al. 1985; Lavie and Milani, 2001; Sandercock, et al. 2011; McKee, et al. 2013; Marchionni, et al. 2003; Maniar, et al. 2009; Listerman, et al. 2011; Balady, et al. 1996; Lavie, et al. 1993; Lavie, et al. 1995, Ades and Grunvald, 1990; Ades, et al. 1993; Lavie and Milani 1996; Lavie and Milani 1995; Ades, et al. 2006; St. Clair, et al.

2014), and in ISWT (Arnold, et al. 2007; Sandercock, et al. 2007; Sandercock, et al. 2012; Sandercock, et al. 2013), and in ISWT (Jurgensen, et al. 2011; Probst, et al. 2012; Harrison, et al. 2013), and also supported by the findings of chapter 4 in predictors of performance on ISWT in cardiac patients.

These findings are important for practitioners in setting goals for patients, who should expect lower ΔFitness in older patients, and lower baseline fitness, when fitness is shown in absolute terms as in our analysis. If the ΔFitness levels were shown in relative percentage gains, the changes observed in older patients may be equal or even higher that of younger patients due to lower baseline fitness values.

The findings of chapter 3 (Sandercock, et al. 2011), and those reported elsewhere (Williams, et al. 1985; Lavie and Milani, 2001; McKee, et al. 2013; (Marchionni, et al. 2003; Maniar, et al. 2009; Listerman, et al. 2011; St. Clair, et al. 2014) leads us to the conclusion that tailoring exercise by age/sex tailored CR, will optimize ΔFitness outcomes in CR. It is not clear whether there is a need to stratify by group age (<65, 65 to 75 and 75>) or just have a cut-off point for very elderly (65> or 75> years) where the intervention is most needed and mostly depends on the patients' age group being treated.

Based on the evidence, important implications for better service delivery (service design better prescription of the dose of exercise, setting fitness CR goals, and evaluation of the exercise prescription) are concluded, that exercise groups should be according to age group, in gender-tailored CR or when elderly patients exercising in mixed CR, will benefit as much for CR than younger patients in ΔFitness, if the dose of exercise is higher than younger patients.

6.4.1.2. Modifiable predictors

6.4.1.2.1. Baseline fitness

Better initial pre-CR test performance was associated with smaller gains in fitness in both sexes in the ISWT cohort, as in the ETT cohort. Baseline performance in the performance test at entry to CR has also been reported as a predictor of ΔFitness at CR exit assessed by ETT (Beckie, et al. 2013; Mckee 2008; Lavie and Milani, 1994; Ballady, et al 1996; McKee, et al. 2013). The more sedentary an individual is, the more impact and responsiveness he/she will have to the exercise programme and increase in ΔFitness. This finding was expected and represents the often reported phenomenon known as the law of initial values, or regression to the mean reported in Healthy (Bouchard and Rankinen, 2001) and CHD patients (Swain, 2005; Sakuragi, et al. 2003).

These findings are important for practitioners in setting goals for patients. Lower ΔFitness are expected in older patients, and in females, compared with young and male patients due to CR. However, as we report above, based on our findings and elsewhere, the benefit in higher ΔFitness based on low baseline fitness should be interpreted based within age, and sex groups of CHD, e.g. females young patients with a low baseline will increase less than young males with low baseline fitness.

Based on the evidence, important implications for better service delivery (service design, better prescription of the dose of exercise, setting fitness CR goals, and evaluation of the exercise prescription), it is concluded that patients possessing a higher baseline in mixed-CR, or gender-tailored CR, would benefit and optimise their higher ΔFitness, if their exercise programme is based on a lower dose of exercise than patients with lower baseline values at entry to CR, and can be fast-tracked for community CR.

6.4.1.2.2. Diuretics medication

In the CHD, patients on diuretics medication assessed by ETT have less ΔFitness, although these patients were older, and had a worst ejection fraction, revealing signs of heart failure. This predictor of ΔFitness has never been reported before in literature. In the ISWT cohort, there were no changes in performance among patients under this medication.

If it is confirmed, this has important implications for better service delivery (service design, better prescription of the dose of exercise, and evaluation of the exercise prescription). When exercising in mixed-CR, sex/age-tailored CR programmes, patients on diuretics medication would benefit and optimise their higher ΔFitness, if their exercise programme is based on higher volumes of exercise, than patients not taking diuretics.

6.4.1.2.3. Time wait to CR

Bigger changes in exercise performance are associated with male patients who had waited longer to begin CR (time from event to pre-CR test) in ISWT. This is the opposite of what would be expected, as a longer delay should lead to greater spontaneous recovery after event, although this effect is only seen in patients that wait up to 12 weeks, those that wait longer than 12 weeks had a lower baseline, they could become deconditioned while they wait longer, and also improve less than the patients starting CR up to 12 weeks after event. It is not expected as lower baseline is a predictor of higher ΔFitness. In the ETT cohort, the time from event to CR was the same in all patients making it impossible to determine the influence of time to CR in ΔFitness. Although such finding needs to be further investigated.

If it is confirmed this has important implications for better service delivery in men patients mainly (service design, better prescription of the dose of exercise, and evaluation of the exercise prescription) as patients will benefit more from CR if they are enrolled at CR programmes after 12 weeks from event.

6.4.1.2.4. Waist circumference

In the ISWT cohort females with a bigger waist circumference (WC) are associated negatively with change in ISWT performance at CR exit, this fact has been reported in ΔFitness assessed by ETT (Beckie, et al. 2013). Although was not a predictor in males in ISWT cohort neither in ETT cohort. Waist circumference is a measure of central adiposity. The combined effect of high central adiposity and low CRF is particularly significantly associated with increased mortality in CR (Goel, et al. 2011). WC has also been associated as the best anthropometric measure to determine the risk of CVD in men and woman of central adiposity (Pouliot, et al. 1994). Males with a high WC above 102 cm and females above 88 cm are at high risk of a CHD (Balady, et al. 2007).

Higher BMI has also been associated with less ΔFitness (Lavie and Milani, 1996). Obese CHD patients change less in ΔFitness than non-obese CHD patients. Obesity is an independent risk factor for CHD. In the USA at entry over 80% of patients are overweight and over 50% have metabolic syndrome. CR programmes normally do not include a weight loss component as a primary aim and weight loss outcomes in CR are not effective in the reduction of body weight, or only minimal weight loss occurs in CR programmes (Savage, et al. 2000; Ades, et al. 2010).

Different effective approaches and design of CR programmes have been developed to tackle and optimise the reduction of body weight in CR programmes, such as implementing weight changing behaviour counselling sessions in a CR setting, along with high energy expenditure exercise sessions (long duration), and with a high frequency of exercise sessions per week (mostly daily exercise sessions), and longer programmes lengths (12 weeks, 5 months, 12 months), with outpatient CR complemented with home-based CR. Higher ΔFitness are also associated with higher body weight reduction too (Savage, et al. 2000; Ades, et al. 2009; Araya-Ramírez 2010). Effective weight reduction in CHD patients was also reported by just increasing exercise daily (12 months of continuous exercise) without any restriction in diet (Mertens, et al. 1998).

Based on the evidence, important implications for better service delivery (service design, better prescription of the dose of exercise, and evaluation of the exercise prescription) are concluded. Patients with higher central obesity revealed by higher waist circumference or high BMI (BMI 25>kg/m^2 Overweight, or 30> kg/m^2 Obese) when exercising in mixed-CR, sex/age-tailored CR programmes, would benefit and optimize their higher ΔFitness, if their exercise programme is based on higher volumes of exercise (higher frequency, daily if possible, and long duration of exercise sessions per week) done in outpatient CR complemented with home-CR, as literature reports, than patients with lower WC and BMI at entry to CR. Although to optimise the right dose of exercise for these patients further research is needed.

6.4.1.2.5. Smoking habit

In ISWT, smoking was negatively associated with a change in ISWT performance in females, although smoking was not a predictor in men in either the ISWT cohort or in the ETT cohort. CHD patients that were smokers had lower ΔFitness at the end of CR compared with non-smokers, when assessed by ETT (Weinberger, et al. 2014).

Smoking is a major risk factor for CHD morbidity and mortality, and is considered to be the most preventable cause of death in the world. Cigarette smoke contains more than 4000 chemical substances, including nicotine and carbon monoxide (CO) that have harmful effects on cardiovascular function. These tobacco smoke ingredients cause an increase in oxidative stress that promotes endothelial damage and dysfunction, causing intravascular inflammation, which promotes the development of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being largely thrombotic and CHD. (Ambrose and Barua, 2004; Csiszar, et al. 2009, Tomiyama, et al. 2010).

Female smokers have higher risk of CVD than male smokers (Bolego, et al. 2002; Tan, et al. 2010; Wenger, 2003, Weinberger, et al. 2014) and higher CVD mortality than males (Eisner, et al. 2010; Mosca, et al. 2007; Mosca, et al. 2011). A recent meta-analysis showed that female smokers demonstrated a 25% greater risk of coronary heart disease than male smokers after controlling for other CVD risk factors, reported in a meta-analysis (Huxley and Woodward, 2011).

Continuing smoking after a cardiac event greatly increases mortality risk. Smoking cessation and participation in cardiac rehabilitation (CR) are effective in reducing morbidity and mortality, as improvements in endothelial function, which may mediate part of the reduced cardiovascular disease risk reported after smoking cessation. Hospital-based smoking cessation programmes, as well as referral to cardiac rehabilitation, were strongly associated with increased smoking cessation rates (Dawood, et al. 2008). However smoking status also predicted not attending CR and was a strong predictor of CR dropout (Johnson, et al. 2010; Gaalema, et al. 2015). Females have more adverse cardiovascular consequences from smoking, however cessation of tobacco has greater cardiovascular benefits for women compared to men (Mercuro, et al. 2010). Smokers also have lower baseline fitness at entry to CR (Asthana, et al. 2012).

These findings are important for practitioners in setting goals for smoker patients, lower ΔFitness should be expected in smoker patients, and most important in female smokers. Based on the evidence, important implications for better service delivery (service design, better prescription of the dose of exercise, setting fitness CR goals, and evaluation of the exercise prescription) are concluded, that smoker patients, most importantly female patients, when exercising in sex/aged-tailored CR or when exercising in mixed-CR, would benefit and optimise their higher ΔFitness, if their exercise programme is based on a higher dose of exercise, than non-smoker CHD patients.

6.4.1.2.6. Number of Exercise Sessions

The higher number of sessions (dose of exercise=number of sessions) has a positive influence on ΔFitness in the ETT cohort, being a predictor ΔFitness (exercise based CR based on 24 sessions). In ISWT the number of sessions is very low, from 6 to 8 sessions, which may be a reason for not being a predictor in this cohort. The higher responsiveness on ΔFitness with a higher number of sessions was also reported in Chapter 3 (Sandercock, et al. 2011), CR programmes of >36 sessions resulted in higher gains in patients' fitness than when exercising with a lower number of sessions, the total number of exercise sessions represents a good analysis of the exercise dose used in each programme, and more sessions will represent higher fitness gains, this dose-response relationship is seen in several studies done in CR programmes (Miller, et al. 1984; Soleimani, et al. 2009, Reid, et al. 2006). Chapter 3 also revealed that there was no difference in ΔFitness in different CR programme lengths (less than 12 weeks and more than 12 weeks).

Twelve weeks in our analysis in chapter 3 was the both the median and modal values for the subgroup duration, this being the reference value for CR programmes duration supported by guidelines in U.S. (Thomas, et al. 2010), U.K. (SIGN, 2002) or Europe (Piepoli, et al. 2010). Most of the evidence of ΔFitness reported in the literature is based on a 12 week length programme of 36 sessions of comprehensive-CR programmes (Balady, et al. 1996; Lavie, et al. 1993; Lavie, et al. 1995; Ades and Grunvald, 1990; Ades, et al. 1993; Lavie and Milani, 1996; Lavie and Milani, 1995; Williams, et al. 1985; Lavie and Milani, 2001; Sandercock, et al. 2011; McKee, et al. 2013; St. Clair, et al. 2014; Beckie, et al. 2013; Marchionni, et al. 2003); or 6 m walk test (Maniar, et al. 2009; Listerman, et al. 2011; Almodhy, et al. 2012; Lavie and Milani, 1997; Mckee, 2008; Sandercock, et al. 2011; Savage, et al. 2008; St. Clair, et al. 2014, Beckie, et al. 2013; Mckee, 2008; Lavie and Milani 1994; McKee, et al. 2008, 2013; Pierson, et al. 2004;. Beckie, et al. 2013; BMI (Milani and Lavie, 1994; Milani and Lavie, 1996; Savage, et al. 2008; Savage, et al. 2008; Lee, et al. 2002). In unfit individuals, such as CHD patients, most of the gains in fitness are observed in the first 4 to 12 weeks of a training programme. (Miller, et al. 1984; Soleimani, et al. 2009; Wright, et al. 2002).

These findings are important for practitioners for designing CR programmes and in setting goals for patients, the most important is not so much the length of a CR programme, as reported by findings in chapter 3, but the number of exercise sessions performed by the patients, which can also increase in a longer programme depending on the exercise prescription, and group of patients' needs, as e.g. women with high waist-circumference. The basic design is 12 weeks, 36 sessions, with a frequency of 3 sessions a week. Programmes with this length can incorporate more sessions, the progression in the dose of exercise can increase from 3 to 7 sessions a week.

Existing guidelines for CR programmes implementation are available over much of the developed world such as U.S. (Thomas, et al. 2007) and Europe (Piepoli, et al. 2010), UK (SIGN, 2002) although some variation in written guidance, in local understanding of such guidance and financial restrictions show us that CR programmes could be more heterogeneous than we might have thought, when compared for instance with pharmacological intervention. In the ETT cohort, the CR programme was based in 8 weeks, 24 sessions in Portugal, and the ISWT cohort based on 6 to 8 weeks, 6 to 8 sessions in the UK. Both programmes differ from the guidelines proposed.

Based on the evidence important implications for better service delivery (service design, better prescription of the dose of exercise, setting fitness CR goals, and evaluation of the exercise prescription), and as discussed in above sections, it is concluded that the dose of exercise (1 to 7 sessions a week, in a 12 week length CR programme) should be according to the individuals' needs and characteristics of each age-group and sex of CHD patients. Taking into consideration individual differences such as baseline fitness, waist-circumference, and smoking status, should predict if a higher dose of exercise is needed or not. Further investigation is needed to determine the right dose of exercise for each group of patients.

6.4.3. Summary and Applications of Chapter Findings

Patients' mean age (63 ±11 years) is slightly lower than the typical age (66-70 years) of patients reported nationally (Doherty, 2014). The mean age of male patients (62 ±13 years) was close to the national mean value of 66 years but the mean age of our female patients (63 ±17 years) was seven years lower than the national average. Given this age difference, and the smaller sample size the present reference values may be less generalisable for female CR patients than for males. The smaller sample of females is to be expected when accessing data from patient records. Nationally, men account for 70% of cardiac rehabilitation patients slightly lower than the 76% value in our sample. The proportion of white participants (79.5%) was similar to national data (80%). Our median time from event to ISWT was 53 days. Post-MI patients typically start rehabilitation 40 days following treatment with PCI; patients receiving CABG start an average of 54 days after referral (Doherty, 2014). Comparable times for our sample were 42 days (for Post-MI, patients receiving PCI) and 63 days for CABG patients. Again, the both these figures are close to nationally reported values suggesting this was a broadly typical cohort of UK cardiac rehabilitation patients. In Portugal there is no National audit of CR programs.

We confirm in our findings in chapter 4, that performance in ISWT at entry to CR programmes is mostly dependent on non-modifiable predictors such as age and gender. Old, female patients have lower baseline fitness at CR entry. Some predictors of change in performance in ISWT between pre and post-CR are found in this chapter. Age and gender are the best non-modifiable predictors of change in performance in ISWT due to exercise-base CR. Older patients and females change less, or young patients and males change more in performance due to CR. This has several implications for the optimisation of CR service design, better dose of exercise, and evaluation of the exercise prescription. Leading us to the conclusion that CR should be tailored according to sex/age groups, dose of exercise should be increased in women and elderly patients. In sex/age-tailored CR groups, patients with low baseline fitness and high waist circumference, who smoke, should have a higher dose of exercise than others.

6.4.5. Limitations

It was impossible to compare between the ISWT cohort with a final outcome measured in metres, and the ETT cohort with an outcome in seconds. In this study it was also impossible to discriminate between variables of the service of CR in predicting change in performance at exit of CR in CHD patients assessed by ETT or ISWT, as reported in Chapter 3. The only variable assessed of the service was longer time from event to start of CR until 12 weeks in males in ISWT cohort, will predict higher ΔFitness, although further confirmation of this finding is needed. Different predictors such as diabetes and other comorbidities were also impossible to assess in our cohort. There was not enough information in the data to discriminate between differences in dose of exercise and changes in performance in the exercise tests.

There is a need to understand the effect of the different components of dose of exercise on the impact in changes in performance in ISWT and ETT due to CR in cardiac patients, such as the intensity of the exercise prescription. The exercise principle of overload (stress greater than normal encountered) applied in progression of intensity over time is fundamental to the patients to be able to achieve high levels of exercise work and intensity. Exercising at high intensities is important for subjects who are already relatively fit. Subjects with a very low level of fitness will need to progress from lower, moderate to high intensities in time (Swain and Franklin, 2006). Intensity is more of a determinant than volume in exercise prescription for obtaining optimal gains in $V'o_{2peak}$ (Swain, 2005; Gormeley, et al. 2008; Gormeley, et al. 2008; Warburton, et al. 2005; Guiraud, et al. 2009; Guiraud, et al. 2011).

More studies are needed to understand the predictors of change in performance in cardiac patients due to CR programmes, and as seen in ISWT predictors of change further studies are needed to identify and confirm predictors according sexes. Taking into consideration individual differences such as sex, age, baseline fitness, waist-circumference, and smoking status, should predict if a higher dose of exercise is needed or not. Further investigation is needed to understand the right dose of exercise according to patients individual characteristics and needs.

6.5. Conclusion

Identifying patient-level characteristics meaningfully associated with changes in fitness is useful in managing patient expectations, and setting them goals for changes in fitness during CR. These findings are important for practitioners, having several implications in the optimisation of CR service design, better dose of exercise, and evaluation of the exercise prescription. The degree of change in fitness due to exercise-based CR programme depends on patients' individual modifiable and non-modifiable characteristics. We intend to explain for the first time the heterogeneity seen in changes in performance assessed by ISWT at exit of Cardiac rehabilitation.

We recommend that CR should be tailored according to sex/age group. Sex/age-tailored CR including patients with high waist circumference, who smoke, should have a higher dose of exercise than others. Patients with high baseline fitness can be fast-tracked to community CR programmes. Females and older patients exercising in mixed-CR should exercise in higher doses to benefit as much as young and male patients in cardiorespiratory fitness changes due to CR programmes. Further research is needed to clarify the right dose of exercise according to different patients characteristics and needs.

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Thesis final summary

The overarching aims of this thesis are to increase the benefits of CR (exercise-based Cardiac Rehabilitation), by improving assessment of patients' exercise capacity, or cardiorespiratory capacity, and optimizing current delivery models. UK has an ageing population, being cardiovascular diseases one of the most commune diseases among elderly. The Department of Health and several National Health Institutions have endorsed outpatient- hospital CR guidelines and goals to service deliver, despite this multi efforts UK outpatient- hospital CR service deliver is insufficient, and suffer from NHS service cuts. There is also little National evidence produced to test the effectiveness of CR delivery models. The review of literature and Chapter 3 based in international studies summarise state of play at the start of this thesis, Chapters 4, 5, and 6 are studies based in UK data. In chapter 3 and 6, evidence produced helps to a better interpretation of changes in cardiorespiratory capacity, and predictors of change in performance assessed during CR. Chapter 4 and 5 evidence helps to improve the interpretation of the outcomes of the Incremental Shuttle-Walking Test (ISWT), what helps in a better and more accurate assessment of changes in performance, or cardiorespiratory fitness in patients participating in CR. The evidence produced will result in a better CR delivery models.

There is a wealth of evidence that CR reduces all-cause and, cardiac mortality (Oldridge, et al. 1988; O'Connor, et al. 1989; Jolliffe, et al. 2001; Taylor, et al. 2004; Taylor, et al. 2006; Clark, et al. 2005; Heran, et al. 2011). Despite numerous systematic reviews of CR; and exercise-based intervention; no review had concerned the simple matter of whether outpatient- hospital CR actually improved cardiorespiratory fitness (fitness). Gains in fitness achieved by patients in outpatient-hospital CR are closely, inversely, related to patient mortality and morbidity and the evidence for this is strong and abundant, changes in fitness reported in studies are heterogeneous, and none of studies have given a standard reference for change in fitness to be used in CR. In **Chapter 3**, the meta-analysis performed, provides an estimate of the magnitude and moderators of fitness gains. The increase in cardiorespiratory fitness found is clinically important, providing further evidence of the effectiveness of using CR as a therapeutic approach to achieve higher levels of fitness. Chapter 3 provides an international estimate of fitness gains, the reference of magnitude of change will result in a better CR delivery models Our review it also highlighted the stark lack of published evidence for UK CR, and the differences in exercise prescription practices seen in International studies compared with UK.

Data from European and American studies form the basis of most meta-analyses. Like our own meta-analysis of studies evaluating changes in fitness due to CR (Chapter 3). The dose of exercise prescribed to CHD patients in European (Piepoli, et al. 2010) and American (Balady, et al. 2007) guidelines support a minimum of 3 sessions a week, for a minimum of 8 (24 exercise sessions) to 12 weeks (36 exercise sessions), progressing to 4 or 5 exercise sessions a week during the CR. The Department of Health recommendations for CR are based in lower doses of exercise prescribed. SIGN guidelines (SIGN 2002) support a minimal dose of 16 exercise sessions, in 8 weeks, and NSF guidelines (DOH 2000) 12 sessions, in 6 weeks. It appeared questionable, therefore, as to whether UK CR programs could be as clinical effective as those comprising the evidence base, due to their lower dose of exercise prescribed. It was clear that UK studies were need to support this affirmation, and to understand if the exercise prescription in UK CR programmes was actually beneficial in terms of patient outcomes.

Given the lack of UK evidence we undertook a multi-centre study (Sandercock, et al. 2012), in UK outpatient- hospital CR. A minimal dose of median of 8 (6 to 16 sessions) exercise sessions, which is close to minimum guidelines addressed, proves to elicit low gains in fitness (one third less) than international studies as reported in Chapter 3. At this time RAMIT, a multi-centre trial done in UK CR with same levels of exercise dose prescribed as our multi-centre (6 to 8 weeks, exercising once or twice a week), found no significant benefits, at two-year follow-up (West, et al. 2012). This exercise under prescription represented in these recent multi-centres studies, which has also been highlighted in the past in National Surveys, seam to demonstrated the CR reality in UK, and may be the cause of the clinical treatment inefficacy. UK CR, should be set at the level of European, or American Guidelines which prove to be effective in care of CHD patients. There is some variance in fitness gains due to CR as reported in findings in Chapter 3, variance in fitness levels assessed at entry to CR are also expected, as confirmed by studies using the Gold-standard test, however no studies inform how to interpreter the ISWT performance in CHD patients. Chapter 4 aimed to identify factors associated with the performance of Incremental Shuttle-Walking Test (ISWT) in CHD patients at entry to CR.

The Gold-Standard test to assess cardiorespiratory fitness in CHD patients is the treadmill or cycle ergometer, evidence is strong for fitness levels assessed, minimal clinical improvement, and their relation with morbidity and mortality. There are also reference data to help a better interpretation of fitness results according with patients individual differences, at entry to CR. However, this equipment is expensive, needing specialized operators, not being widely available in CR services in UK do to NHS funding cuts, being the assessment of fitness normally made by the use of the ISWT. This field test is simply to use with no need of specialized operators, with no additional cost associated, besides the need of a radio, and CD with instructions, being endorsed to use in outpatient- hospital CR practices by National Health Guidelines. After closer scrutiny of the exiting evidence in the literateur review of this thesis, and current practice, we identified several limitations of the ISWT; the most widely-used test in UK CR. There is little evidence of clinical utility in terms of stratifying risk, prescribing exercise, assessment change of performance, and whole service delivery. There are no studies at all that link final outcome of the performance in the test, meters, and a minimal clinical change, with morbidity and mortality, as in the assessment by the Gold-Standard test. No reference data were available for the ISWT despite evidence of large inter-individual differences in performance at entry to CR.

In **Chapter 4** reference values and centile curves of ISWT performance in CHD patients at entry to CR were produced, based on the best individual patients' characteristics identified as correlated of ISWT performance. This reference values and centile curves may aid clinical decision making, by providing a more meaningful and individualised assessment of patients' functional and exercise capacity, better risk stratification, exercise prescription, goal setting, and magnitude of change in cardiorespiratory fitness expected at entry in outpatient- hospital CR, as better assessment of goal setting achievement at exit of CR. Consequently, this may help ‘triage’ patients by better interpreting ISWT performance, at entry to CR and potentially identifying individuals who can be ‘fast tracked’ to community CR or in exit of CR define who can be referred back. This will result in a better CR delivery models. Chapter 4 explained that ISWT performance at entry to CR is heterogeneous, not only dependent on fitness, but also in individuals’ characteristics. Reviewing the literature, we found that a consensus on the estimated, and direct measure of $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) or metabolic equivalents METs) values from the ISWT was also lacking. Chapter 5 aimed to better define the $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) of the ISWT in the hope to produce a scientific consensus. We also reported stage-by-stage values for CHD patients as $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) and in METs, to enable use by clinicians and CR practitioners.

Clinicians and health practitioners, really in $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) results or METs, given by the fitness assessment by the Gold-standard test, to prescribe exercise, risk stratify, and better assess the prognostic of CHD patients, as assessment of whole service delivery. Evidence for this in literateur is strong, and is the reason why Chapter 3 review was based in the assessment of fitness by treadmill test, and results reported in METs. In UK only three studies have reported the $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) by stage for the ISWT in CHD patients or age-matched controls (Woolf-May and Ferrett 2008; Woolf-May and Meadows 2013; Almodhy, Beneke et al. 2014). These three studies report different results in $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) by CHD patients performing the ISWT, also the data from these studies report that $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) estimates from the ACSM equation (ACSM 2013), underestimates $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) in CHD patients’.

Such inconsistencies mean that cardiac rehabilitation professionals are currently faced with some confusion over estimating, and the real $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) of the ISWT whether for the purpose of exercise prescription or risk stratification, and prognostic of CHD patients.

Chapter 5 resulted in the confirmation of the curvilinear nature of $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) as a function of walking speed, as old studies reported; as opposed to the assume a linear relationship between increments in walking speed and $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}), used by ACSM estimation equations that underestimate performance and improvement in $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) in patients attending outpatient- hospital CR. New values of $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) or METs in CHD patients performing the different stages of the ISWT were produced, clarifying the doubts emerged by past studies. Oxygen demands of the ISWT in CHD patients are as much as 30% higher than those of age-matched controls. Further research should try to understand why there is higher $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) in ISWT performance in CHD patients compared with healthy individuals, or why there is $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) differences for same exercise dose between CHD patients and healthy individuals. This new $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) or METs values produced will help in a better clinical practice, improving risk stratification and exercise prescription in CR, as better patients prognostic. This will result in a better CR delivery models. Chapter 4 and 5 findings improve the assessment of performance, and changes in performance. Chapter 4 revealed that performance in test at entry to CR among CHD patients is heterogeneous. Chapter 3 demonstrated the heterogeneity of response to exercise, evidenced by variation in treadmill test performance at completion of CR. As few studies have examined differences in response to exercise training in CR patients this became the aim of chapter 6.

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Chapter 6 identify further predictors of change in performance in ISWT, which are associated with improved or worsened changes in performance in patients attending CR. Individual non-modifiable characteristics as predictors confirm findings from chapter 3, female and older patients change less in performance. Patients individual modifiable characteristics were also confirmed as predictors, lower baseline performance, waist circumference, and status of smoking were associated with less change in performance in ISWT. Optimal CR service should be tailored according to sex/age group, although for cost service-efficacy is not wise to recommend. Patients with high baseline fitness can be fast-tracked to community CR. Females and older patients exercising in mixed-CR should exercise in higher doses to benefit as much as young and male patients in cardiorespiratory fitness changes due to outpatient-hospital CR. These findings will result in a better CR delivery models. Further research is needed to clarify the right dose of exercise according to different patients' characteristics and needs.

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Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis

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ABSTRACT

Background/objectives: Improving patients' cardiorespiratory fitness is an important therapeutic outcome in cardiac rehabilitation. The ability of cardiac rehabilitation to reduce mortality and morbidity has been evidenced through several meta-analyses. Whether cardiac rehabilitation can increase cardiorespiratory fitness and which factors may influence such gains are less well quantified.

Methods: We performed detailed literature searches of electronic databases and manually searched papers concerning changes in cardiorespiratory fitness in cardiac rehabilitation patients. We performed random-effects meta-analysis of mean improvements in cardiorespiratory fitness and subgroup analyses to determine potential sources of heterogeneity.

Results: Data from 31 studies produced 48 groups ($n = 3827$) with a mean improvement of 1.55 (95% CI 1.21–1.89) METs, ($p < 0.001$); equivalent to standardised effect size of $ES = 0.97$ (95% CI 0.80–1.13). As this value was highly heterogeneous ($Q = 852$, $p < 0.001$) we performed subgroup analyses on the effect size data. Gains in fitness were highest in patients receiving >36 exercise sessions in studies where fitness was assessed using the Naughton Protocol. Patient characteristics associated with the highest fitness gains were age (being young) and sex (being male training in a male-only exercise group). Changes in fitness were unrelated to programme type (comprehensive or exercise-only), duration or study design. There was no association with patient's baseline fitness levels.

Conclusion: This is the first meta-analysis of changes in cardiovascular fitness in cardiac rehabilitation patients and shows clinically significant improvements in a large sample of patients from a variety of rehabilitation programmes. This analysis helps describe the characteristics of cardiac rehabilitation programmes which can increase patients' cardiorespiratory fitness.

1. Introduction

There is an abundance of high quality evidence for the effectiveness of cardiac rehabilitation as a therapeutic intervention to reduce all cause mortality, cardiovascular mortality and morbidity [1–6]. Much of the reduction in mortality and morbidity can be attributed to the positive influence that cardiac rehabilitation can have on cardiovascular risk factors such as smoking, hypertension and hypercholesterolemia [7].

In addition to adding years to the life of cardiac patients, it has also been proposed that rehabilitation should add 'life to years' [8]. Whilst pharmacotherapy can effectively modify many risk factors, exercise-based rehabilitation can increase functional capacity, mobility and independence by improving patients' cardiorespiratory fitness (herein fitness). Increased fitness is independently associated with improved quality of life in cardiac patients [9] and fitness is an excellent prognostic marker for future cardiovascular events [10–12]. Increases in cardiorespiratory fitness observed in patients during rehabilitation are closely associated with the reported reductions in mortality and morbidity [13–19]. Despite recognition of the clinical importance of fitness in cardiac patients, only limited attempts to synthesise the literature in this have been made [5, 20].

Recently, Conn et al. [5] found a significant improvement in physical activity levels of wide range of cardiac patients. The authors also meta-analysed changes in fitness as a secondary outcome. This analysis largely concentrated on quantifying standardised differences between post-test groups from randomised controlled trials. Whilst this approach ensured data quality it excluded the type of cohort-design and observational studies often performed in the more naturalistic setting of clinical practice. The effectiveness of CR as a therapy makes it unethical to withhold it from patients [21], making cohort-design studies increasingly necessary and common. The inclusion criteria that exercise testing be used as a behaviour change mechanism restricted the available studies in the meta-analysis of Conn et al. [5]. These authors were unable to perform subgroup analysis to determine which features of exercise (frequency, intensity, duration, modality) influenced changes in fitness. Whilst the effect size for change in

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physical activity was insightfully converted to energy expenditure (1984 kcal·week^{-1}) there was no common-language estimate for gains in fitness such as in $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) or metabolic equivalents (METs).

The aim of the present study was to determine the overall increase in fitness observed in CR studies expressed in easily interpreted units (METs) which are potentially more useful to clinicians than standardised effect sizes. The second aim was to determine patient characteristics and programme features including exercise dose information associated with changes in fitness. The latter aim was designed to provide further guidance to clinicians in designing and refining cardiac rehabilitation provision to maximise patients' fitness gains.

2. Methods

2.1. Search strategy

Three authors independently searched PubMed, Ovid, Web of Science and The NIH library. Using broad search terms: exercise, cardiac (or cardiovascular) rehabilitation, training, functional capacity, fitness (cardiovascular fitness), $\dot{V}O_{2peak}$, $\dot{V}O_{2max}$. Initial results produced 7104 potential studies for review. Our aim was to perform an analysis on outpatient cardiac rehabilitation programmes provided to the 'core' cardiovascular patient population. To narrow the search terms we limited the date range (1970–2010) and age range (>18 years) and included the Boolean operator 'NOT' with the search terms: heart failure, home-based and walking programme. This yielded 4321 abstracts which were manually scanned for eligibility. We also manually scanned the reference sections of existing meta-analyses concerning other aspects of cardiac rehabilitation and national clinical guidance documents [1, 2, 4, 5, 7, 13, 21, 22]. After removing reviews and meta-analyses we included primary research studies which met the criteria outlined in Table 1.

The exclusion of unsupervised or home-based interventions was justified due to the gross difficulties in monitoring overall adherence to such programmes as well as the difficulties in assessing exercise dose variables. Evidence for the efficacy of home-based CR as therapy to reduce mortality and morbidity is also lacking [23]. The inclusion of only incremental load-bearing exercise testing was made in an attempt to standardise the measurement of fitness. Lower values are often obtained from cycle ergometry and while field tests can estimate MET or $\dot{V}O_{2peak}$ values, the prediction equations used often have large standard errors of estimation [24]. These two criteria were designed to restrict the analysis to the most commonly-provided model of cardiac rehabilitation, similar to the criteria used in meta-analysis demonstrating the efficacy of CR in reducing mortality, morbidity and reducing risk factors [4, 7]. These exclusion criteria differentiate this study from the meta-analysis of Conn et al. [5] which included highly varied models of CR provision and any available estimate of fitness [5]. We purposefully did not exclude non-randomised trials. Previous analysis has shown little difference in values from comparisons of distal post-test values in control versus treatment groups and pre- versus post-test values in treatment groups. During searches we noticed that many studies did not have control groups as they appeared to be 'service evaluation' type studies often performed in naturalistic environments. Given the high potential external validity of such trials, we included them whilst also including this particular element of study design in our subgroup analyses.

Table 1
Study inclusion and exclusion criteria.

Inclusion criteria
1. Published 1970–December 2010.
2. English language publication or translation available.
3. Participants with diagnosis of cardiovascular disease for whom exercise-based rehabilitation is internationally recommended: post-myocardial infarction, patients receiving revascularisation therapy, valvular replacement recipients and those suffering angina pectoris.
4. Intervention met our definition of cardiac rehabilitation. Supervised exercise training as a hospital outpatient or in a structured setting in the local community or at a residential centre.*
5. Experimental or quasi-experimental design (randomised controlled trial, non-randomised trial or cohort observation).
6. Fitness assessed by weight bearing incremental test pre- and post-rehabilitation and expressed as a unit which could be converted to Metabolic Equivalents (METs VO_{2peak} or VO_{2max} in ml·kg^{-1}·min^{-1} or l·min^{-1}).*
7. Necessary data to compute mean change in exercise capacity (mean, SD, t-value, F-value, p-value and sample size).

*Additional information: exclusion criteria.
4a - We excluded the following types of intervention; home-based exercise programmes (supervised or unsupervised); telephone, internet or email based programmes, home walking programmes, group walking programmes.
6a - We also excluded all non-weight bearing exercise tests (cycle ergometry) and did not include field tests of functional capacity such as timed walk tests, incremental shuttle-walking test, step tests and non-exercise estimates of fitness.

2.2. Data extraction and treatment

From studies which met our inclusion criteria we extracted means and standard deviations from exercise testing carried out before and after rehabilitation. In most cases this was available as METs, and where not available, METs were calculated by dividing reported oxygen consumption by 3.5. Given the paucity in reporting correlations between pre- and post-test data in studies (no studies reported this), we estimated the magnitude of this relationship using data from a local hospital. After ethical approval, we examined the records of 149 patients who underwent the Bruce Treadmill Protocol before and after a standard CR programme. A repeated measures t-test demonstrated a significant improvement in $\dot{V}O_{2peak}$ ($p<0.001$) and a correlation between pre- and post-test scores of $r=0.535$. This correlation coefficient was used in our meta-analysis. A total of 31 studies yielding 48 independent groups of patients were included in the final analysis. We chose to represent the overall change in fitness as the mean difference in pre- versus post-test fitness in METs, as this is readily understood by both researchers and clinicians. We also used random effects modelling to report the effect size (ES) for standardised mean difference in fitness to allow comparison with previous studies. This effect size was then used in subgroups analyses exploring heterogeneity.

2.3. Data coding for subgroup analysis

We performed subgroup analyses using pre-selected moderator variables to investigate possible sources of heterogeneity [25]. The possibility of generating spurious findings from subgroup analyses is well documented [25, 26]. We therefore performed only a small number of subgroup analyses; all subgroups themselves were determined *a priori* and were based on potential causal mechanisms, magnitude of effects, and statistical significance in existing studies. Each subgroup analysis was methodologically or physiologically justified and each grouping was agreed by all authors.

We developed two broad categories of data to be coded. We first coded data relating to the study design and CR programme design, then data regarding patient characteristics. We coded length of the programme in weeks, the total number of exercise sessions per programme and whether the exercise modality was: aerobic, resistance or mixed. We coded whether the CR programme was comprehensive (included education and/or behaviour change) or was exercise-only and whether the study was a cohort design or part of a (randomised or non-randomised) trial involving a control group. Finally we performed subgroup analyses based on treadmill protocol reported. Quantitative patient characteristics coded were age (young <50; old 50–65 and oldest >65 years) and baseline level of fitness (median split at >/<6.6 METs). We coded patient groups according to sex (males, females or mixed). The primary reason for CR attendance was coded as Revascularisation, Post-myocardial infarction (MI) or Mixed. Details of all subgroups and cut-offs can be found in Table 2.

Despite potential mechanisms by which they might influence study outcomes, we were unable to create satisfactory subgroups for several variables. Prescribed exercise intensity was commonly given as broad and often overlapping categories (e.g. 60–85% heart rate maximum) or using poorly quantified terms (e.g. 'symptom limited' or 'Borg Scale').

3. Results

The overall effect for CR interventions of on fitness measures in metabolic equivalents (METs) is shown in Fig. 1. The 31 studies yielded 48 separate groups which had a mean pre- vs. post-test difference in fitness of 1.55 (95% CI 1.21–1.89) METs which was highly significant ($p<0.001$). Using a random effects model, the effect size for the standardised mean difference in pre- vs. post-test fitness was: ES = 0.97 (95% CI 0.80–1.13). This difference was statistically significant ($p<0.0001$) but was also, highly heterogeneous ($Q=852$, $p<0.001$). Visual inspection of the forest plot showed four groups from four different studies [27–30] with larger than expected (>2SD higher) mean effects. Removal of these groups reduced slightly the mean standardised difference (ES = 0.80; 95% CI 0.63–0.94). This value remained statistically significant ($p<0.001$) but also retained a large degree of statistical heterogeneity ($Q=591$, $p<0.001$). We could identify no common features of these groups and they were retained in all further analyses.

3.1. Subgroup analyses: tests for heterogeneity

There were a number of programme design characteristics which showed significant between-group heterogeneity (Table 2). Observed changes in fitness did not vary according to overall programme length (>/≤12 weeks). There was no statistically significant differences

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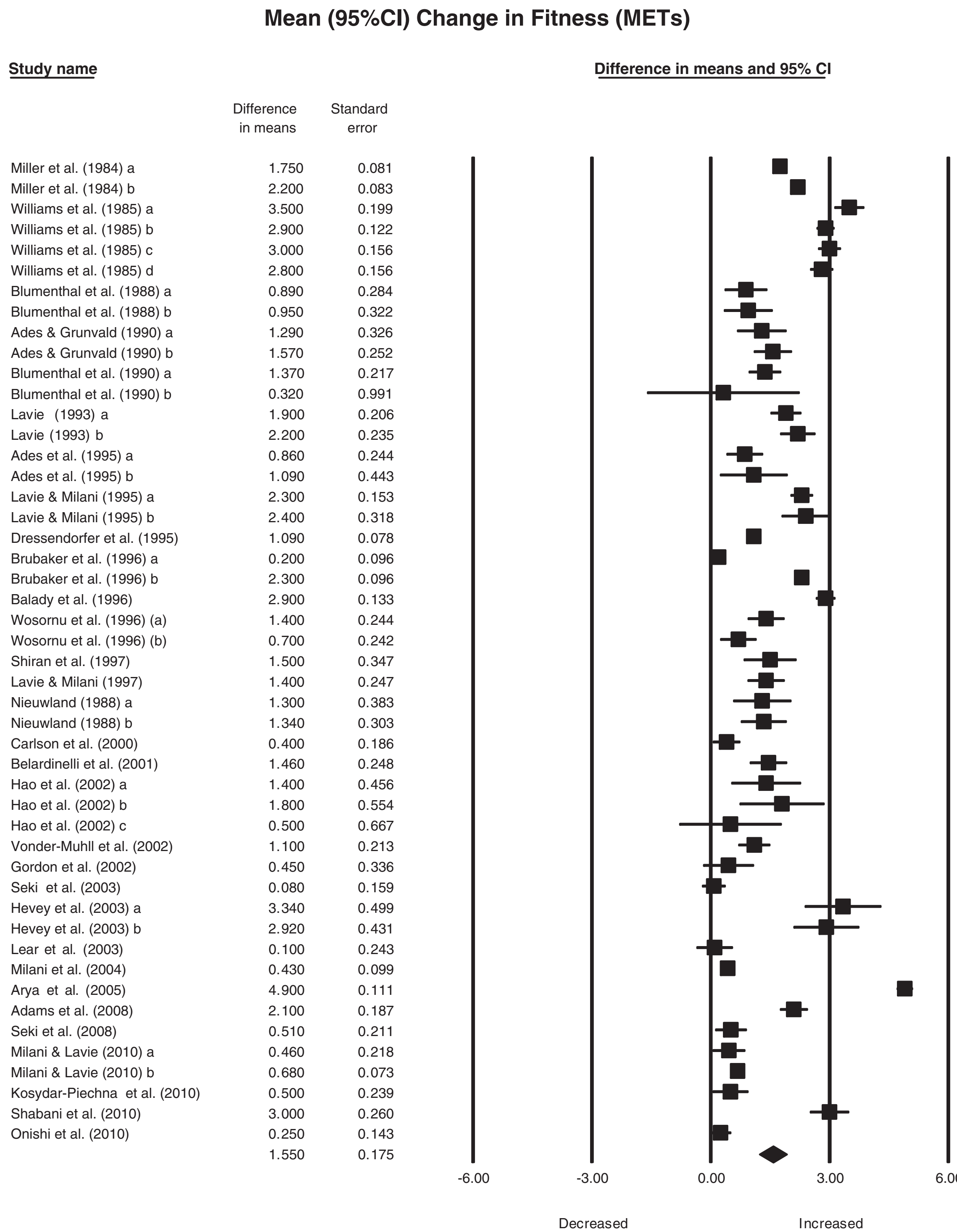

Fig. 1. Forest plot for mean point estimate of change in fitness due to cardiac rehabilitation. Legend: Points are mean point estimate (squares) with upper and lower 95% confidence intervals for the difference between pre- and post-cardiac rehabilitation measures of cardiorespiratory fitness (in metabolic equivalents). The overall mean point estimate (±95% CI) is based on a random effects model. Miller et al. [27]; Williams et al. [31]; Adams et al. [32]; Ades et al. [33]; Ades and Grunvald [34]; Arya et al. [30]; Balady et al. [16]; Blumenthal et al. [35,36]; Brubaker et al. [29]; Carlson et al. [37]; Dressendorfer et al. [38]; Gordon et al. [39]; Hao et al. [40]; Hevey et al. [41]; Kosydar-Piechna et al. [42]; Lavie [43]; Lavie and Milani [44]; Milani et al. [45]; Milani and Lavie [46]; Lear et al. [47]; Wosornu et al. [48]; Shiran et al. [49]; Nieuwland et al. [50]; Ayra et al. [30]; Adams et al. [32]; Seki et al. [51]; Seki et al. [52]; Milani and Lavie [45]; Shabani et al. [53]; Onishi et al. [54].

according to number of exercise sessions. However, the small number ($k=5$) of programmes that did include >36 sessions reported much larger gains in fitness than those with exactly 36 or <36 session. The effect size for change in fitness in the latter two groups, was very similar. Programmes comprising aerobic or mixed exercise modalities were equally effective and significantly ($p=0.024$) more so than the few ($k=2$) which prescribed resistance exercise. Gains in fitness were not significantly different between comprehensive cardiac rehabilitation exercise-only programmes despite a trend towards the latter appearing more effective. There were no differences in fitness gains between studies grouped according to whether they were a trial or a cohort study. Programmes which assessed fitness using the

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Table 2
Subgroup analysis for moderators of fitness gains expressed as standardised mean difference.

Moderator	Groups	k	Standardised mean difference	95% CI	P	Between group Q	P-value (between)	Within group Q	P-value (within)
Study characteristic subgroups									
Duration of programme	≤12 weeks	37	1.00	0.81–1.18	<0.001			204	<0.001
	>12 weeks	11	0.89	0.51–1.27	<0.001			630	<0.001
						0.2	.640		
Number of exercise sessions	<36	14	0.81	0.47–1.14	<0.001			158	<0.001
	=36	26	0.98	0.77–1.20	<0.001			520	<0.001
	>36	5	1.74	0.78–2.69	<0.001			116	<0.001
						3.4	.183		
Exercise modality	Aerobic	19	1.04	0.67–1.40	<0.001			375	<0.001
	Mixed	26	0.98	0.79–1.18	<0.001			462	<0.001
	Resistance	2	0.33	0.11–0.78	0.140			2.1	0.152
						7.4	.024		
Programme type	Comprehensive	28	0.83	0.65–1.03	<0.001			453	<0.001
	Exercise-only	20	1.13	0.81–1.15	<0.001			328	<0.001
						2.5	.117		
Treadmill protocol	Balke	6	0.70	0.49–0.92	<0.001			9.4	<0.001
	Bruce	14	0.79	0.60–0.98	<0.001			114	<0.001
	Naughton	5	2.41	1.08–3.74	<0.001			96.1	<0.001
	Own	14	1.12	0.70–1.55	<0.001			330	<0.001
	Not specified	8	0.48	0.22–0.74	<0.001			96.4	<0.001
						12.1	<0.001		
Study design	Cohort	22	0.98	0.80–1.20	<0.001			260	<0.001
	Trial	26	0.96	0.71–1.19	<0.001			450	<0.001
						0.1	.740		
Patient characteristic subgroups									
Sex	Females	3	0.92	0.08–1.76	<0.001			23.7	<0.001
	Males	19	1.44	0.98–1.89	<0.001			429	<0.001
	Mixed	21	0.65	0.48–0.62	<0.001			219	<0.001
						10.1	.011		
Age	Young	17	1.45	1.00–1.90	<0.001			235	<0.001
	Old	16	0.90	0.63–1.17	<0.001			143	<0.001
	Oldest	15	0.64	0.42–0.79	<0.001			359	<0.001
						13.5	<0.001		
Primary diagnosis	Post MI	5	2.08	0.87–3.30	<0.001			98.1	<0.001
	Revascularisation	4	0.96	0.34–1.86	<0.001			33.2	<0.001
	Mixed	38	0.86	0.69–1.04	<0.001			637	<0.001
						3.8	.144		
Baseline fitness	≥6.6 METs	25	0.97	0.74–1.20	<0.001			403	<0.001
	<6.6 METs	23	0.97	0.74–1.21	<0.001			445	<0.001
						0.0	0.993		

Legend: Duration of programme: as reported in manuscript 3 months assumed to be equal to 12 weeks. Number of exercise sessions: total reported in study (not the number actually attended). Exercise modality: aerobic — described as continuous exercise e.g. cycle ergometry, treadmill walking (home walking programmes excluded). Treadmill protocol: as given except 'own' — where authors described a highly modified or bespoke protocol with enough detail to replicate; 'Not given' — authors described using progressive/incremental exercise but did not provide enough detail to replicate. Study design: all values calculated as within-group, pre- vs. most distal post-test value, cohort describes studies in which not control group was used. Trial describes studies in which a waiting list, volunteer (selective) or random group of patients acted as controls. Sex — the characteristics of the group in which exercise training took place. Primary diagnosis — the reason given for patients attending CR. MI — myocardial infarction, revascularisation included coronary angioplasty procedures and coronary artery bypass grafting. Where emergency revascularisation took place following MI patients are classed as MI. Mixed — includes patient groups with mixed revascularisation and MI classifications as well as valvuloplasty and angina patients. Baseline fitness is maximal capacity derived from pre-rehabilitation treadmill testing grouped according to median split. Note; k values may not always sum to 48 due to missing data in some studies.

Naughton protocol showed larger gains in fitness than those which reported using the Bruce, Balke or their own protocols. The smallest gains in fitness were observed in studies which did not report the exact nature of the incremental protocol they used.

Groups of male patients and those in the youngest age group (<55 years) showed significantly larger gains in fitness than female or mixed-sex patient groups and the two groups of older patients. While there was no significant between group heterogeneity in subgroups based on primary diagnosis, patients who had suffered an MI, had much larger fitness gains than those with other diagnoses. This trend did not reach significance due probably to the very small number of groups (k = 5) representing only post-MI patients. Patients' fitness gains were very similar in groups based on low or high baseline fitness measures.

3.2. Publication bias

Funnel plots of precision (standard error) against effect size (standard difference in mean) were created. Fig. 2. Shows the studies included in the present analysis in open circles with the imputed studies represented by closed circles. The asymmetry of the plot and clustering of imputed points provide strong evidence for publication bias in the pre- versus post-rehabilitation changes in fitness.

4. Discussion

Cardiac rehabilitation is acknowledged as an effective intervention to reduce mortality and morbidity in patients with variety of cardiovascular diseases [1–5]. The earliest meta-analysis on the topic exclusively contained studies which only used exercise training as an intervention and despite the increase in comprehensive CR programmes exercise training remains a mainstay of most rehabilitation programmes [55–61].

It is agreed that increased cardiorespiratory fitness is a desired outcome of CR [59, 60] and probably represents the mechanism by which CR exerts much of its positive influence on health [4, 7]. Systematic review [22] and meta-analysis [5] have both provided evidence for the effectiveness of CR programmes as a means to increase fitness. A paucity of detailed randomised trials on the topic has, so far, prohibited authors from fully exploring variables which might explain

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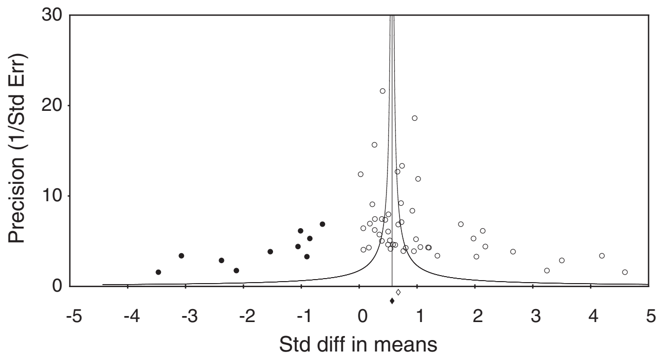

Fig. 2. Funnel plot of precision by standard difference in means. Legend: Open circles represent studies included in the meta-analysis. Closed circles are imputed values demonstrating the significant publication bias in studies analysed.

the large inter-individual and inter-study differences in cardiorespiratory fitness gains. The lack of studies eligible for meta-analysis in the study of Conn et al. [5] was due mostly to their inclusion criteria of study design: being a controlled trial or quasi-experimental study. As the authors noted, the efficacy of CR as a therapy means patients cannot always be randomised to a control condition due to ethical constraints [21].

The aims of the present study were to describe more fully the gains in fitness researchers and clinicians might expect to observe in patients undertaking CR programmes and to identify characteristics of CR programmes and patients which may modulate the magnitude of such gains. We modified the design of this meta-analysis specifically to meet these aims so that it could build on the existing research and reviews in this area. This was achieved in three specific ways.

First, to make the analysis easily understood to researchers and clinicians alike, we first represented change in fitness in well-accepted and easily understood metric of metabolic equivalent (METs). This metric is transferable across a number of exercise modalities and can be used in all patient groups. It is used routinely by researchers to describe aerobic exercise capacity and work rates as well as by clinicians in everyday tasks like risk stratification and exercise prescription [16, 59, 62].

Second, we included cohort studies in our analysis and did not limit it to controlled trials. This allowed us to analyse data from many more study groups (k = 48) than in the only previous meta-analysis [5] on this topic (k = 28). An obvious limitation of this design is that it may overestimate the mean point estimate of the intervention's effectiveness. We therefore took the step of calculating a within-group correlation coefficient based on our own empirical data and entered this correlation into the analysis to control for this inflation.

Third, we used random effects models in all analyses and undertook nine mixed-effects subgroup analyses to investigate the source of the expected heterogeneity of changes in fitness. Random effects models are recommended when the intervention being analysed is likely to be heterogeneous [63] as exercise interventions have previously been described [5, 22].

Heterogeneity is an expected product of most meta-analyses [25] and as such, researchers should be prepared to undertake pre-planned subgroup analyses to determine its sources [26]. Subgroup analyses were deemed impossible by Conn et al. [5] due to what they described as '*scant data*' on the topic. This was most likely due probably to their stringent study inclusion criteria. From a programme design perspective, details of which elements of CR (exercise frequency, intensity and dose) or which patient characteristics (sex, age and condition) may affect fitness gains may be very valuable.

4.1. Discussion of results

The CR programmes and interventions evaluated comprised n = 3827 patients in 48 separate groups from 31 published studies. The analysis showed that cardiac rehabilitation was associated with an increase in fitness of more than one and a half metabolic equivalents (1.55; 95% CI 1.21–1.89 METs). This is an impressive and clinically important increase and provides further evidence for the efficacy of CR as a therapeutic tool to increase exercise capacity, decrease mortality and morbidity and to increase patients' quality of life.

Converting this value to $\dot{V}O_{2peak}$, patients enrolled in CR programmes can expect their cardiorespiratory fitness to improve by an average of 5.4 (95% CI 4.2–6.6) $ml \cdot kg^{-1} \cdot min^{-1}$. Measures of the body's ability to use oxygen, commonly referred to as functional capacity, aerobic capacity, cardiorespiratory fitness or simply fitness as we have done are predictive of mortality and morbidity in both the general population [12, 15, 17] and cardiac patients [17–19, 64].

In addition to cross-sectional associations between fitness and mortality, several studies have demonstrated the degree to which gains in fitness due to exercise programmes can reduce mortality. Kavanagh et al. [19] found that each 1 $ml \cdot kg^{-1} \cdot min^{-1}$ gain in $\dot{V}O_{2peak}$ was associated with a 10% reduction in cardiac mortality. Vanhees et al. [64] found each 1% increase in $\dot{V}O_{2peak}$ was associated with a 2% reduction in mortality. Myers et al. [17] found that a 1 MET increase in fitness was associated with a 12% decrease in mortality, whereas Dorn et al. [18] found a 1 MET gain produced a 10% reduction in mortality in male MI patients. The improvement shown in the present analysis (1.55; 95% CI 1.21–1.89 METs) could, therefore, equate to reductions in mortality anywhere from 16% [17] to 54% [19]. The average estimate from all four of the above studies [17–19, 64], and using our mean value was 32%. This figure is broadly similar to the actual reductions in mortality (20–30%) reported in previous meta-analyses of survival data from CR patients [1–5] and summarised previously [65].

Conn et al. [66] recently meta-analysed the effects of various interventions on the physical activity of cardiac patients including an estimate of the effect size for increases in fitness. It is important to outline how the present study differs from this existing work. First, Conn et al. primarily studied physical activity. The comparable effect size for their primary outcome was ES = 0.49 (random effects model; pre- versus post-test values). Converting physical activity to energy expenditure, the authors suggested CR was associated with an additional 1984 kcal per week expenditure. Their effect size for fitness (ES = 0.43) was not, however, converted to any other metric. Conn et al. had strict inclusion criteria which limited their analyses to trials with a control group, and we feel this may have biased their results away from more naturalistic CR studies such as those carried out as part of service evaluations, audits or as staff-led research in existing CR programmes. Under these circumstances it would be neither possible nor ethical to withhold or delay CR to patients by placing them in control group. In contrast to their strict inclusion criteria for study design, Conn et al. employed a very broad definition of cardiac patients which resulted in the analyses of patient groups as diverse as; those 'at risk' from CVD, intermittent claudication patients, angina patients, hypertensive patients through to patients with advanced stages of heart failure. Internationally, only a few of these patient groups are routinely offered outpatient CR as it is defined in our study [55–61]. Whilst our criteria were less stringent regarding design, they were more stringent regarding patient group; we included only core cardiac rehabilitation patients: MI-sufferers, elective and emergency revascularisation recipients and valvuloplasty patients. These criteria, the use of fitness as our primary outcome and the undertaking of subgroup analysis on this outcome make the two studies very distinct from one another.

Within the literature, two generalised models of CR have been investigated; both of which contain an exercise training element. Comprehensive cardiac rehabilitation refers to programmes which contain elements of patient education or behaviour change (such as smoking cessation) in addition to exercise training and it is of note that these seem to be less effective in reducing cardiac and all-cause mortality when compared with exercise-only interventions [3, 65].

These differing models of CR delivery (comprehensive or exercise only) is just one of many examples showing the heterogeneous manner of interventions described as CR. Guidelines for the delivery of CR programmes are available over much of the developed world including the US [57] and Europe [67] but variations in written guidance, in local interpretation of such guidance and financial constraints mean service delivery is far more heterogeneous than might be expected of, for instance, a pharmacological intervention. It was for this reason that we expected heterogeneity of our findings (which was confirmed; $Q=852$, $p<0.001$) and also why we performed sub-group analyses.

4.2. Subgroup analyses: exploring the heterogeneity in responses to cardiac rehabilitation

It is widely accepted that there are large individual differences in response to exercise training [68]. The varied nature of exercise prescription also means that variations in how exercise is prescribed are likely to contribute to the heterogeneous between-study response observed. To our knowledge no previous study has investigated the heterogeneity of patients' fitness responses to CR although an overall estimate of CR's impact on fitness has been made [66]. Swain et al. [20] assessed the cardioprotective effects of exercise training by compared the responses of subjects trained at different exercise intensities. In general, they found that higher intensity exercise resulted in more pronounced changes in blood pressure and blood lipids and proposed a threshold of 6 METs as a lower limit for the intensity of exercise considered cardioprotective. Other authors have suggested no lower limit exists and suggested that intensities as low as 45% $\dot{V}o_{2max}$ may be sufficient [69]. Differences in prescribed exercise intensity may account for some of the very large degree of heterogeneity observed in our analysis. Unfortunately, the heterogeneous methods used for reporting training intensities (%$\dot{V}o_{2max}$, %$\dot{V}o_{2peak}$, %HR_{max}, RPE scores or being 'symptom limited') coupled with the often wide and overlapping values prescribed (50–85% of $\dot{V}o_{2peak}$) made subgroup analysis of this exercise variable impossible. While intensity is widely regarded as the most important determinant of an exercise prescription's effectiveness at increasing $\dot{V}o_{2peak}$ and improving health [20, 22, 69] there are many other factors which may affect the response. The next section discusses each of our subgroup analyses systematically including; justification for the subgroup selection, an explanation of the results, potential explanations for the findings and limitations.

4.3. Programme duration

The duration of the programmes reported ranged from 4 weeks to 12 months. The duration of an exercise programme typically shows positive relationship with the increases in fitness observed. In untrained individuals, however, most gains are realised in the first 4–12 weeks of a training. Twelve weeks was both the median and modal value for duration and conforms with some local recommendations for programme duration [57, 58]. Most programmes were ≤12 weeks long but the 11 groups of patients involved in longer programmes showed only very slightly greater increases in cardiorespiratory fitness. Significant within-group heterogeneity remained evident in both these subgroups. These results agree with studies that have compared interventions of different lengths and show little or no further increases in fitness following initial gains [27, 33, 51]. Duration is limited as a component of exercise prescription and a better assessment of total exercise 'dose' of exercise was performed by analysing differences between subgroups created according to the total number of exercise sessions prescribed.

4.4. Number of exercise sessions

There was a wide variety in the number of exercise sessions prescribed in programmes (range $n=4$–144). Total sessions represents a measure of the total exercise 'dose' and we hypothesised that more sessions would result in greater fitness gains. Like programme duration, there was a common mode and median value ($n=36$) for the number of exercise sessions prescribed. This most often represented three weekly exercise sessions over 12 weeks.

Patients in programmes including >36 exercise sessions had much greater gains in fitness than those receiving less than this number. There was no further difference between groups of patients receiving exactly 36 or <36 sessions although the latter did show the smallest overall gains in fitness. The data suggest 36 sessions is sufficient to promote gains in fitness close to the overall mean difference, but that there may be some additional benefit in prescribing more than this number of sessions. The number of studies including >36 sessions was small ($n=5$), due probably to the potential cost implications and the burden placed on the patient. Further research is needed to determine just how important any benefits gained from >36 sessions really are. One limitation of this analysis was the large variance in session number in the <36 group (4–28 sessions). Identifying the minimum 'dose' of exercise capable of eliciting a meaningful change in patients' fitness should be a research priority as shorter programmes have lower costs and may promote better adherence.

4.5. Exercise modality

The mode of exercise undertaken directly influences the physiological adaptations observed. Given that we analysed measures representing change in peak oxygen uptake, we assumed that aerobic-type exercise would promote the largest changes. Our data supported this idea, suggesting that aerobic exercise was more effective than resistance training alone, although the small number of resistance training studies suggests caution. Studies which have directly compared resistance and aerobic training in other populations support this notion [70]. Gains in fitness were almost identical between the aerobic and 'mixed' exercise groups. The latter typically combine aerobic and resistance training and this findings supports the idea that improvements in cardiorespiratory fitness can be gained by adding resistance training to aerobic activities, particularly in patients who are detrained and may lack muscle strength needed to perform vigorous aerobic exercise [71]. A combination of exercise modalities may also be more appealing, manageable and results in better adherence to programmes than a single modality prescription. As very few studies contained any details of adherence, we cannot comment on this point.

4.6. Comprehensive vs. exercise-only cardiac rehabilitation programmes

This subgroup analysis was logically determined based on existing meta-analytical differences in patient survival between the two broad models of CR. Based both on survival data and the well-documented relationship between changes in fitness and survival we hypothesised that exercise-only programmes would show the largest improvements in fitness. Whilst there was no significant between-group heterogeneity in these findings, there was a clear trend toward larger gains in exercise-only programmes. Exercise-only programmes are associated with higher patient survival rates than comprehensive CR programmes. There is also some rather counterintuitive evidence that exercise-only programmes can reduce certain behavioural risk facts like smoking [4] while psychological interventions used during CR may be less effective [72]. Given the importance of low fitness as a risk factor, the relationship between gains in fitness and reduced mortality and the trend towards greater gains in exercise-only programmes seen here, we recommend that CR should focus primarily on delivery of exercise sessions. There is little evidence that additional psychological or educational input to programmes has benefit for patients. This analysis is, however, limited by the way in which comprehensive CR is described in the literature. Few studies gave details regarding the nature of any additional interventions, when these were identified, it was not stated whether educational sessions

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were additional to the exercise programmes or whether they displaced exercise sessions. Few data on the number of sessions provided and no data on patient attendance at these sessions were given.

4.7. Treadmill protocol

It is well documented that the modality of testing can affect the outcome of any fitness test. It was for this reason that we limited our results to incremental treadmill protocols. Within these studies there remained a variety of protocols reported. Whereas most authors gave sufficient detail to replicate the test, data from six studies merely reported that an 'incremental test' was used. These were grouped together (Not Specified) as were a rather homogeneous subgroup of studies in which the authors devised and used their own protocols; the latter being usually well-described. The changes in fitness observed in patients from studies where treadmill protocol was not specified were well below the overall mean (ES = 0.48; 95% CI 0.22–0.74 METs) but are difficult to comment on due to this lack of detail. Estimates were similar between the remaining subgroups except for those studies which reported using the Naughton protocol, in which the effect size was much larger than all other subgroups and the overall mean difference (ES = 2.4, 95% CI 1.08–3.74 METs). Overall, these data suggest caution when comparing fitness gains between studies using different protocols. The studies using Naughton protocol were unremarkable in terms of duration, modality or patient factors which may influence gains in fitness except for containing one large group with exceptionally large increases [30]. We can only speculate as to why these studies show such large gains but it may be that the Naughton protocol's shorter stages with more gentle transitions between workloads is better-suited to cardiac patients than the next most commonly-reported protocol, Bruce. Typically, where researchers used their own protocol (which resulted in the next highest subgroup mean estimate) the protocols also tended to have smaller transitions and shorter stages and be more like Naughton's protocol than that of Bruce. These differences warrant further investigation.

4.8. Study design: cohort vs. trial

The cohort versus trial subgroup analysis was performed to determine whether trials of CR, designed and implemented primarily by researchers produced different changes in fitness compared with more naturalistic observations drawn from service evaluations, or cohort studies. The analysis was designed to confirm whether we were justified in combining data from wide variety of study designs. We hypothesised that trials might produce larger gains in fitness (pre- versus post-test) due to better adherence, the influence of researchers, the selective nature of study participants, and patients' knowledge that they were in a trial.

There was no difference in fitness gains between the two study designs. Effect sizes were near identical and, logically, also very close to the overall mean value. These findings are analogous to those of Conn et al. [5] who found that study funding status had no mediating effect on changes in patients' physical activity levels. We are therefore, confident that we have introduced no bias into our results by including this mixture of study designs. This analysis was limited by the subjective nature of subgroup allocation. We found a number of cohort studies (with no control group) which had received funding and some studies were difficult to classify due to poor description of purpose and patient recruitment.

4.9. Summary: programme-level moderators

It appears that some of the heterogeneity in fitness gains observed can be explained by the choice of different treadmill protocols between studies. There was a moderate modifying effect of exercise modality, where mixed-modality exercise programmes faired best and with total exercise dose, with 36 sessions proving most favourable. Programme length, being exercise only or comprehensive and whether the programme was part of a trial had no significant effect on patients' fitness gains. There are, however, also differences at the level of the patient which may moderate changes in fitness observed.

4.10. Patient-level subgroup analyses

There is little information on how the sexes may benefit differently from CR, but there is a well-documented gender-bias in CR toward male patients [73–75] who also tend to report better programme adherence [76, 77]. The bias in CR may be historical as CVD is more prevalent in males and whilst it may still be perceived as a predominantly male disease, CVD remains the biggest killer of adult women in most developed countries [78].

This gender-bias was supported in our analysis, with only three female-only patient groups versus 19 which were male only. While this small number makes interpretation difficult, significant between-group heterogeneity was observed. Males had higher gains in fitness than females but the difference was much greater between male-only and mixed groups. This was surprising as most of the mixed groups were predominantly male. We did not analyse group gender composition but a previous report found only 25% of CR participants were female [79]. This may represent difficulties in running mixed-sex exercise training groups. Given the group-exercise nature of most CR programmes it may be that males in mixed groups do not work at the same intensity as they would in a male-only environment. It may be that male-only groups provide a more competitive environment in which male patients 'push' themselves more. The main limitation of this analysis is that whilst of interest, it has little clinical significance except to suggest that if possible, patients may benefit more from exercising in same-sex classes. Whether financial, spatial or temporal limitations will practically allow this in CR clinics is questionable.

Like patients' sex, their age is a non-modifiable factor. In agreement with previous studies [31, 34], we found significantly greater gains in fitness in younger patients than in older (or the oldest) patients. This may represent some reduction in physiological adaptability, particularly in the oldest patients, in whom the effect size was less than half that of the young patients. This is of note for practitioners when setting goals for patients, as older individuals would be expected to show lower gains when fitness is expressed in absolute terms as in this analysis. If expressed as percentage gains, the changes in the older patients may be equal to or even exceed those of younger patients due to lower baseline fitness values.

4.11. Baseline fitness values

The pattern by which individuals with low initial fitness may demonstrate the largest overall gains due to a training programme is referred to as the law of initial values. Statistically, this phenomena represents regression to the population mean; it is well-documented in general exercise physiology [68] and has been shown in cardiac rehabilitation patients [80]. We divided patients into two groups according to their baseline fitness values, hypothesising that lower baseline fitness would be associated with greater fitness gains. The hypothesis was not supported by the data, which showed almost no between-group difference. The similarities may be due to effective implementation of exercise prescription at the level of the individual, as reported in most studies. By doing this, patients can exercise as similar relative exercise intensities thereby realising similar overall gains in fitness. While this result is encouraging the subgroup analysis itself is limited as it is based on the arbitrary figure of 6.6 METs determined simply by median split, limiting the generalisability of this finding to patients with more varied baseline fitness values.

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4.12. Primary diagnosis

There was a trend toward greater gains in fitness in post-MI patients than those being rehabilitated for revascularisation or other reasons. The between-group heterogeneity was not significant and the small number of studies in each specific subgroup makes interpretation problematic. This is a limitation of the analysis but is due mostly to the mixed patient-group nature of studies which simply reflects the wide range of patients eligible for cardiac rehabilitation.

4.13. Summary: patient-level moderators

In summary, despite a large degree of heterogeneity between studies, gains in fitness were only significantly moderated by patients' sex (being male) and age (being younger). Practitioners may wish to take note of these non-modifiable factors when designing CR services as it seems that younger, male patients may particularly benefit from exercising separately from other patients where they are able to exercise in more vigorous manner to promote fitness gains.

5. Conclusions and limitations

Previous meta-analyses have confirmed the efficacy of cardiac rehabilitation as a treatment to reduce patient mortality and morbidity. Rehabilitation programmes produce these reductions through the modification of cardiovascular disease risk factors and by promoting gains in cardiorespiratory fitness. Higher cardiorespiratory fitness is associated with reduced risk of cardiovascular mortality and morbidity, as is the magnitude of gains in fitness due to exercise training.

A recent meta-analysis of wide-ranging interventions aimed at increasing physical activity in cardiac patients found that programme features including; more contact time with practitioners, greater exposure to supervised exercise sessions and fitness testing were associated with higher levels of physical activity. Fitness is a more powerful predictor of health than physical activity but Conn et al. [5] did not examine the factors which were associated with increases in fitness. Despite the inherent aim of cardiac rehabilitation to improve cardiovascular fitness and the direct relationship fitness has with many patient outcomes [6, 17–19, 64] no study has systematically analysed the factors which may modulate fitness gains.

This is the first detailed evaluation of changes in cardiorespiratory fitness in cardiac rehabilitation patients and shows patients can expect a 1.5 metabolic equivalent (MET) increase in cardiorespiratory fitness. This increase could equate to a 16–54% reduction in cardiac mortality depending on the estimate used. The studies reviewed here which were used to provide this mean estimate are, however, highly heterogeneous. We found that the optimal features of CR to promote these changes were that it comprised >36 sessions of aerobic or mixed aerobic and resistance exercise delivered over a 12 week period. We found no evidence that longer programmes had additional benefits and no evidence that the addition of patient education (comprehensive cardiac rehabilitation) increased fitness gains. From a scientific perspective, it seems that the treadmill protocol chosen has a major potential impact on fitness gains and caution should be employed when comparing studies which use different protocols. From a patient perspective, young patients and males may benefit more from cardiac rehabilitation than older patients and females. Provision for same-sex exercise groups to which patients are allocated according to their age may help patients achieve optimal gains in cardiorespiratory fitness.

We found strong evidence of systematic publication bias, whereby significant findings from larger studies were substantially more likely to have been published. Conclusions from this analysis are limited due to the inclusion of non-randomised and cohort-based study designs but it is the inclusion of these that allowed us to perform subgroup analysis to determine the potential moderators of the cardiovascular fitness response to cardiac rehabilitation.

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The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology [81].

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ORIGINAL ARTICLE

Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study

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ABSTRACT

Background Exercise training is a key component of cardiac rehabilitation but there is a discrepancy between the high volume of exercise prescribed in trials comprising the evidence base and the lower volume prescribed to UK patients.

Objective To quantify prescribed exercise volume and changes in cardiorespiratory fitness in UK cardiac rehabilitation patients.

Methods We accessed n=950 patients who completed cardiac rehabilitation at four UK centres and extracted clinical data and details of cardiorespiratory fitness testing pre- and post-rehabilitation. We calculated mean and effect size (d) for change in fitness at each centre and converted values to metabolic equivalent (METs). We calculated a fixed-effects estimate of change in fitness expressed as METs and d.

Results Patients completed 6 to 16 (median 8) supervised exercise sessions. Effect sizes for changes in fitness were d=0.34–0.99 in test-specific raw units and d=0.34–0.96 expressed as METs. The pooled fixed effect estimate for change in fitness was 0.52 METs (95% CI 0.51 to 0.53); or an effect size of d=0.59 (95% CI 0.58 to 0.60).

Conclusion Gains in fitness varied by centre and fitness assessment protocol but the overall increase in fitness (0.52 METs) was only a third the mean estimate reported in a recent systematic review (1.55 METs). The starkest difference in clinical practice in the UK centres we sampled and the trials which comprise the evidence-base for cardiac rehabilitation was the small volume of exercise completed by UK patients. The exercise training volume prescribed was also only a third that reported in most international studies. If representative of UK services, these low training volumes and small increases in cardiorespiratory fitness may partially explain the reported inefficacy of UK cardiac rehabilitation to reduce patient mortality and morbidity.

INTRODUCTION

Current UK national service guidelines for cardiac rehabilitation[1 2] cite evidence from systematic reviews[3–5] of randomised controlled trials showing a ~20% reduction in mortality for patients who complete exercise-based cardiac rehabilitation. The trials from which this figure was synthesised were largely completed 20–30 years ago and represent a historical vision of modern cardiac rehabilitation,[6] a version particularly unrepresentative of current pharmacological practice.[6] A more recent meta-analysis[7] provided a more conservative estimate of the effectiveness of cardiac rehabilitation to reduce mortality and rejected its efficacy in reducing secondary cardiac events. The exact studies included within each of the numerous systematic reviews published vary due to inclusion/exclusion criteria, but common to all these reviews is the paucity of UK data. The UK's contribution to the evidence-base is two studies, both completed >20 years ago.[8 9] Neither significantly reduced the risk of either total mortality or cardiac mortality in patients receiving cardiac rehabilitation compared with the usual practice group.

The recent publication of data from the RAMIT group[6] has posed some serious doubts as to the efficacy of the UK cardiac rehabilitation programme's ability to reduce patient mortality[10] and morbidity or increase quality of life. It has been suggested that data from RAMIT are already outdated and do not fully represent current practice guidelines.[11] Nevertheless, RAMIT still represents the most detailed randomised controlled trial of comprehensive cardiac rehabilitation in the UK. The authors suggest that the decline in the apparent effectiveness of cardiac rehabilitation is due to improved medical management (that received by intervention as well as usual practice).

Historical data suggest exercise training is an effective and fundamental element of cardiac rehabilitation (CR),[4 5] and more recent large-scale trials of psychological interventions alone report poor efficacy of such approaches when used in isolation.[12 13] A primary outcome of any exercise programme is the measurement of individuals' response to training such as changes in strength, or, as more typically reported in cardiac rehabilitation trials, cardiovascular fitness.

A 1% increase in $\dot{V}O_{2peak}$ is associated with a 2% reduction in mortality[14]; each 1 metabolic equivalent (MET) increase in fitness may infer a 12% decrease in mortality.[15] Increases in fitness are independently associated with reduced mortality and morbidity and improved quality of life.[16] Individuals who have good levels of fitness are significantly less likely to suffer cardiovascular disease.[17–19] Our recent systematic review suggested cardiac rehabilitation may produce a 1.55 (95% CI 1.22 to 1.89) MET increase in fitness.[20] There is a relative paucity of data on changes in cardiorespiratory fitness in UK cardiac rehabilitation patients; we were not able to include any in our meta-analysis.

A fundamental difference between UK cardiac rehabilitation services and the practice reported in many international trials which make up the body of evidence supporting the efficacy of cardiac rehabilitation is the exercise 'dose'. In general, a greater volume of training is associated with greater improvements in fitness,[20] but UK cardiac rehabilitation patients are typically only prescribed around one third the volume of exercise training[21] typically received by patients in the USA or Europe.[20]

Along with changes in clinical practice improving survival of 'control' patients, it may simply be that UK cardiac rehabilitation does not elicit a large enough training response to provide secondary prevention of cardiovascular disease. The RAMIT study[6] was detailed, but provided no information on changes in patient fitness due to cardiac rehabilitation. Given the paucity of such data, the aim of this study was to quantify the changes in cardiorespiratory fitness in a large, contemporary, multicentre sample of UK cardiac rehabilitation patients.

METHODS

Study design and service characteristics

Cardiac rehabilitation services were recruited through an email invitation sent by the British Association of Cardiovascular Prevention and Rehabilitation (BACPR) via their mailing list of UK centres. Inclusion criteria were that the cardiac rehabilitation service routinely performed cardiorespiratory fitness testing pre- and post-cardiac rehabilitation and that their clinical practice conformed to the recommendations of the then BACPR.[22] This organisation, now the BACR, has recently updated these recommendations.[23] Multicentre study ethical approval was obtained via the Integrated Research Application Service, and permission to access specified parts of records without patients' consent was obtained via the National Information Governance Bureau. However, local ethical approval could still not be obtained in two centres. Of the six services which originally volunteered, the study was completed in only four.

Data were obtained via retrospective analysis of patient records obtained during supervised outpatient cardiac rehabilitation. Patients' age, sex, body mass and primary diagnosis (reason for attending CR) were recorded from individual records. Patients' reason for attending cardiac rehabilitation was classified as being due to myocardial infarction (post-MI), having received elective revascularisation therapy including coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or other (angina pectoris, valvuloplasty). We did not include patients with congestive heart failure. We also recorded the type of test used and individual performance on the test at both pre- and post-CR. The metric used to describe performance depended on the test performed.

At the level of the service, we recorded the types of exercise test used and reasons for test selection. We also recorded the average duration (weeks), frequency (sessions per week) and type of exercise training used in the rehabilitation programme. All services included a core component of supervised exercise training and some aspect of formal patient education or counselling on lifestyle change. All services used mixed circuit-based (aerobic and resistance) exercise training sessions of 60 min duration, including a 15 min warm-up and cool-down performed at beginning and end.[1] The characteristics of the four services evaluated are given in table 1 and are broadly comparable with national survey data.[21]

Data extraction and treatment

The cardiac rehabilitation services used four different exercise tests: the Bruce treadmill protocol, the 6-min walk test (6MWT), the incremental shuttle walking test (ISWT), and an incremental cycle ergometer test. The data extracted from records to compare these are briefly described below; pre- and post-cardiac rehabilitation tests were treated identically in all cases. The Bruce treadmill protocol is a standardised incremental treadmill test with 3-min stages. Time completed on the test was recorded as a measure of test performance. Time was converted first to $\mathrm{VO_{2peak}}$ (ml/kg/min) and then to METs. One centre used an incremental cycling test using an electronically-braked cycle ergometer. The test comprised 2-min stages of increasing speed which was titrated at individual level based on sex, body size and self-reported fitness and physical activity. Final work-rate (Watts) was recorded as a measure of test performance for each patient and converted to METs based on standard equations.[24] The 6MWT is a self-paced field test of functional capacity most commonly used in patients with heart failure. The total distance walked by patients in 6 min was recorded as a measure of test performance and converted to average walking speed, then METs.[24] The ISWT is currently recommended for use in cardiac rehabilitation patients.[1] Distance walked by each patient was recorded as a measure of test performance, then converted to $\mathrm{VO_{2peak}}$ (ml/kg/min)[25] and then to METs for comparability with other tests.

Statistical analysis

Each of the tests used reported performance in different units. For each test, we calculated the pre- versus post-test difference in performance measures and reported mean change with 95% CI for the given units.[26 27] We also reported change in performance in METs and as standardised effect size (Cohen's d) as these are both readily understood and make our findings easily comparable with those of other studies. Finally, we calculated a fixed-effects pooled estimate of change in performance pre- versus post-cardiac rehabilitation expressed as METs and effect size (d).

RESULTS

The descriptive characteristics of the different patient groups within the four cardiac rehabilitation centres are given in table 1. There were differences in routine testing practice between centres. Centre A used the Bruce treadmill protocol to assess post-MI and valve replacement patients, but used the ISWT to assess revascularisation patients. Centre A used the 6MWT to assess a more heterogeneous group of patients, mainly those receiving valvuloplasty. Centre B used a mixture of cycle ergometry and ISWT to assess all patients eligible for cardiac rehabilitation (choice of test was dependent on space and availability of equipment). Centres C and D exclusively used the ISWT in all patients. Patients in centre B were equally likely to be attending cardiac rehabilitation following elective revascularisation or MI, but the majority of patients in centres C and D were attending cardiac rehabilitation following elective revascularisation. Table 2 shows the changes in cardiorespiratory fitness test performance in each group of patients in each cardiac rehabilitation centre. Patients in centre A showed a large improvement ($d=0.85$) in time spent on the Bruce treadmill protocol, corresponding to an increase of 0.76 METs. The mixed patient group from centre B, assessed by cycle ergometry, showed a moderate increase in cardiorespiratory fitness, expressed as peak volitional work-rate achieved (W) ($d=0.57$); equivalent to an increase of 0.50 METs.

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Table 1 Sample characteristics by exercise test groups and basic exercise prescription data at each centre for all patients (n=950)

Centre	Patient groups and exercise tests	Sample size, n	Dates	Mean (SD) age (years)	Sex	Primary diagnoses	Programme duration (weeks)	Weekly exercise sessions
A	i. Bruce treadmill test	125	2006–10	64.1 (10.2)	Male: 73% Female: 27%	Post-MI: 76% Other: 34%	8	1
	ii. ISWT	104	2006–10	67.5 (10.2)	Male: 82% Female: 18%	Post-MI: 2% Revasc: 76% Other: 12%		1
	iii. 6-min walk test	54	2006–10	69.4 (7.7)	Male: 73% Female: 27%	Post-MI: 37% Revasc: 22% Other: 41%		1
B	Incremental cycle ergometry and ISWT	221	2009–11	69.5 (9.7)	Male: 73% Female: 27%	Post-MI 40% Revasc: 42% Other: 18%	8	1 or 2
C	ISWT	81	2007–10	57 (11)	Male: 85% Female: 15%	Post-MI: 25% Revasc:71% Other: 4%	6	1 or 2
D	ISWT	365	2001–10	62.9 (15.2)	Male: 73% Female: 27%	Post-MI: 34% Revasc: 64% Other: 2%	8	1

ISWT, incremental shuttle walking test; Post-MI, post-myocardial infarction; Revasc, post-elective revascularisation therapy (CABG or PCI); Other, patients receiving cardiac rehabilitation for other treatments and conditions (angina pectoris, valvuloplasty recipients, resynchronisation therapy).

Change in distance walked on the 6MWT in the patients receiving elective revascularisation and valvuloplasty (centre A) was small (d=0.34), equivalent to only 0.33 METs.

All centres reported using the ISWT in at least some patients; in two centres (C and D) this was the only test routinely used and was employed in the assessment of all patients who could complete it. The predominantly elective revascularisation patients (centre A) improved their test performance by a mean of 160 m, producing a large effect size (d=0.99). Patients from mixed MI and revascularisation groups (centres B, C, D) showed relatively homogenous changes in ISWT performance, with means ranging from 67.0 to 82.5 m (d=0.46–0.49). Converting these changes in distance to METs, patients from centre A improved their fitness by an average of 0.70 METs which resulted in a larger effect size (d=0.96) than patients from centres B, C and D, who improved by 0.40, 0.37 and 0.51 METs respectively (effect sizes: d=0.57, d=0.46 and d=0.58).

The pooled fixed effect estimate for mean change in cardiorespiratory fitness in all (n=950) patients was 0.52 (95% CI 0.51 to 0.53) METs. This was equivalent to a moderate overall effect size for change in fitness of d=0.59 (95% CI 0.58 to 0.60).

DISCUSSION

The aim of this study was to quantify changes in cardiorespiratory fitness in patients receiving cardiac rehabilitation in the UK. The results of this study suggest that the supervised exercise training prescribed as part of UK cardiac rehabilitation does not produce changes in cardiorespiratory fitness comparable with international studies. It also appears that changes in fitness vary greatly between UK cardiac rehabilitation centres, all of which adhere to the same practice guidelines, and that the assessment protocols used to measure change in fitness may account for at least some of this heterogeneity.

Compared with a recent meta-analysis of international studies,[20] which reported a mean increase of 1.55 METs, the overall increase reported here (0.52 METs) is very conservative. The meta-analysis was based on treadmill test data, the gold standard assessment for cardiorespiratory fitness, and concluded that the treadmill test protocol was a significant source of the between-trial heterogeneity. There are very few comparable UK studies of change in fitness due to cardiac rehabilitation, but survey data suggest this gold standard measure is rarely used in routine assessment of patients both pre- and post-cardiac rehabilitation. One study,[28] which was not included in the recent meta-analysis due to omissions in data reporting, demonstrated a 90 s increase in treadmill time for CABG patients assessed using the Bruce protocol; the same protocol used to assess as post-MI patients in centre A. This is equivalent to an increase of approximately 0.60 METs, which is less than the value reported here. This was despite patients receiving 16 supervised exercise sessions compared with only eight in

Table 2 Changes in cardiorespiratory fitness test performance in original units and METs pre- vs post-cardiac rehabilitation (CR)

Test*	Sample size	Pre-CR	Post-CR	Change (95% CI)	Effect size (d)	Pre (METs)	Post (METs)	Change (95% CI)	Effect size (d)
[a]Bruce treadmill test (s)	n=125	329 (132)	451 (153)	121 (81 to 140)	0.85	6.8 (2.1)	7.5 (2.4)	0.76 (0.40 to 1.12)	0.58
[a]Incremental shuttle test (m)	n=104	295 (132)	455 (190)	160.1 (136.2 to 184.1)	0.99	4.4 (0.59)	5.1 (0.85)	0.70 (0.58 to 0.86)	0.96
[a]6-min walk test (m)	n=54	279 (144)	329 (148)	50.3 (18.8 to 81.6)	0.34	3.2 (0.97)	3.6 (0.99)	0.33 (0.13 to 0.54)	0.34
[b]Incremental cycle ergometry (W)	n=103	87.6 (19.1)	98.5 (19.1)	10.9 (8.6 to 12.2)	0.57	5.6 (0.8)	6.0 (0.8)	0.40 (0.31 to 0.51)	0.55
[b]Incremental shuttle test (m)	n=118	295 (139)	362 (155)	67.0 (51.6 to 83.6)	0.46	4.6 (0.7)	5.0 (0.7)	0.40 (0.30 to 0.52)	0.57
[c]Incremental shuttle test (m)	n=81	420 (157)	503 (179)	82.5 (53.9 to 111.3)	0.49	5.2 (0.76)	5.5 (0.84)	0.37 (0.25 to 0.48)	0.46
[d]Incremental shuttle test (m)	n=365	341 (165)	411 (230)	71.5 (57.6 to 85.4)	0.46	4.9 (0.83)	5.4 (0.94)	0.51 (0.46 to 0.56)	0.58
Pooled fixed effect model:	n=950							0.52 (0.51 to 0.53)	0.59 (95%CI 0.58 to 0.60)

*Superscripts a–d designate the four centres which participated.
Effect size (d), Cohen's d; MET, metabolic equivalent; Post-CR, exercise test at exit from phase III cardiac rehabilitation; Pre-CR, exercise test at entry to phase III cardiac rehabilitation.

the present study. One reason for the larger increase in fitness observed in the present study may be differences in the clinical characteristics of the patient groups. Post-MI patients increased their fitness by more than elective revascularisation patients in our recent meta-analysis (d=2.08 vs d=0.97). Both these effect sizes are well in excess of that reported presently (d=0.77), but our estimate is actually quite similar to that which we previously reported for change in studies using the Bruce treadmill protocol (d=0.79). The Bruce protocol is characterised by large increments[29] and may not be the most suitable protocol for the assessment of older patients, such as cardiac rehabilitation recipients who often present with orthopaedic co-morbidities.

Treadmill testing is also costly and time consuming, which has lead to many UK cardiac rehabilitation centres employing field-based estimates of cardiorespiratory fitness. There are relatively few data regarding the value of incremental cycle ergometry in assessing cardiac rehabilitation patients. Exercise test performance during cycle ergometry appears to be sensitive to changes in fitness due to cardiac rehabilitation and can provide important prognostic information.[30] Di Valentino *et al*[30] reported differences of 148 (±47) versus 124 (±38) W between surviving and non-surviving cardiac rehabilitation patients. They also reported an improvement in work capacity of 24 W; more than twice that observed in the patients from centre B (10.4 W). Differences in the test protocol may account for some of the variation in improvement, but the very large differences in exercise training seem more likely. Di Valentino *et al*[30] describe in detail the exercise training protocol in this German rehabilitation programme as comprising a 4-week build-up phase with daily rehabilitation activities taking up to 3 h per day, then a consolidation phase of 8 weeks, exercising 3×2 h per week. The total exercise dose over 12 weeks was, therefore, 132 h (84 intense plus 48 h consolidation). In comparison, patients at centre B received either 1- or 2-hourly sessions over a maximum of 8 weeks, equating to only 8–16 h total exercise.

The 6MWT is commonly used in the assessment of patients with heart failure, but few data are available in typical cardiac rehabilitation patients[31] and we found no data comparable to those for changes in fitness due to exercise programmes like those reported here. Even in patients with heart failure, the 6MWT does not appear to be as sensitive to changes in fitness as the ISWT[32]; this lack of sensitivity may explain the small effect size for change in test performance observed here.

The most commonly used field test in UK cardiac rehabilitation centres is the ISWT,[21] and a number of studies have reported changes in ISWT performance of 60–100 m due to cardiac rehabilitation.[33–36] Little has been reported on the potential dose–response between exercise and changes in fitness test performance using this protocol. Arnold *et al*[37] recently reported no difference in a sample of cardiac patients exercising once or twice per week, but their results are difficult to interpret due to differences in test performance at baseline.[38] A more recent study in patients with very similar baseline scores also reported no differences in training response of patients exercising either once or twice per week.[38] Of interest, this study is one of the few to report ISWT performance in METs as opposed to the distance walked during the test. This detail may be of some importance and deserves elucidation.

The ISWT, as the name implies, is an incremental test in which the patient is required to walk faster during each sequential stage. The use of distance to describe fitness test performance is clearly useful in the clinical setting. Distance is a metric readily understood by practitioners and patients and changes in shuttle walking tests can be easily monitored and expressed as change in m. The magnitude of change in walking distance is commonly reported to be around 100 m in patients receiving outpatient cardiac rehabilitation.[33–38] Cardiorespiratory fitness itself, however, represents the ability to produce and maintain a given work rate, not a work capacity. From an exercise physiology perspective therefore, it would be more correct to express ISWT performance as walking speed (m/s or km/h), or better still, as estimated VO_{2peak} (ml/kg/min)[25] or METs. This practice is uncommon within the scientific literature and to our knowledge only two studies have reported such metrics.[38 39] There are additional drawbacks with the use of distance as an expression of an individual's fitness. While study results are often highly statistically significant ($p<0.01$), there is little evidence of power analyses in any of the published data. Due to this, such changes have been interpreted as clinically significant despite no clinically meaningful lower cut-off being available. Like any fixed stage time incremental protocol, there are many more shuttles per level in the latter stages of the test than there are early on. This means that changes in distance walked in excess of 100 m can be attained without the need for and individual to increase walking speed (work rate). Changes in walking speed (and therefore estimated METs) are therefore commonly much smaller than changes in distance walked, with many patients not increasing work rate (fitness) at all. In the quest for easily interpretable values and statistical significance, it appears that some authors have neglected to assess whether the changes in distance walked during the ISWT represent a clinically meaningful improvement in cardiorespiratory fitness.

Our data suggest that patients attending UK cardiac rehabilitation centres can only expect a 0.59 MET increase in their cardiorespiratory fitness over a typical 6–8-week programme. This value may be slightly smaller if their fitness is assessed using the ISWT (0.54 METs). These values represent approximately one third the improvement in fitness reported in the literature.[20] While testing modality may account for some of this difference, it is of interest that even in the group who improved most in the present study (post-MI patients tested on a treadmill), the magnitude of change was less than half the value synthesised from international studies.

The starkest difference between the studies analysed in the recent systematic review and the present groups is the total volume of exercise completed during outpatient cardiac rehabilitation. We previously found that total number of exercise bouts was a significant mediator of change in fitness. Using a median split of the number exercise sessions, we have previously reported greater gains in fitness for patients receiving >36 exercise sessions than in those receiving 36 or less. Brodie *et al*[21] reported that UK patients undertake a mean of 11.6 exercise sessions. In common with the magnitude of change in fitness, the UK exercise dose is also one third that reported in the literature.[20] Patients in the present study received a modal value of 8 exercise sessions (range 6–16); the lower end of this range is similar to the exercise prescription which had no significant impact on clinical outcomes in RAMIT.[6]

There is a clear dose–response between increases in fitness and reductions in mortality.[14] Given that a 1 MET increase in fitness is needed to elicit a 12% reduction in mortality,[15] it seems unsurprising therefore that the UK cardiac rehabilitation services examined in RAMIT did not significantly reduce mortality.[6]

Strengths and limitations

The strengths of the present study lie in the large sample size and the inclusive nature of the study population afforded by the retrospective design. Conversely, a major limitation is the lack of any control group. The cohort design means we cannot quantify how much of the reported improvement in fitness is due to cardiac rehabilitation *per se*. There is evidence of some spontaneous recovery in fitness in patients following revascularisation and MI,[40 41] suggesting that the current study is likely to overestimate the real effect that cardiac rehabilitation has on patients' cardiorespiratory fitness. The use of patient records allowed us to quickly gather a large sample without the bias of requiring consent to participate in a research study; it was also a limitation as there were differences in the recording methods used between centres. All centres described the testing protocols as 'symptom limited' and all included attainment of 85% peak predicted maximum heart rate as termination criteria. While not reported here, patient records indicated that volitional termination was by far the most common reason for stopping the incremental exercise tests. All centres reported that they applied the ISWT according to national guidance,[1] but this was often performed by a variety of individuals (nurses, physiotherapists, exercise physiologists) within each centre. Our retrospective design does not allow us to standardise test variables such as 'encouragement' or 'patient motivation' either within or between centres.

For the purpose of this study we only included patients with complete data necessary for this analysis. This meant the rejection of >1200 patient records due primarily to having either incomplete or insufficient data, but also due to the patients' failure to complete the rehabilitation programme or to return for retesting.

CONCLUSIONS

Our findings suggest that the outpatient cardiac rehabilitation programmes sampled in our study commonly prescribed a dose of exercise insufficient to provide meaningful benefits to patients. The volume of exercise prescribed is equivalent to approximately one third that which a patient in North America typically receives. Many of the trials systematically reviewed to produce estimates of cardiac rehabilitation's ability to reduce mortality contain a much higher volume of exercise than typical UK services prescribe. While we cannot confirm the representativeness of our sample in terms of UK outpatient cardiac rehabilitation, these findings may offer some insight to explain the somewhat disappointing results of RAMIT.[6] When increases in patient fitness are quantified, the response of the UK cardiac rehabilitation patients receiving between 6 and 16 supervised exercise sessions is much less than that reported in our systematic review of international trials in which a median of 36 sessions was prescribed.[20] We suggest that cardiac rehabilitation patients in the UK are not receiving the full potential benefit available from supervised outpatient cardiac rehabilitation. As an example, if international trials of a drug demonstrated its efficacy at a daily dose of 600 mg, it seems unlikely that doctors would routinely prescribe 200 mg to UK patients. Whether this is through ignorance of the fineries of exercise prescription, or to spatial, temporal and financial restrictions in service provision, such under-prescription of exercise seems to be common practice in UK cardiac rehabilitation.

In summary, there is clear incongruence between the evidence base for cardiac rehabilitation and current clinical practice in the UK. Clearly, further trials and systematic reviews of UK cardiac rehabilitation data are needed to confirm our findings, but it seems likely that increased funding to facilitate a greatly increased frequency and/or duration of exercise training during outpatient rehabilitation is needed. Such changes will of course produce new challenges to cardiac rehabilitation practitioners, not only financial in nature but also with regard to patients' motivation to take up and adhere to exercise training.

Contributors GRHS designed the study and wrote the manuscript. MA and GP collected, treated and analysed the data. All authors reviewed and copy-edited the manuscript prior to submission. GRHS is the guarantor for this article.

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Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study

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CORRESPONDENCE

Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study

The Authors' reply We welcome the comments of Dr Ingle and Professor Carroll comparing our recent work[1] and their own important findings.[2] We agree with their suggestion that exercise test modality partially explains the relatively small gains in fitness reported for UK cardiac rehabilitation patients. The 1 metabolic equivalent (MET) gain reported by Carroll *et al*[2] appears clinically important and such findings should serve to illustrate to commissioners that important health-related gains in fitness can be achieved in outpatient cardiac rehabilitation. The 1 MET fitness gain is broadly comparable with that reported for one of our[1] centres which used treadmill testing (0.76 METs (95% CI 0.4 to 1.12)). We[3] have previously illustrated that exercise testing modality mediates fitness gains by reporting substantially larger effect sizes (ES) for fitness gains in patients assessed using the Naughton (ES=2.4, 95% CI 1.08 to 3.74) rather than the Bruce (ES=0.79, 95% CI 0.60 to 0.98) treadmill protocol.

Our treadmill data and those of Carroll *et al*[2] still suggest that fitness gains of UK cardiac rehabilitation patients remain below international values. We strongly believe this to be due to the relatively small dose of exercise routinely prescribed to UK patients.[4] To discern the degree to which exercise prescription influences fitness gains in cardiac rehabilitation independent of exercise test protocol we currently seek to recruit more centres and expand our current multicentre patient record study better-represent typical UK cardiac rehabilitation.

Such data will help us to discern the relative impact of exercise dose and exercise test protocol in fitness gains. We concur with Ingle and Carroll that test protocols may influence gains in cardiac rehabilitation but believe that there is a need for a controlled trial using gold-standard exercise assessment to directly compare fitness improvements in UK cardiac rehabilitation patients receiving usual care (n=8–12 exercise sessions)[4] with an exercise dose more typical (n=24–36 sessions) of that prescribed internationally.[3]

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Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study

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Pilot investigation of the oxygen demands and metabolic cost of incremental shuttle walking and treadmill walking in patients with cardiovascular disease

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ABSTRACT

Objective: To determine if the metabolic cost of the incremental shuttle-walking test protocol is the same as treadmill walking or predicted values of walking-speed equations.

Setting: Primary care (community-based cardiac rehabilitation).

Participants: Eight Caucasian cardiac rehabilitation patients (7 males) with a mean age of 67±5.2 years.

Primary and secondary outcome measures: Oxygen consumption, metabolic power and energy cost of walking during treadmill and shuttle walking performed in a balanced order with 1 week between trials.

Results: Average overall energy cost per metre was higher during treadmill walking (3.22±0.55 J kg/m) than during shuttle walking (3.00±0.41 J kg/m). There were significant post hoc effects at 0.67 m/s ($p<0.004$) and 0.84 m/s ($p<0.001$), where the energy cost of treadmill walking was significantly higher than that of shuttle walking. This pattern was reversed at walking speeds 1.52 m/s ($p<0.042$) and 1.69 m/s ($p<0.007$) where shuttle walking had a greater energy cost per metre than treadmill walking. At all walking speeds, the energy cost of shuttle walking was higher than that predicted using the American College of Sports Medicine walking equations.

Conclusions: The energetic demands of shuttle walking were fundamentally different from those of treadmill walking and should not be directly compared. We warn against estimating the metabolic cost of the incremental shuttle-walking test using the current walking-speed equations.

Strengths and limitations of this study

- We provide the first direct comparison of the metabolic cost of shuttle walking and treadmill walking in cardiac patients.
- Our data suggest that metabolic demands of these exercise modalities appear fundamentally different.
- We suggest that current methods to estimate the metabolic cost of shuttle walking are flawed. We warn against risk stratification of cardiac patients based on estimated oxygen costs using the American College of Sports Medicine walking equations during the incremental shuttle-walking test.
- The sample size limits generalisability, particularly in female patients who are not represented at higher walking speeds—a larger study of metabolic cost of the incremental shuttle-walking test is warranted.

INTRODUCTION

Since its conception as an alternative to incremental treadmill testing of patients with chronic obstructive pulmonary disease, the incremental shuttle-walking test (ISWT) has gained popularity as an estimate of functional capacity in numerous clinical populations. The ISWT appears adequately reliable[1] and is sensitive to changes in functional capacity.[2 3] However, the ISWT's validity as an estimate of cardiovascular fitness is only moderate,[3] and the use of the test to estimate oxygen consumption exercise capacity in metabolic equivalents (METs) is questionable.[4]

Woolf-May and Ferret[4] reported acceptable agreement between the energy cost of treadmill walking and the ISWT in healthy volunteers using linear regression analyses, but did not assess this relationship in cardiac patients. The authors reported higher energy demands of shuttle walking in cardiac patients compared with healthy controls. They suggested this may be due to poorer walking economy in the former; they did not report walking economy during ISWT or make comparisons between shuttle-walking and treadmill-walking economy.

Treadmill-walking and shuttle-walking tests are routinely used to assess patients with cardiovascular disease and we have previously reported discrete values for change in fitness measured using these tests.[5] Prior to undertaking a proposed multicentre study to identify predictors of change in cardiorespiratory fitness due to cardiac rehabilitation, we performed the present pilot study. We examined whether there were differences in the metabolic demands and energy cost of treadmill and shuttle walking in cardiac rehabilitation patients in order to determine whether we could combine data from these tests in our multicentre study. We also compared metabolic cost of the ISWT with values predicted from treadmill-walking equations[6] and published estimates.[4 7]

METHODS

Participants (n=8; 7 males; 67±5.2 years: 86.6±10.1 kg) were stable cardiac patients attending community-based rehabilitation following elective cardiac revascularisation. All patients gave written, informed consent.

Equipment

The ISWT was performed on a non-slip floor using two cones placed 9 m apart and a portable CD player. The treadmill test was performed on a motorised treadmill (Quaser, HP Cosmos, Nussdorf, Germany). During both tests a portable gas analyser (K4b2 Mobile Breath by Breath Metabolic System, COSMED Pulmonary Function Equipment, Rome, Italy) was used to record expired gas collected via a face and nose mask (Hans Rudolph, Shawnee, Kansas, US A). This was calibrated using gases of a known concentration and a syringe before each test.

Protocol

Patients completed the ISWT and the treadmill test in a balanced order with 1 week between trials. The ISWT was performed in accordance with national recommendations for cardiac patients.[8] Briefly, the 12-stage protocol starts at a walking speed of 0.5 m/s (1.12 mph) and increases by 0.17 m/s (0.38 mph) each minute. An identical incremental protocol was programmed into the treadmill. Patients were accustomed to treadmill walking but received a brief period of familiarisation in which they were required to walk without holding the treadmill handles before the ISWT protocol was also performed.

Calculation of metabolic power and energy cost of walking

We assumed a standard resting metabolic rate of 4 mL/kg/min based on reference standards.[9] Metabolic power was then calculated via indirect calorimetry from $\dot{V}O_2$ and $\dot{V}CO_2$ above rest and from body mass: metabolic power [W/kg]=($\dot{V}O_2$ - $\dot{V}O_{2\,rest}$) [mL/kg/s] respiratory exchange ratio adjusted caloric equivalent [J/mL].[10 11] To analyse the relationship between speed and metabolic power of walking, the metabolic power was predicted as a quadratic function of speed: metabolic power=a+b v^2.[10 12–16] The energy cost of walking per metre distance was calculated by: energy cost [J/kg/m] =metabolic power [W/kg]/speed [m/s].[10 11 17]

Statistical analyses

Descriptive results are presented as mean±SD. A test modality-by-walking speed analysis of variance (ANOVA) with shuttle versus treadmill walking as within-participants factor and walking speed as the between-participants factor was performed. Significant interactions and main effects were further analysed using one-way ANOVA and paired samples t tests as appropriate. Based on the classical descriptions of walking energy cost,[18–20] non-linear regression models were chosen to identify significant inter-relationships between metabolic power, energy cost per metre and walking speed, respectively. All analyses were completed using SPSS V.19.0 (SPSS Inc and IBM Company, Chicago, Illinois, USA) and statistical significance was defined as $p<0.05$.

RESULTS

Figure 1 shows the oxygen uptake at each of seven stages completed by at least seven patients. There was a significant main effect for walking speed on oxygen uptake and a significant interaction between treadmill walking and shuttle walking on the ground. Oxygen uptake was higher in treadmill walking than shuttle walking at 0.67 m/s ($p=0.006$; n=8) and 0.84 m/s ($p=0.003$; n=8) but the significantly steeper increases in oxygen demand during shuttle walking meant the opposite was true at 1.69 m/s ($p<0.006$; n=7).

Figure 2 shows the metabolic power of treadmill walking and shuttle walking. There was a main effect for walking speed on metabolic power during treadmill as well as shuttle walking ($p<0.05$). The different effects of walking modality on metabolic power were more pronounced if power was predicted as a function of walking

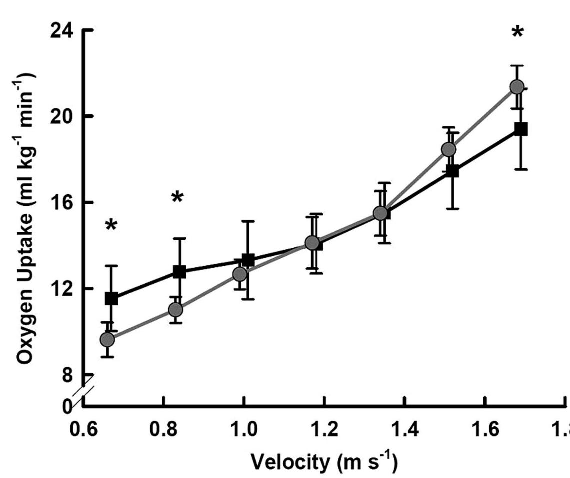

Figure 1 The oxygen uptake of treadmill walking (black line) and shuttle walking (grey line) at each of the seven stages; * treadmill walking different from shuttle walking, p<0.05.

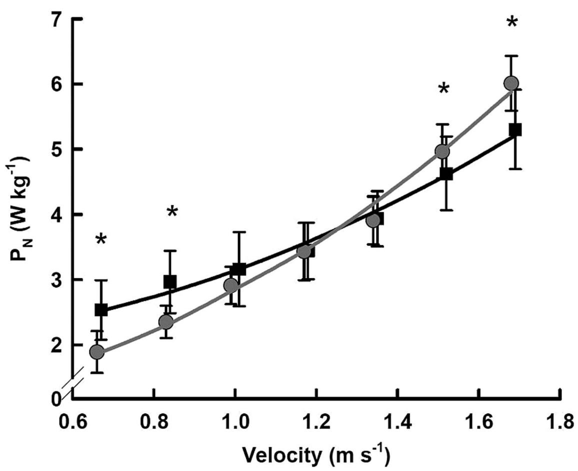

Figure 2 Metabolic power above rest (P_N) of treadmill walking (black line) and shuttle walking (grey line) at each of the seven stages, * treadmill walking different from shuttle walking, p<0.05.

speed with power treadmill walking=2.028+1.115 v^2 and power shuttle walking on the ground=1.126+1.665 v^2 where 99% of the variance of power was explained by the quadratic curve fits in both modalities (both $p<0.001$). The difference in response to each modality was indicated by a significant interaction between modality and speed. There were significantly higher metabolic power requirements for treadmill walking at 0.67 m/s ($p<0.004$; n=8) and 0.84 m/s ($p<0.001$; n=8). Owing to the steeper increase observed in shuttle walking the metabolic power was significantly higher at 1.52 m/s (p=0.042; n=7) and 1.69 m/s (p=0.007; n=7) compared with treadmill walking.

Figure 3 shows the relative energy cost (per metre) of walking for both modalities. There were significant main effects for modality and speed in relative energy cost of walking, which was well described as a function of speed by the above approximated parameters for both walking modalities (energy cost treadmill walking=2.028/v+1.115 v and energy cost shuttle walking on the ground=1.126/v+1.665 v; both $p<0.001$). Average overall energy cost per metre (kg/m) was higher during treadmill walking (3.22 ±0.55 J kg/m) than during shuttle walking (3.00 ±0.41 J kg/m). There were significant post hoc effects at 0.67 m/s ($p<0.004$; n=8) and 0.84 m/s ($p<0.001$; n=8), where the energy cost of treadmill walking was higher than that of shuttle walking. Again, this pattern was reversed at higher walking speeds of 1.52 m/s ($p<0.042$) and 1.69 m/s ($p<0.007$) where shuttle walking had a greater energy cost per metre (for the n=7 patients achieving this level) than treadmill walking.

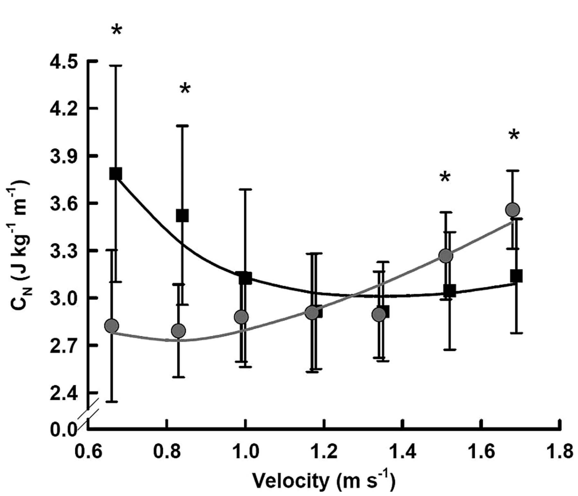

Figure 3 Energy cost above rest (C_N) per metre distance of treadmill walking (black line) and shuttle walking (grey line) at each of the seven stages, * treadmill walking different from shuttle walking, p<0.05.

DISCUSSION

This is the first comparative investigation of the metabolic demands and energy cost per metre walking of incremental treadmill walking and shuttle walking in cardiac rehabilitation patients. We found differences in the oxygen requirements and energy cost of shuttle and treadmill walking large enough to suggest results from these exercise modalities should not be pooled in any future analyses.

Economy and energy requirements recorded during level 1 are difficult to interpret as they are most affected by oxygen kinetics and patients' unusually long stance phase during their gait cycle at this very slow walking speed and were excluded from our figures. The change in walking energy cost per metre on the treadmill show the expected pattern. Slow speeds are associated with higher cost per metre, which decreases as optimal (comfortable) walking speed approaches. Continuing to increase walking speed above this pace requires a greater cost per metre. In contrast to this, the energy cost per metre in shuttle walking decreases only very little and only following the first (very slow) walking pace in the initial stage. The energy cost then increases stage-by-stage throughout the protocol. The cost is only consistent between treadmill and shuttle walking between 1.2 and 1.4 m/s (close to comfortable walking speed) and the increase in energy requirements is much greater in shuttle walking. Based on these pilot data, we intend to report cardiorespiratory fitness values separately according to test modality and recommend this practice to others.

The classical description of the energy cost during locomotion is of a U-shaped relationship[18]—as speed increases or decreases from the optimal (1.11–1.3 m/s[18–20]) the energy cost of locomotion increases. For the treadmill protocol our data support this relationship. At slow speeds (0.6–0.8 m/s), energy cost was greater than at optimal speeds (1.2–1.4 m/s). As walking speed increased (1.6–1.8 m/s) the energy cost again began to increase. This is comparable to Berryman *et al*,[21] who reported a similar energy cost pattern for their participants (healthy elderly aged 68.9±4.6 years) when walking on a treadmill at speeds ranging from 0.67–1.56 m/s and the optimal walking speed was 1.33 m/s. Furthermore, our results also suggest that at lower speeds (0.50–0.84 m/s), the energy cost of walking on a treadmill is greater than on the ground. Berryman *et al*[21] also showed that there was greater energy cost of treadmill walking compared with ground walking at all the speeds they tested. The reason for the increased energy cost may be due to a greater need for stabilisation via muscular contraction while treadmill walking than when walking on the ground.[21]

Conversely, the oxygen requirements of shuttle walking are comparatively higher from level 7 (1.52 m/s) onwards than for treadmill walking at the same speed. The requirements are also much higher (18 mL/kg/min) than the value predicted by the American College of Sports Medicine (ACSM) walking speed equations[6] (12.6 mL/kg/min) that are used to estimate cardiorespiratory fitness from ISWT performance.[4] In addition to differences in oxygen requirements of ground and treadmill walking, shuttle walking may have a higher cost due to repeated acceleration/deceleration phases or the negotiation of turns.[7] We propose, therefore, that any clinical cut-offs for walking tests should be developed using the same testing modality as those for which they are proposed for use in (ie, treadmill or ground).

Cardiac patients' exercise capacity is commonly expressed as METs. We calculated metabolic cost in METs (gross $\dot{V}O_2$ [mL/kg/min]/3.5) and compared MET values at all ISWT stages with those reported previously[4] and the ACSM-predicted values (table 1). It should be noted that the values predicted using the ACSM walking equations by Woolf-May and Ferret[4] are incorrect. The MET values they reported in cardiac patients are almost double the predicted values using the ACSM equations and much higher than those reported presently. Woolf-May and Ferrett's[4] MET values further appear anomalous as they are more than double those of age-matched controls and significantly higher than recently reported values in cardiac patients during the ISWT.[7] These latter values[7] do, however, broadly agree with those presently reported.

Current recommendations suggest patients be classed as high risk if their exercise capacity is <5 METs. Failure to reach this criterion standard may lead to patients being prevented from entering community-based rehabilitation.[22] Woolf-May and Ferret's[4] suggestion that ISWT level 4 elicits a 5 MET energy cost in cardiac patients is inconsistent with recent data from Woolf-May and Meadows[7] and those of the present study, both of which suggest the 5 MET threshold is nearer level 7 or 8.

Fitter patients can be successfully 'fast tracked' to community rehabilitation, saving capacity and money to the health providers.[23] However, where exactly in the ISWT protocol this threshold occurs should be determined in a larger, more representative cohort of cardiac patients.

Beyond level 7 (1.52 m/s, 3.8 mph) shuttle walking incurred an additional extra energy cost compared with treadmill walking, which may make it difficult to show small improvements in functional capacity if reported as estimated MET values. The exercise capacity of cardiac patients measured before outpatient rehabilitation tends to be lower when estimated from ISWT[24] than when standard treadmill protocols are used.[25 26]

Study limitations and conclusions

Along with sample size, this study is also limited due to including predominantly male patients and indeed only including data from male participants at the highest

Table 1 Comparison of predicted values, published values and measured metabolic cost (METs) of the incremental shuttle-walking test

ISWT protocol level	Walking speed (m/s)	ACSM predicted METs	Published ISWT METs	Recorded METs: treadmill walking Mean (range)	Recorded METs: shuttle walking Mean (range)
1	0.50	1.9	3.0	2.3 (1.6–2.6)	2.0 (1.6–2.2)
2	0.67	2.1	3.7	3.3 (2.8–4.0)	2.7 (2.5–3.1)
3	0.84	2.4	4.4	3.6 (3.1–4.3)	3.1 (2.8–3.3)
4	1.01	2.7	5.1	3.8 (3.2–4.6)	3.6 (3.2–3.8)
5	1.18	3.0	5.9	4.0 (3.6–4.7)	4.0 (3.6–4.6)
6	1.35	3.3	6.6	4.4 (4.3–5.9)	4.4 (4.0–4.9)
7	1.52	3.6	7.3	5.0 (4.6–6.2)	5.3 (4.8–5.6)
8	1.69	3.9	8.0	5.5 (5.0–6.7)*	6.1 (5.7–6.6)*
9	1.86	4.2	8.7	–	–
10	2.03	4.5/7.9**	9.4	–	–
11	2.20	4.8/8.5**	10.2	–	–
12	2.37	5.1/9.1**	10.9	–	–

ACSM, American College of Sports Medicine; ISWT, incremental shuttle walking test; MET, metabolic equivalent (calculated as: gross $\dot{V}O_2$ [mL/kg/min]/3.5).
Published ISWT METs in cardiac patients from Woolf-May and Ferrett.[4]
*n=7 participants only. Predicted METs calculated using formula for walking or jogging** from ACSM.[6]

walking speeds. The comparison of treadmill and shuttle walking may have been improved by increasing treadmill gradient, as is common practice. We omitted to do this for comparability with previous work.[4 6] The accuracy of energy costs calculations would also be improved by including a resting metabolic measure pre-exercise instead of an assumed value of 4 mL/kg/m.[9]

In conclusion, the ISWT may have clinical utility as a measure of functional capacity to use in exercise prescription and patient monitoring, but we question its use as an estimate of cardiorespiratory fitness in cardiac patients. Importantly, the ACSM walking equations grossly underestimate the actual energy cost of shuttle walking and should not be used in research or clinical practice. Our comparison using METs also reveals that some published[4] estimates of the ISWT's energy cost in cardiac patients appear erroneously high. Given these two shortcomings, we strongly warn against clinical decision-making or patient risk stratification based on achieving the 5 MET threshold estimated using the ISWT. We recommend a more accurate assessment of the ISWT's energy cost be performed in a larger, more generalisable sample of cardiac patients.

Contributors GRHS, RB and MJDT devised the experimental design. MA and FC collected and analysed the data. RB performed the metabolic modelling and advanced statistical analysis. GRHS and MJDT drafted the manuscript. RB, MA and FC revised the manuscript. All authors contributed to the final preparation and drafting of the manuscript.

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Patient consent Obtained.

Ethics approval University of Essex.

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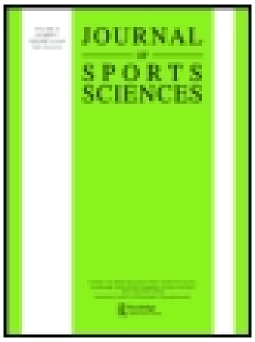

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Reference values for the incremental shuttle walk test in patients with cardiovascular disease entering exercise-based cardiac rehabilitation

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ABSTRACT

The incremental shuttle walk test (ISWT) is used to assess functional capacity of patients entering cardiac rehabilitation. Factors such as age and sex account for a proportion of the variance in test performance in healthy individuals but there are no reference values for patients with cardiovascular disease. The aim of this study was to produce reference values for the ISWT. Participants were $n = 548$ patients referred to outpatient cardiac rehabilitation who underwent a clinical examination and performed the ISWT. We used regression to identify predictors of performance and produced centile values using the generalised additive model for location, scale and shape model. Men walked significantly further than women (395 ± 165 vs. 269 ± 118 m; $t = 9.5$, $P < 0.001$) so data were analysed separately by sex. Age (years) was the strongest predictor of performance in men ($\beta = -5.9$; 95% CI: −7.1 to −4.6 m) and women ($\beta = -4.8$; 95% CI: −6.3 to 3.3). Centile curves demonstrated a broadly linear decrease in expected ISWT values in males (25–85 years) and a more curvilinear trend in females. Patients entering cardiac rehabilitation present with highly heterogeneous ISWT values. Much of the variance in performance can be explained by patients' age and sex. Comparing absolute values with age-and sex-specific reference values may aid interpretation of ISWT performance during initial patient assessment at entry to cardiac rehabilitation.

ARTICLE HISTORY
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KEYWORDS
Cardiovascular disease; functional capacity; GAMLSS; centiles

Introduction

The incremental shuttle walk test (ISWT) is recommended as a measure of functional capacity in cardiac rehabilitation (SIGN, 2002) and is the most commonly used exercise test in UK programmes (Brodie, Bethell, & Breen, 2006). The ISWT is a useful adjunct to risk stratification and exercise prescription when performed as patients enter cardiac rehabilitation programmes (SIGN, 2002). Repeat-testing on completion of rehabilitation is less common (Brodie et al., 2006), but the ISWT offers a safe and reliable (Jolly, Taylor, Lip, & Singh, 2008) tool with which to evaluate changes in patients' functional capacity (Almodhy, Sandercock, & Richards, 2012; Sandercock, Grocott-Mason, & Brodie, 2007).

Patients' ISWT performance is typically expressed as the total distance walked during the test (Almodhy et al., 2012; Arnold, Sewel, & Singh, 2007; Robinson, Samani, & Singh, 2011). In common with other walking tests (Enright & Sherrill, 1998; Fiorina et al., 2007), the distance patients walk during initial application of the ISWT varies according to their age, sex (Harrison et al., 2013) and anthropometric characteristics (Jurgensen et al., 2011; Luxton, Alison, Wu, & Mackey, 2008; Pepera, Cardoso, Taylor, Peristeropoulos, & Sandercock, 2013; Probst et al., 2012). The National Audit of Cardiac Rehabilitation (NACR) shows UK programmes cater for patients of both sexes, from 17 to 106 years-of-age, who may present with numerous clinical diagnoses and comorbidities (Doherty, 2014). Such a varied population results in highly heterogeneous ISWT performance values when patients are assessed at entry to cardiac rehabilitation (Almodhy et al., 2012; Arnold et al., 2007; Sandercock, Cardoso, Almodhy, & Pepera, 2013; Sandercock et al., 2007). Despite numerous studies showing how ISWT performance differs according to the age, sex and anthropometric characteristics of healthy adults (Harrison et al., 2013; Jurgensen et al., 2011; Probst et al., 2012), there are as yet no reference values available for patients with cardiovascular disease.

Our aim, therefore, was to produce reference values for ISWT performance in patients with cardiovascular disease assessed at entry to outpatient cardiac rehabilitation. Our hope is that these reference values may be used to improve clinicians' interpretation of initial ISWT values and patients' understanding of their own functional capacity.

Methods

Participants

Ethical approval for this study was obtained through the Integrated Research Application Service (REC reference: 09/H0305/102). Individuals' consent to participate in the study was not obtained, instead approval to assess patient records was sought via a request to the National

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Information Governance Bureau (Request: ECC 1-04(e)/2010). We accessed clinical records of n = 547 (n = 415, 76% males) patients aged 63.1 (±11.3) years who had entered outpatient cardiac rehabilitation at four UK hospitals. We included data from patients eligible for referral to outpatient cardiac rehabilitation according to current UK guidelines (NICE, 2007). We excluded the records of patients with severe orthopaedic limitations and patients with a primary diagnosis of congestive heart failure.

Table 1 describes patients' demographic, anthropometric and clinical characteristics. Primary diagnosis indicates the acute coronary event or the underlying condition which had prompted referral to cardiac rehabilitation. Primary treatment was the most-recent intervention patients had received either electively or as part of their treatment following an acute coronary event.

Procedures and data collection

All participating hospitals delivered cardiac rehabilitation in keeping with UK national standards (BACPR, 2012). All routinely assessed patients using the ISWT in accordance with national guidance including; standardised test administration, test termination criteria and employed the same contraindications to exercise testing (SIGN, 2002).

Table 1. Descriptive characteristics of patients at entry to outpatient cardiac rehabilitation.

Demographic and clinical characteristics	Mean (SD) or % (n =)
Number of patients	n = 547
Sex	Males 76% (n = 415)
	Females 24% (n = 132)
Ethnicity	White[a] 79.5% (n = 435)
	South Asian[b] 20.1% (n = 110)
	Black[c] 0.4% (n = 2)
Age (years)	63.1 (11.3)
Height (cm)	170.6 (8.7)
Weight (kg)	81.5 (17.3)
Body mass Index (kg m^{-2})	27.8 (5.2)
Diabetic	28.0% (n = 153)
Current smoker	25.6% (n = 140)
Time from event (or treatment) to ISWT (days)	53 (34–95)[d]
Primary diagnosis	
Post-MI	68.6% (n = 375)
CHD (elective revascularisation)	21.8% (n = 119)
Other	9.6% (n = 53)
Primary Treatment	
CABG	48.1% (n = 263)
PCI	42.1% (n = 230)
Valvuloplasty	6.6% (n = 36)
None	3.3% (n = 18)

Primary Diagnosis – extracted from patient records as most recent event and reason for attendance at cardiac rehabilitation. Primary treatment – extracted from patient record as most recent intervention received (Overall percentage is >100 due to some patients receiving multiple interventions, e.g., emergency PCI followed by CABG). CHD: coronary heart disease; MI: myocardial infarction; Other include: valvular dysfunction, arrhythmia, angina pectoris and peripheral vascular disease. CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention (includes balloon angioplasty emergency and non-emergency stenting).
[a]Includes White British, Irish and any other white category.
[b]Includes Indian, Pakistani, Bangladeshi and any other South Asian background.
[c]Includes Caribbean, African and any other black category.
[d]Indicates median value (interquartile range) due to skewed distribution.

Statistical analysis

Independent t-tests were used to confirm expected between-sex differences in ISWT performance (expressed as total distance walked). Stepwise linear regression was used to identify the strongest, independent predictors of ISWT performance and determine the most appropriate variables to use when creating reference data. We decided a priori to consider only those variables accounting for >5% additional variance in each regression model. These analyses were performed using SPSS 18.0 (SPSS, an IBM Company, Armon, NY).

Reference data were provided as tables and centile curves were constructed to describe ISWT performance (total distance walked) using the generalised additive models for location, scale and shape (GAMLSS) (Rigby & Stasinopoulos, 2006). GAMLSS models are part as a package in the statistical software R and this method is used by the World Health Organization Multicentre Growth Reference Study Group (Borghi et al., 2006).

Results

The demographic and clinical characteristics of patients are provided in Table 1. Patients' mean age was (63 ± 11) and 76% of the sample was male. ISWT performance ranged from 75 to 1145 m, with a mean of 365 (±164) m. Men (395 ± 165 m) walked significantly (t = 9.5, P < 0.001) further than women (269 ± 118 m). As sex accounted for 11% of total variance in distance walked, regression analyses to identify the predictors of ISWT performance were performed separately for males and females.

Table 2 shows age was negatively associated with distance walked in males (β = –5.9, 95% CI: –7.1 to –4.6 m) and females (β = –4.8, 95% CI: –6.3 to –3.3 m). As age was the strongest predictor of ISWT performance in both sexes, we constructed reference data according to age and sex.

Reference data: centile curves

Figures 1 and 2 show the centile curves for each sex (reference values are shown in Table 3). Male values were higher than those of females across the age range (25–85 years) for which centiles were constructed. In males, the relationship between

Table 2. Predictors of incremental shuttle walk test performance (distance walked, m) in n = 415 male and n = 127 female patients assessed at entry to outpatient cardiac rehabilitation.

Predictors: Males	β (95% CI)	R^2	SEE (m)
Age (years)	β = –5.9 (–7.1 to –4.6) m	0.16	152
Height (cm)	β = 5.0 (3.1 to 6.8) m	0.20	148
BMI (kg/m^2)	β = –5.1 (–7.9 to –2.2) m	0.23	145
Presence of diabetes	β = –48.7(–17.3 to –80.2) m	0.25	144
Predictors: Females	β (95% CI)	R^2	SEE (m)
Age (years)	β = –4.8 (–6.3 to –3.3) m	0.20	108
Presence of diabetes	β = –80 (–39.5 to –120.5) m	0.23	103
Height (cm)	β = 2.8 (0.11 to 5.5) m	0.24	102

Multivariate β coefficients provided using a stepwise model (final model only-shown with strongest predictor first). Only significant (P < 0.05) predictors are shown. R^2: cumulative variance accounted for by each (additional) factor; SEE: standard error of estimation for each model.

Table 3. Centile values for total distance walked during the incremental shuttle walk test by patients (age 25–85 years) with cardiovascular disease assessed at entry to outpatient cardiac rehabilitation.

Males age	C3	C10	C25	C50	C75	C90	C97	Mean	SD
25	277	413	413	609	699	860	1145	635	237
30	256	381	492	579	676	833	1092	603	221
35	236	351	458	549	651	803	1036	571	208
40	217	322	424	519	625	771	978	539	196
45	199	295	392	489	597	735	918	507	186
50	182	269	361	459	569	698	858	475	176
55	166	245	331	429	539	658	798	444	166
60	150	221	302	399	507	618	739	412	156
65	135	199	274	369	475	575	680	380	146
70	120	178	247	339	441	532	621	349	136
75	106	157	221	309	406	488	564	317	126
80	93	137	196	279	370	443	507	286	116
85	79	118	171	250	333	397	450	254	105
Females age	**C3**	**C10**	**C25**	**C50**	**C75**	**C90**	**C97**	**Mean**	**SD**
25	150	263	384	507	616	704	784	495	168
30	132	237	349	466	570	655	732	455	159
35	116	214	318	428	527	609	684	455	150
40	103	193	290	393	487	567	640	386	143
45	93	175	265	361	451	527	600	356	134
50	85	160	242	332	417	491	562	329	126
55	79	148	222	305	386	458	528	304	119
60	77	138	205	281	358	427	496	282	111
65	76	130	189	259	332	399	467	263	104
70	77	123	176	239	308	373	441	245	97
75	77	117	163	221	286	349	417	228	90
80	77	111	151	204	265	327	395	213	85
85	75	104	140	189	246	307	375	199	81

Age (years) grouped according to 5-year increments using patients' decimal age rounded down to nearest whole year. C: centile value for age grouping (distance walked in m); SD: standard deviation.

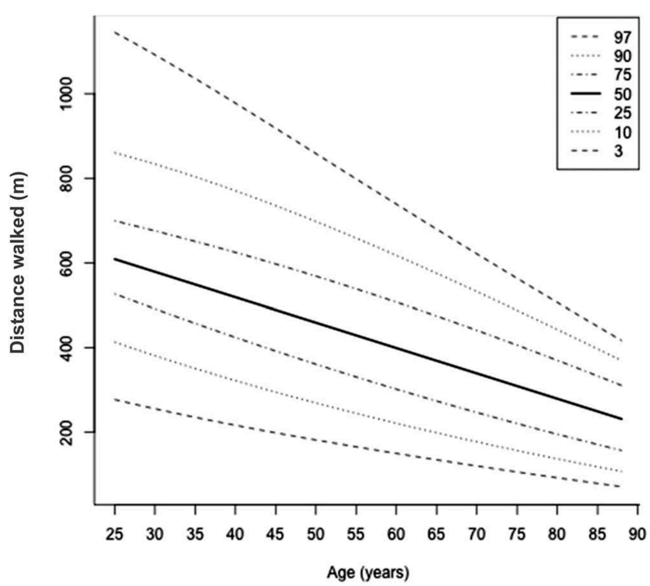

Figure 1. Smoothed centile curves showing incremental shuttle walk test performance in male patients (age 25–85 years) assessed at entry to outpatient cardiac rehabilitation.

age and performance was broadly linear. The median ISWT performance of females was more curvilinear with a steeper decrease in younger women (25–60 years) followed by a more-shallow, linear decrease from age 60 onwards.

The median (50th percentile) expected value for the youngest patients was more than double that of the oldest in males and females. There was still, however, a twofold difference in expected values between the 3rd and the 97th percentile in both sexes and at all ages.

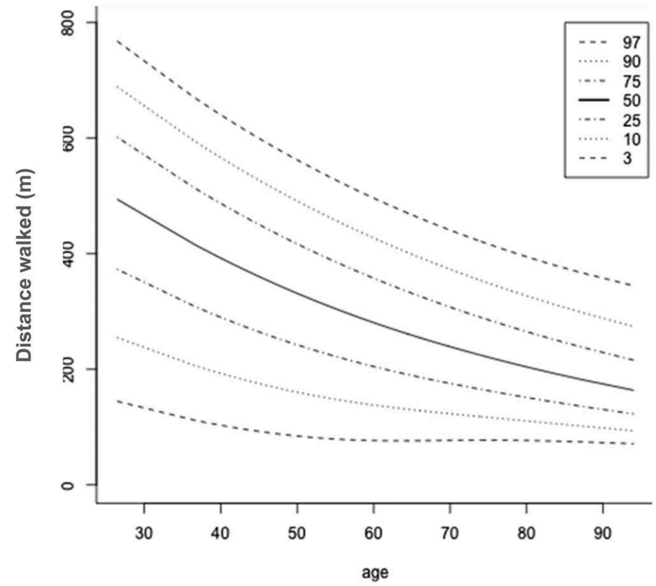

Figure 2. Smoothed centile curves showing incremental shuttle walk test performance in female patients (age 30–90 years) assessed at entry to outpatient cardiac rehabilitation.

Discussion

We present reference values for the ISWT in patients with cardiovascular disease at entry to outpatient cardiac rehabilitation. Patients' mean age (63 ± 11 years) was slightly lower than that of typical UK cardiac rehabilitation patients (66–70 years) reported in the NACR (Doherty, 2014). Male patients had a mean age (62 years) similar to that reported for men in the NACR (66 years). The mean age of female patients (63 years) meant they were, on average, 7 years younger than females (70 years) typically attending cardiac rehabilitation in the UK (Doherty, 2014). The age difference and smaller sample size mean our reference values for female patients may be less generalisable. A smaller sample of females is to be expected in a study accessing the records of consecutive patients. Nationally, men account for 70% of cardiac rehabilitation patients slightly lower than the 76% value in our sample. The proportion of white participants (79.5%) was similar to national data (80%). Our median time from event to ISWT was 53 days. Post-MI patients typically start rehabilitation 40 days following treatment with percutaneous coronary intervention (PCI); patients receiving CABG start an average of 54 days after referral (Doherty, 2014). Comparable times for our sample were 42 days (for post-MI, patients receiving PCI) and 63 days for CABG patients. Again, both these figures are close to nationally reported values suggesting this was a broadly typical cohort of UK cardiac rehabilitation patients. Age and sex accounted for 25% of variance in test performance in the population as a whole. Age alone explained the highest proportion of variance in ISWT performance in both male (16%) and female (20%) patients.

Median distance walked varied more than twofold across the age-range in females; the 50th percentile fell from 507 m at age

25 years to only 189 m at age 85. Age-related variation in the median value for males was even also more than twofold; the 50th percentile at age 25 years was 609 m falling to only 250 m by age 85. The centile curves provide the first set of reference values in cardiac patients. These age- and sex-specific values now allow practitioners to individualise the interpretation of patient's ISWT performance at entry to cardiac rehabilitation.

Predictors of ISWT performance

Verification of age and sex as important predictors of ISWT performance in patients agrees with data from healthy individuals (Dourado, Guerra, Tanni, Antunes, & Godoy, 2013; Dourado, Vidotto, & Guerra, 2011; Harrison et al., 2013; Jurgensen et al., 2011; Probst et al., 2012). Such studies are only of value in cardiac rehabilitation if the factors which predict ISWT performance of healthy individuals also predict the performance of cardiac patients. Unfortunately, none of the equations developed in healthy populations have been cross-validated in a sample of cardiac patients. Healthy individuals tend to walk twice as far during the ISWT (600–800 m) than cardiac patients (300–400 m). Such large differences hinder any generalisation of findings in healthy individuals to cardiac patients entering rehabilitation.

The difference in distance walked between males and females agrees with the limited data which are available in cardiac patients (Pepera et al., 2013). These authors (Pepera et al., 2013) also found height predicted 17% of variance in ISWT performance in their small sample including both men and women. We could not confirm this in our analysis in females, but height (cm) did explain a further 5% of variance in males' ISWT performance. In an additional *post hoc* analysis using a binary dummy variable for height (short vs. tall based on a median split), we found tall males walked 52 m further than shorter patients independent of age. There may be some benefit from future studies which create different sets of reference values for taller and shorter males although this may cause confusion when interpreting scores of patients whose height sits just above and below any cut-off value.

The presence of diabetes accounted for a significant additional proportion of the variance in distance walked by female patients. Diabetics walked 80 m less than non-diabetic female patients. There may be some need to take diabetes into consideration when interpreting ISWT performance. However, this finding should be interpreted cautiously as it was based on a very small (n = 35) sample of female patients.

Clinical use and interpretation of ISWT performance

Patients' results from initial assessment using the ISWT are currently used in risk stratification and exercise prescription. Results can also be used in goal setting and if a retest is performed at the end of rehabilitation change in ISWT is an excellent way to evaluate improvements in functional capacity (Sandercock et al., 2013). Improved functional capacity is one of the goals for exercise-based cardiac rehabilitation, and assessing groups of patient's change in ISWT performance during outpatient CR allows researchers and clinicians to identify the elements of effective programmes (Sandercock, Hurtado, & Cardoso, 2011).

However, the heterogeneity of patients entering contemporary cardiac rehabilitation programmes (in terms of sex, age, diagnosis, treatment, comorbidities) and variation in the time between patients' cardiac event or surgery and when they first perform the ISWT (median 53 [34–95] days) are all likely contributors to the large inter-patient variation in initial ISWT performance. Numerous studies have demonstrated that non-modifiable characteristics are associated with ISWT performance (Dourado et al., 2013; Harrison et al., 2013; Jurgensen et al., 2011; Pepera et al., 2013; Probst et al., 2012). To our knowledge, there is currently no guidance available as to how clinicians should account for such factors when interpreting patients' ISWT performance. Where age is associated with an outcome variable, it is common practice to interpret actual (raw) scores by comparing them with reference data in the form of centile curves (Cole & Green, 1992). This is common practice in anthropometry but also when assessing children's performance on tests of motor function (Hanna, Bartlett, Rivard, & Russell, 2008) or cardiorespiratory fitness (Sandercock, Voss, Cohen, Taylor, & Stasinopoulos, 2012). Performance on the 6-min walk test is commonly expressed as a relative score by calculating patients actual test performance as a percentage of typical values derived from healthy age-matched individuals (Dourado et al., 2011; Enright & Sherrill, 1998). The ISWT is the protocol most commonly used to assess patients' functional capacity in UK cardiac rehabilitation centres (Brodie et al., 2006), but no comparable use of reference data or expression of test performance relative to patients' age or sex has yet been adopted.

The ISWT has been successfully used to "triage" patients more accurately at entry to outpatient CR; by identifying individuals to be "fast tracked" to community rehabilitation (Robinson et al., 2011) Interpretation of ISWT performance in absolute (distance walked) terms creates an obvious preference for younger, male patients to meet potential fast-track criteria regardless of their actual functional capacity. This is clearly evident in the population characteristics of the fast-tracked patients (Robinson et al., 2011).

We suggest practitioners may be able to make more meaningful interpretation of test scores when combined with these reference data. This practice may aid clinical decision-making, improve patient understanding and goal setting at entry to outpatient cardiac rehabilitation. For example, an 80-year-old female walking 200 m is performing at the expected level (50th Percentile) and her goal during rehabilitation may be to improve by 50 m – taking her performance to the 70th percentile whereas the same absolute ISWT distance of 200 m would place a 50-year-old male below the 5th percentile for age and sex. Creating relative scores from reference data like ours demonstrates the need to improve fitness is greater in the latter patient; he could be set a greater goal for improvement such as 200 m, which would still be well within the expected range of values for ISWT performance. Setting the same 200 m goal for the 80-year-old female would be inappropriate; she simply would not be expected to be able to perform to this level at her age. There are as yet, no cut-offs to define a meaningful improvement on the ISWT; such as there are for changes in the 6-min walk test (Cacciatore et al., 2012). A recent suggestion that 38.5 m (4 shuttles) could represent a minimal clinically important difference (MCID) was based on perceived improvement in patients' symptoms (Houchen-Wolloff, Boyce, & Singh, 2015). The ISWT protocol is itself reproducible (Jolly et al., 2008), but the subjective symptom ratings used by Houchen-Wolloff et al. (2015) were not; neither did these ratings correlate well with actual changes in ISWT. Research to identify age- and sex-specific MCIDs for the ISWT is needed to improve its utility both in patient monitoring and prediction of risk.

Patients ISWT performance is sometimes converted to metabolic equivalents using a linear equation to predict the oxygen cost of walking. We recently reported that the oxygen cost of walking during the ISWT is actually curvilinear (Almodhy, Beneke, Cardoso, Taylor, & Sandercock, 2014) especially at the higher walking speeds required in later test stages. This means that patients who perform well during initial testing may express smaller than expected gains in absolute performance when retested. This problem might be particularly acute in older patients; especially older females with good initial test performance if clinicians rely only on the difference in absolute test scores to describe changes in functional capacity. Expressing ISWT performance in relative terms would demonstrate to patients that their initial score is already higher than expected for their age and sex and could be used to set more realistic goals for functional capacity gains. Future research should determine whether using centile curves or calculating age- and sex-specific relative scores can improve clinical interpretation and patient understanding of results from the ISWT performed as part of cardiac rehabilitation.

Study limitations

Our sample is broadly typical of cardiac rehabilitation patients in England but may not be internationally generalisable. Given the potential influence of height (males) and presence of diabetes (females), these reference data should be used with caution in males at extremes of the normal height distribution and diabetic patients. Future research is needed to confirm or refute the predictors of ISWT performance identified here and the shape and distribution of our centile curves. Future research should identify whether it is necessary to produce additional reference data for specific populations such as diabetics. The LMS method provides robust estimates of centile values across the age-range of sample and we can be more confident in our estimates (including the youngest and oldest patients) than if we had used regression to predict ISWT performance as others have (Jurgensen et al., 2011; Luxton et al., 2008; Pepera et al., 2013; Probst et al., 2012). Nevertheless, due to the relatively small number of females, reference values presented here for female patients should be interpreted with some caution.

These reference values provide only expected walking distances in patients entering cardiac rehabilitation and we cannot suggest an MCID or clinical cut-off for "good" test performance nor assess how ISWT performance may change due to cardiac rehabilitation (Sandercock et al., 2013). Our findings do not address the usefulness of ISWT performance in patient risk stratification. To improve the ISWT's role in risk stratification and exercise prescription, research is needed to identify predictors of change in ISWT performance in patients receiving exercise-based cardiac rehabilitation.

Conclusion

We provide the first reference data for the incremental shuttle walking test in patients at entry to cardiac rehabilitation. We propose that clinicians should assess test scores by comparison with these age- and sex-specific reference values. This practice will provide a more meaningful and individualised assessment of patients' functional capacity at the start of their cardiac rehabilitation programmes.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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ORIGINAL RESEARCH ARTICLE

Oxygen Costs of the Incremental Shuttle Walk Test in Cardiac Rehabilitation Participants: An Historical and Contemporary Analysis

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Abstract
Background The incremental shuttle walk test (ISWT) is a standardised assessment for cardiac rehabilitation. Three studies have reported oxygen costs (VO_2)/metabolic equivalents (METs) of the ISWT. In spite of classic representations from these studies graphically showing curvilinear VO_2 responses to incremented walking speeds, linear regression techniques (also used by the American College of Sports Medicine [ACSM]) have been used to estimate VO_2.
Purpose The two main aims of this study were to (i) resolve currently reported discrepancies in the ISWT VO_2-walking speed relationship, and (ii) derive an appropriate VO_2 versus walking speed regression equation.
Methods VO_2 was measured continuously during an ISWT in 32 coronary heart disease [cardiac] rehabilitation (CHD-CR) participants and 30 age-matched controls.
Results Both CHD-CR and control group VO_2 responses were curvilinear in nature. For CHD-CR $VO_2 = 4.4e^{0.23 \times \text{walkingspeed (km/h)}}$. The integrated area under the curve (iAUC) VO_2 across nine ISWT stages was greater in the CHD-CR group versus the control group ($p < 0.001$): CHD-CR = 423 (±86) ml·kg^{-1}·min^{-1}·km·h^{-1}; control = 316 (±52) ml·kg^{-1}·min^{-1}·km·h^{-1}.
Conclusions CHD-CR group vs. control VO_2 was up to 30 % greater at higher ISWT stages. The curvilinear nature of VO_2 responses during the ISWT concur with classic studies reported over 100 years. VO_2 estimates for walking using linear regression models (including the ACSM) clearly underestimate values in healthy and CHD-CR participants, and this study provides a resolution to this when the ISWT is used for CHD-CR populations.

Key Points

The change in oxygen cost (VO_2) during a standardised incremental walking test in healthy and cardiac rehabilitation participants responds in a classic curvilinear nature; linear regression should not be used to estimate oxygen uptake (VO_2/metabolic equivalents) from walking speed.

Coronary heart disease patients performing incremental walking tests require up to 30 % more oxygen compared with age-matched non-CHD controls.

1 Introduction

The 10-m incremental shuttle walk test (ISWT) was originally developed in 1992 for assessing peak exercise capacity in patients with pulmonary disease [1, 2]. The concept of the shuttle protocol ('bleep test') was derived from a 20-m shuttle test for athletes [3]. The ISWT has

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now become a standardised tool for assessing aerobic fitness in cardiac populations attending exercise-based rehabilitation [4–7]. A known or estimated peak oxygen consumption (VO_2peak) attained during exercise can provide valuable information for decision making in cardiac rehabilitation, including patient risk stratification [6, 8, 9]. The gold-standard measurement for assessing VO_2peak is an incremental and maximal exercise test (e.g. treadmill or cycle ergometer), but in its absence the ISWT has been widely recommended for cardiac rehabilitation [6, 7, 10, 11]. The ISWT can provide practical valuable information for physical activity guidance and exercise prescription, along with more traditional information for evaluating changes in exercise capacity, either as an outcome measure for individual patients or whole service delivery [12, 13].

To date, only three studies (summarised in Fig. 1) have reported the oxygen cost (VO_2) or metabolic equivalents (METs) for each stage of the ISWT in cardiac populations compared with age-matched controls [12, 14, 15]. The data from these studies make it possible to compare measured VO_2 values with VO_2 estimates derived from a linear regression equation recommended by the American College of Sports Medicine (ACSM) [9]. In all cases, the values reported in both the healthy and, in particular, cardiac populations were greater than those estimated by the ACSM [9]. The first study by Woolf-May and Ferrett [14] reported VO_2 values for cardiac patients up to 40 % greater than estimated by the ACSM during the initial test stages of the ISWT, and up to 90 % greater during the latter stages. In comparison to age-matched healthy individuals, the measured VO_2 of cardiac patients was 26 and 47 % greater at the lower and upper stages, respectively. However, the second study from the same group [15] reported recorded

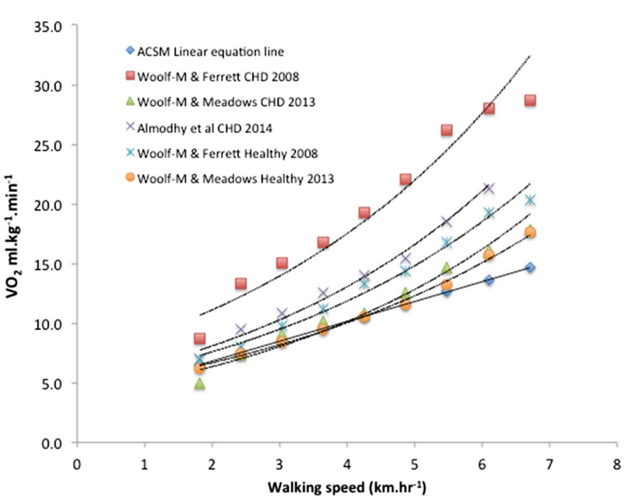

Fig. 1 Oxygen cost of the incremental shuttle walk test in cardiac rehabilitation participants and age-matched healthy controls [9, 12, 14, 15]. *ACSM* American College of Sports Medicine, *CHD* coronary heart disease

VO_2 values during the ISWT that were similar to the ACSM estimates at stages 1–5. The values then increased in a curvilinear fashion until they were 20 % greater than estimated by the ACSM equation at stage 9—far less than the 90 % difference they previously reported in a similar population. Also contrary to their former study, the VO_2 values differed very little between cardiac rehabilitation participants and age-matched controls. Such inconsistencies without any comment from the same group of researchers means that cardiac rehabilitation professionals are currently faced with some confusion over estimating the oxygen costs of the ISWT, whether for the purpose of exercise prescription or risk stratification.

An initial step towards resolving these ISWT VO_2 inconsistencies has more recently been provided by Almodhy et al. [12], albeit in a small pilot study of cardiac patients ($n = 8$). As illustrated in Fig. 1, these investigators reported VO_2 values residing between those reported previously by Woolf-May et al. [14, 15]. Almodhy et al. [12] also demonstrated that VO_2 responses to the ISWT were fundamentally different to those of treadmill exercise, the gold-standard method of assessing VO_2peak in cardiac patients and the reference standard for the ACSM equations.

Another area of concern with the extant descriptions of the ISWT's oxygen cost reported by Woolf-May et al. are the authors' interpretations of recorded data and the application of the ACSM estimation equations [9]; both assume a linear relationship between increments in walking speed and VO_2 [14, 15]. This assumption is contrary to the accepted findings of numerous studies dating back to the classic work by Douglas and Haldane in 1912 [16], which have all consistently reported VO_2 responding as a positive curvilinear function of speed during walking exercise. Figures 2 and 3 illustrate the historical findings of such classic works from 1912 to 1976, including a composite estimate of the VO_2 response from studies published up to 1938 by Passmore and Durnin [17], followed by Margaria et al. [18], Menier and Pugh [19], and Falls and Humphrey [20]. The ACSM equations have been based on the work by Dill [21], Naughton and Nagle et al. [22], and Margaria et al. [18] (for VO_2 during incremental treadmill exercise speed and gradient, and box stepping). The total number of participants in the walking assessments was only five. The approach the ACSM has applied has involved creating two different equations for walking and running, but because they have not employed a curvilinear analysis for walking as the classic studies demonstrated, a >50 % gap or 'jump' in the VO_2 estimates occurs during the transition speed from walking to running (approximately 7–8 $km \cdot h^{-1}$). The range of horizontal walking speeds reported in the three participants assessed by Dill [21] ranged between 3.6 and 7.2 $km \cdot h^{-1}$ and clearly showed a classic positively accelerating curve. Dill [21] cited the work of both Margaria

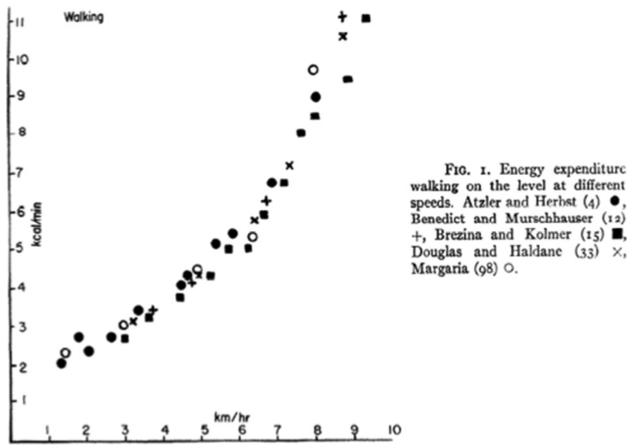

Fig. 2 Summary of historical studies (1912–1938) on the energy expenditure response to walking speeds 1–9 km·h^{-1} (0.6–5.6 mi·h^{-1}). Reproduced from Passmore and Durnin [17], with licensed permission from Physiological Reviews, American Physiological Society

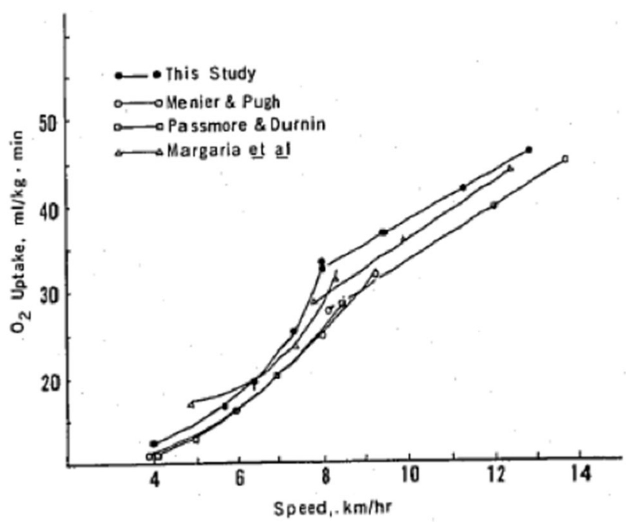

Fig. 3 Relationship between energy expenditure and speed of progression in walking and running. Reproduced from Falls and Humphrey [20], with licensed permission from Medicine and Science in Sports and Exercise

et al. [18] and Passmore and Durnin [17] but did not note the curvilinearity in these data. One of the most popular exercise physiology text books from the US, first published in 1981 and its latest edition published in 2014, has consistently highlighted, with each successive edition, the curvilinearity of VO_2 as a function of walking speed [23]. The VO_2 curvilinearity related to treadmill walking speed has been further supported in young, healthy participants by more recent detailed mathematical modelling [24].

Just as the historical data have shown, upon simple visual examination of the more recent ISWT studies (Fig. 1), there is clearly a curvilinear relationship between VO_2 and walking speed for both treadmill and overground walking. The curvilinearity of these values is made very apparent when the predictive linear equation recommended by the ACSM [9] is plotted as a reference line. The responses of heart rate and ratings of perceived exertion (RPE) reported by Woolf-May and Meadows [15] also demonstrated clear and corresponding curvilinear patterns, confirming the traditional assumption that these measures are strong correlates of measured VO_2. The VO_2 values in Fig. 1 for the ISWT have been reported from stages 1–9; stages 10–12 have not been included because these represent speeds for running (7.5–8.0 km·h^{-1} or 4.7–5.0 mi·h^{-1}). Traditionally, VO_2 for running has shown a linear relationship (Fig. 3) [20].

The disparity of findings between studies, the potentially flawed assumption of a linear relationship, and the inadequacy of the prediction equation to estimate the ISWT's oxygen cost are problematic. Further data are needed to promote confidence in cardiac rehabilitation professionals when wishing to apply assumptions of the VO_2 values in patients who have been assessed with the ISWT.

2 Aims

The aims of this study have therefore been twofold: (i) to determine an appropriate VO_2 estimation equation (curvilinear or linear?) for walking speeds during the ISWT; and (ii) to resolve the currently reported discrepancies in the VO_2-walking speed relationship for cardiac patients.

3 Methods

3.1 Participants

Following ethical approval from the University of Essex, the University of Chester and the National Health Service's Northwest Region (Liverpool/Manchester) ethics committees, cardiac rehabilitation participants from two standardised community-based cardiac rehabilitation programmes (using British Association for Cardiovascular Prevention and Rehabilitation [BACPR] standards, 2013) [25] were recruited via open invitations to any patient diagnosed with and being treated for cardiac disease as per national guidelines [26]. Inclusion criteria were based on standard eligibility for a UK cardiac rehabilitation service [27]. Patients were excluded from participating for the following reasons: an auditory impairment that did not allow them to hear the audio shuttle-pacing bleeps of the ISWT; cognitive impairment that prevented them from understanding how to perform the test or comprehend instructions to remain in independent control of their walking pace; a diagnosis of heart failure or chronic obstructive pulmonary disease that would affect normal pulmonary responses to exertion; or a significant neuromusculoskeletal or vascular condition that impaired them from being able to safely perform and complete at least five stages of the ISWT while comfortably tolerating walking up to a steady vigorous pace. Age-matched controls were then recruited, under the same exclusion criteria as the coronary heart disease (CHD) patients, but with inclusion criteria set for people within the same age range as the agreed volunteering CHD group. The control group was already attending the same community centres, either for personal health-promoting exercise or as participants from their local primary-care exercise referral programme who had been referred for an elevated risk of cardiometabolic disease. As this was a convenience sample, exact matching for numbers and gender was not possible, but previous reports on VO_2 during walking have shown little difference between genders [20, 28].

3.2 Sample Size

For 85 % power, a VO_2 of 1.75 ml·kg^{-1}·min^{-1} was determined to represent a clinically important difference in oxygen cost, based on the pilot data from Almodhy et al. [12]. In conjunction with this clinical significance, and where participants were assumed to have enough fitness to complete five stages at an estimated VO_2 of 14 ml·kg^{-1}·min^{-1}, 30 participants per group were deemed suitable for achieving the effect size of at least 10 %, as well as an α of $p < 0.05$ and $\beta = 0.8$.

3.3 Procedures

Prior to testing, all participants were health screened for clearance to perform moderate to vigorous exercise by way of standarised procedures [6, 11], which were employed by qualified cardiac rehabilitation staff. Measurements included resting heart rate, blood pressure, height, age and body mass, where all of these were also required for measuring the cardiopulmonary gas exchange.

All participants performed the recommended ISWT practice test [1, 5], which also included familiarisation in wearing the respiratory face mask although not connected to the gas analysis system. Participants then rested for the required 30 min before performing the actual data collection test. The test endpoint, in keeping with BACPR (2015) and Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR; 2015) [6, 11] recommendations, was the attainment of 75 % of heart rate reserve (approximately 80–85 % HR_{max}) and/or an RPE of 14–15 on Borg's scale [29]. During the ISWT, cardiopulmonary gas exchange was measured continuously via a portable gas analysis system (K4b2 Mobile Breath-by-Breath Metabolic System; COSMED, Rome, Italy). The expired air and gas concentrations were measured via a pneumotach connected to the face mask (Hans Rudolph, Inc., Shawnee Mission, KS, USA). The system was calibrated for each participant using known concentrations of oxygen and carbon dioxide and a 3-l syringe to calibrate for the volume of pulmonary air exchanged. Heart rate was measured using a Polar chest strap telemetry system (Polar Electro, Kempele, Finland). For data analyses, the average VO_2, heart rate and RPE captured in the last 15 s of each of the 1-min stages was recorded and entered into the statistical analyses computer software package (SPSS for Windows, version 20; IBM Corporation, Armonk, NY, USA).

3.4 Data Analyses

Group descriptive data are represented as means $\pm$ 1 standard deviation (SD). Curvilinear exponent regression analysis of VO_2 responses was performed as a function of the ISWT stage (transformed into continuous data as walking speed in kilometres/hour; km·h^{-1}), where $y = VO_2$; b is the constant y-intercept value when $x = 0$; $e =$ the natural exponent constant of 2.71828183 raised to the power of a (representing the acceleration component of the regression curve); and $x =$ walking speed in km·h^{-1}. Due to the expected curvilinear nature of the data and multiple stages of the ISWT, the oxygen cost for each participant's completed test was calculated using an integrated area under the curve (iAUC) trapezoidal method. Independent t tests were performed to compare data between the cardiac group and the age-matched controls. Where data were compared with group mean values from previous studies, a one-sample t test was performed.

4 Results

4.1 General Participant Data

Thirty-two cardiac rehabilitation participants and 30 age-matched controls completed the ISWT to stage 5 or higher. Group comparisons are summarised in Tables 1, 2 and 4. The control group walked 152 m further ($p < 0.001$) than the cardiac group (Table 2), and this difference remained when participants were divided into subgroups of males and females.

Participants' age (64.5 $\pm$ 7.8 years) was near to the mean age of those attending cardiac rehabilitation in the UK (66 years), but our study had a greater proportion of females 44 % compared with the national average of 30 % [7].

Table 1 Descriptive characteristics of participants

	Cardiac group	Age-matched controls
N (no. on β-blocker medication)	32 (20)	30
Sex, male (%)	18 (56)	11 (35)
Age, years	64.5 ± 7.8	63.4 ± 8.6
Height, cm	173.1 ± 8.2	168.8 ± 7.1*
Mass, kg	85.4 ± 11.2)	78.7 ± 16.9
Body mass index	28.6 ± 3.2	27.6 ± 5.2
Walking distance, m		
Male	548 ± 183	687 ± 158**
Female	464 ± 152	650 ± 192**
Total	512 ± 173	664 ± 179**

Data are expressed as mean ± standard deviation unless otherwise stated

Control versus cardiac group

* $p = 0.032$

** $p \leq 0.001$

Table 2 Participants' conditions/treatments

Cardiac group	n	Age-matched controls	n
Angina	3	Hypertension	4
Myocardial infarction	7	Orthopaedic	5
Angioplasty	8	Obese	3
Coronary bypass	9	Smoking	2
Others	5	Others	3
		Nothing reported	13

Others: atrial fibrillation, dilated cardiomyopathy, pacemaker, valve replacement

Age-matched controls others: stroke, chronic fatigue, diabetes

4.2 Oxygen Cost of the Incremental Shuttle Walk Test (ISWT) Within this Study

Within the control group, a subgroup analysis was performed between those with identified health conditions ($n = 17$) and those without ($n = 13$). No difference was observed in the oxygen cost of walking in these two groups at any stage, which allowed the data to be pooled into one complete control group ($n = 30$). The same was true for male and female participants. Analyses of the data was capped at ISWT stage 9 so as to focus on the evaluation just for walking; all participants who proceeded on to stage 10 or higher had to run, which is commensurate with a similar walk–run threshold reported in classic studies (Fig. 3) [20]. Both the cardiac and control group VO_2 responses were curvilinear in nature (Fig. 4). While there was no significant difference in the VO_2 y-intercept values between the two groups (cardiac = 4.5, control = 5.1; $p = 0.064$), the cardiac participants' responded with a significantly steeper growth curve exponent of 0.27 ± 0.06 versus 0.20 ± 0.04 ($p < 0.0001$) (Fig. 4).

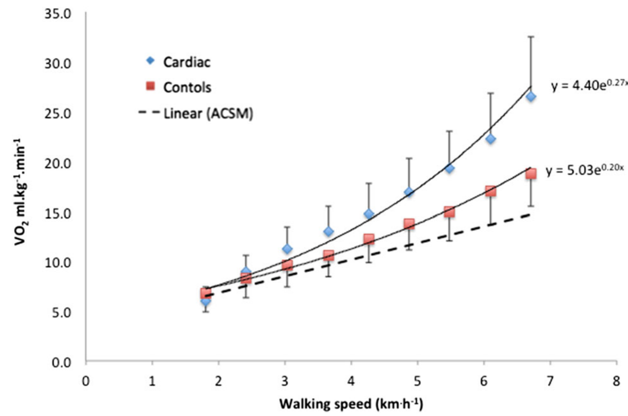

Fig. 4 Curvilinear regression analysis of the oxygen cost of the incremental shuttle walk test in coronary heart disease cardiac rehabilitation participants and age-matched controls. *ACSM* the linear regression line for estimating the oxygen cost of walking by the American College of Sports Medicine [9]

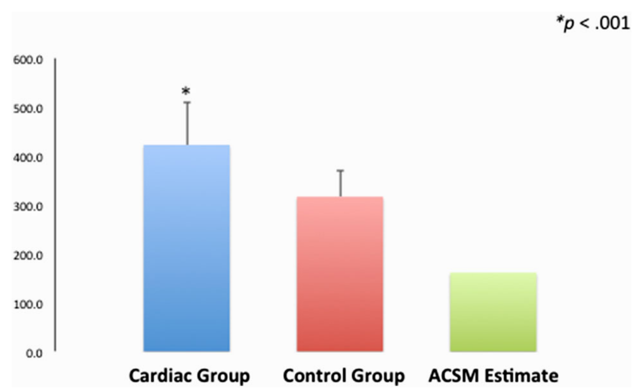

Fig. 5 Integrated area under the curve for the oxygen costs (VO_2 × walking speed; ml·kg^{-1}·min^{-1}·km·h^{-1}) of cardiac rehabilitation participants and age-matched controls performing the incremental shuttle walk test up to stage 9. *$p < 0.001$ cardiac group compared with control, and control with ACSM estimate [9]. *ACSM* American College of Sports Medicine

For the purpose of comparing the between-groups total ISWT VO_2 from the iAUC, only data from those participants in both groups who completed nine stages of the ISWT were included for analysis ($n = 18$ of 32 cardiac patients, $n = 25$ of 30 controls). As illustrated in Fig. 5, the total ISWT iAUC oxygen cost across these nine ISWT stages was significantly greater in the cardiac group compared with the control group ($p < 0.0001$), for which the values were:

– iAUC cardiac group = 423 (±86) ml·kg^{-1}·min^{-1}·km·h^{-1}

– iAUC control group = 316 (±52) $ml\cdot kg^{-1}\cdot min^{-1}\cdot km\cdot h^{-1}$

With the reduced sample size of the cardiac group down to 18 from 32 for these iAUC differences between cardiac and controls analysis, the effect size was 1.24, with a power of 95 %.

4.3 Oxygen Cost Trend Comparisons with Previous Studies

Curvilinear regression equations and iAUC VO_2 values were calculated from and compared with previous ISWT studies and historical data. The historical data were reproduced from values presented in Figs. 1 and 3, and with regression equations formulated from these data (Table 3). Regression lines from Passmore and Durnin [17] and Menier and Pugh [19] (Figs. 2, 3) were almost identical, therefore these data were pooled to create a single regression equation (Table 3). The ACSM [9] linear equation returned the lowest iAUC VO_2 value compared with all other studies (Table 3; Fig. 5).

No significant difference was observed in the iAUC VO_2 of the cardiac group in this current study when compared with the cardiac group of Almodhy et al. [12], and also with the healthy young participants from the historical and classic studies (1912–1938) summarised by Passmore and Durnin [17] and Falls and Humphrey [20] (Table 3). The original ISWT METs study by Woolf-May and Ferrett [14] (cardiac group) had iAUC VO_2 values significantly greater than the cardiac group of this present study; the remaining data sets all had significantly lower iAUC VO_2 values (Woolf-May and Ferrett [14], healthy; Woolf-May and Meadows [15], cardiac and healthy). It was decided not to include the athletes' study of Margaria et al. [18] in the comparative analysis because only two participants were assessed within a narrow range of walking speeds, with the lowest speed being 5 $km\cdot h^{-1}$.

In the data sets of six of the eight previous studies, the y-intercept value 'b' of the regression equations, which theoretically represents the VO_2 at walking speed as zero (standing), were all within ±0.5 $ml\cdot kg^{-1}\cdot min^{-1}$ of the y-intercept value of this current study's cardiac group. Although the differences were statistically significant, they were small in terms of the clinical significance threshold as set by the expected effect size of 1.75 $ml\cdot kg^{-1}\cdot min^{-1}$. In the remaining cardiac group data set of Woolf-May and Ferrett [14], the y-intercept VO_2 was significantly greater (statistically and clinically) by up to 2.5 $ml\cdot kg^{-1}\cdot min^{-1}$. These differences corresponded to the much greater iAUC VO_2 values noted above. The steepness of the regression curve in the cardiac group of this current study, as denoted by the 'exponent x' value ($0.27x$), was significantly greater compared with the data sets of all other studies (cardiac and healthy) (Table 3).

4.4 Conversion to Metabolic Equivalents (METs) for Cardiac Groups

For the purposes of practically applying this information in monitoring or guiding exercise intensity in cardiac rehabilitation, Table 4 summarises the oxygen cost in units of METs at each ISWT stage. These values are based on the assumption that 1 MET equals a VO_2 of 3.5 $ml\cdot kg^{-1}\cdot min^{-1}$ [30]. MET values from Almodhy et al. [12] agree most closely with this current study, where the mean difference for stages 1–8 is 0.2 METs (range 0.1–0.4 METs). At stage 9, the values differed by 0.7 METs. This agreement is statistically corroborated by the non-significant difference in the iAUC reported in Table 3.

Compared with this current study, Table 4 shows that the Woolf-May and Meadows [15] cardiac participant values were lower at all stages—0.6 METs lower at stage 2, increasing to 1.7 METs lower at stage 8 and 2.6 METs at stage 9. In comparing the values of this current study with the original study on METs by Woolf-May and Ferrett [14], this range of differences was of a similar magnitude, but these values were systematically greater across the nine ISWT stages, ranging in difference by 0.8–2.0 METs, respectively.

5 Discussion

The ISWT is widely used during patient assessment at entry to and exit from outpatient cardiac rehabilitation. This most recent study on the oxygen costs of walking during the ISWT in CHD cardiac rehabilitation patients provides the first comprehensive comparison of a new data set with data from similar previous studies. We believe this is the first published critique of such studies against the historical background of classic studies on the energy costs of walking. It terms of this being a representative sample (64.5 years, 85 % with CHD), it was similar to the national averages for age (66 years) with regard to CHD [7]; however, future evaluation is required to apply these findings for other typical and older populations now attending cardiac rehabilitation (heart failure, valve disease, arrhythmia or those with other morbidity, i.e. diabetes and pulmonary disease).

The present data demonstrate that the oxygen cost of overground walking in people with CHD responds as a positively accelerating (curvilinear) function of speed, which is independent of testing protocol, participant age and clinical status. In light of this finding from our data alone, or when combined with findings from extant studies that have reported this phenomenon for over a century, it is

Table 3 Oxygen costs expressed as an integrated area under the curve (iAUC = VO_2 × walking speed; ml·kg^{-1}·min^{-1}·km·h^{-1}) and curvilinear regression equations from this current study compared with previous ISWT reports and classic walking studies [12, 14, 15, 17–20]

Study	*n*	iAUC VO_2	iAUC vs. current cardiac (*p* value)	iAUC vs. current control (*p* value)	Regression equation (*y* value)	*Y*-intercept difference to current cardiac group (*p* value)	*Y*-intercept difference to current control group (*p* value)	Exponent difference to current cardiac group (*p* value)	Exponent difference to current control group (*p* value)
Current study, cardiac group	32	422.6 ± 85.7			$y = 4.4e^{0.27x}$				
Current study, control group	30	316.4 ± 52.4			$y = 5.0e^{0.20x}$				
Previous ISWT studies									
Woolf-May and Ferret [14], cardiac	31	488.5	0.005	<0.001	$7.0e^{0.23x}$	<0.001	<0.001	<0.001	0.003
Woolf-May and Meadowscardiac [15],	20	289.8	<0.001	0.018	$4.0e^{0.24x}$	0.019	<0.001	0.002	<0.001
Almodhy et al. [12]*, cardiac*	*8*	*392.9*	*0.159*	<0.001	$5.0e^{0.24x}$	0.006	0.913	0.006	<0.001
Woolf-May and Ferrett [14], healthy	19	339.2	0.001	0.04	$4.9e^{0.22x}$	0.038	0.476	<0.001	0.015
Woolf-May and Meadows [15], healthy	20	291.9	<0.001	0.028	$4.4e^{0.20x}$	0.986	0.023	<0.001	0.974
Classic walking studies									
Passmore and Durnin [17] *and Menier and Pugh* [19]	*12*	*435.3*	*0.539*	<0.001	$4.5e^{0.21x}$	0.423	0.089	<0.001	0.386
Falls and Humphrey [20]	*7*	*454.2*	*0.137*	<0.001	$4.6e^{0.23x}$	0.423	0.089	0.003	<0.001
ACSM linear equation	–	259.8	<0.001	<0.001	–	–	–	–	–

Regression equation: $y = b \cdot e^{ax}$, where $y = VO_2$; b is the constant y-intercept value when $x = 0$; e = the natural exponent constant of 2.71828183 raised to the power of a (representing the acceleration component of the regression curve); and x = walking speed in km·h^{-1}. Studies and data in the italicized rows are those with the same oxygen costs as the cardiac rehabilitation participants in this current study

ISWT incremental shuttle walk test, *iAUC* integrated-area-under-the-curve, *VO_2* oxygen cost, *ACSM* American College of Sports Medicine

Table 4 METs derived from the oxygen costs of the Incremental Shuttle-Walking Test in cardiac rehabilitation participants: current findings compared with similar studies [12, 14, 15]

ISWT stage	1	2	3	4	5	6	7	8	9
ISWT walking speed $mi \cdot h^{-1}$ ($min \cdot mi^{-1}$)	1.1 (54.5)	1.5 (40.0)	1.9 (31.6)	2.3 (26.5)	2.6 (22.7)	3.0 (20.0)	3.4 (17.6)	3.8 (15.8)	4.2 (14.3)
ISWT walking speed $km.h^{-1}$ ($m \cdot min^{-1}$)	1.8 (30.0)	2.4 (40.0)	3.1 (51.7)	3.7 (61.7)	4.2 (70)	4.8 (80)	5.5 (91.7)	6.1 (101.7)	6.8 (113.3)
METs for cardiac groups									
This study's METs ± SD (*n*)	1.7 ± 0.4 (32)	2.5 ± 0.5 (32)	3.2 ± 0.6 (32)	3.7 ± 0.7 (32)	4.2 ± 0.9 (32)	4.8 ± 1.0 (27)	5.5 ± 1.0 (21)	6.3 ± 1.3 (17)	7.6 ± 1.7 (11)
Almodhy et al. [12]	2.0	2.7	3.1	3.6	4.0	4.4	5.3	6.1	6.9
Woolf-May and Meadows [15]	0.7	2.1	2.6	2.9	3.1	3.6	4.2	4.6	5.1
Woolf-May and Ferret [14]	2.5	3.8	4.3	4.8	5.5	6.3	7.5	8	8.2
Recommended MET values for cardiac rehabilitation derived from $VO_2 = 4.4e^{0.23 \times speed}$	2.1	2.8	3.5	4.2	4.9	5.6	6.3	7.0	7.7

METs metabolic equivalents, *ISWT* incremental shuttle walk test, *SD* standard deviation, VO_2 oxygen cost

surprising that the ACSM [9] continues to recommend the use of a linear regression equation to predict oxygen cost of walking. Such existing linear equations clearly and consistently underestimate VO_2 for walking speeds >3 $km \cdot h^{-1}$ (>2 $min \cdot h^{-1}$) (Table 3).

The median curvilinear exponent value for estimating VO_2 from the walking speed (x) in all studies (including this current study) was $+0.23x$ (range $+0.19x$ to $+0.27x$), where the highest value was in the current data from cardiac patients. This curve exponent value for our cardiac patients was statistically greater than that calculated from similar data sets in all other studies, but was the same for control participants compared with two of the other healthy participant studies [15, 17, 20]. However, from a clinically significant effect-size perspective, the values were close to those reported by Almodhy et al. [12], which supports confidence in the recommended regression equation for estimating VO_2 and METs, i.e. $VO_2 = 4.4e^{0.23 \times speed}$ (Table 4), to be used by cardiac rehabilitation professionals in guiding CHD patients.

We found y-intercept constants (speed of $x = 0$ $km \cdot h^{-1}$; standing still) for the regression lines from this current study to be 4.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in cardiac patients and 5.1 $ml \cdot kg^{-1} \cdot min^{-1}$ in age-matched controls. In six of the eight historical data sets, the y-intercepts were in a similar range of 4.0–5.0 $ml \cdot kg^{-1} \cdot min^{-1}$. This seems to make sense, where standing up adds an additional VO_2 of between 0.5 and 1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ to typically reported resting VO_2s of approximately 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in healthy individuals, or 2.5–3.0 $ml \cdot kg^{-1} \cdot min^{-1}$ in older or β-blocked cardiac patients [30–33]. Even though the VO_2 y-intercept (rest) values in this current study were statistically different from the other studies (Table 3), from a clinical perspective this significance actually represents a small difference (±0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ or one-seventh of an MET), unlikely to be clinically important and within the expected range of measurement error.

Woolf-May and Ferrett [14] reported much higher VO_2 values in cardiac participants when compared with data from all other measures of cardiac groups (including this current study). It would now seem that their values appear systematically inflated from some potential anomaly in their measurements.

Using all other data on cardiac participants, we estimate that a satisfactory median regression equation (Table 4) for estimating VO_2 (y) from walking speed ($km \cdot h^{-1}$) would be $y = 4.4e^{0.23x}$

In general, from the data in Table 3 (iAUC VO_2), and clearly from observation of the regression curves (Figs. 1, 4), any differences in oxygen cost across all studies would therefore be related more to the differences found in the steepness of the regression curve rather than from the differences in the y-intercept constant. It must be acknowledged that some of the statistical power of the iAUC analysis is reduced as it was based on 18 of 31 CHD patients who were able to complete all nine stages of the ISWT. Nonetheless, a general pattern now appearing from the four data sets comparing the VO_2 in cardiac participants with age-matched controls during the ISWT is that most cardiac participants require an oxygen uptake of 25–30 % more than age-matched controls, which is mainly found in the final three walking test stages (stages 7, 8 and 9).

A study by Pepera et al. [34] explored anthropometric factors of height, body mass and body mass index, which can influence ISWT performance, but they did not directly measure VO_2. Taller individuals were found to perform better, and this relationship increased in strength at higher speeds. However, in this current study the cardiac group was significantly taller (Table 1) and yet were still less economical in VO_2 than the control group; no between-group differences in body mass index were observed.

Another phenomenon, which is not accounted for in all the ISWT data sets thus far, is that the ISWT stages are only 1 min in duration. In healthy individuals exercising at a constant intensity, a duration of between 40 and 60 s is required for VO_2 to rise to a submaximal constant, whereas in patients with cardiovascular disease this can take up to 90 s [35, 36]. Under β-blockade, which is standard treatment for patients with ischaemic heart disease or heart failure, the VO_2 kinetics have been reported to be slower [37, 38]. In all cases affected by disease or medication, or both, the VO_2 values during the 1 min stages of the ISWT should theoretically be diminished in cardiac patients compared with non-β-blocked healthy individuals; therefore, the differences in cardiac patients versus healthy controls could potentially be even greater than what is currently being reported. Future studies in comparing VO_2 between cardiac patients and healthy controls at a point after the VO_2 slow component [39] are required to determine a possible correction factor if practitioners wish to transpose exercise intensity information from the ISWT into steady-state exercise prescriptions of other activities. However, once steady-state exercise is established, β-blockade has been reported to not significantly alter VO_2 for any given submaximal work rate; it only appears to reduce VO_{2max}, but not in all cases, and the effect diminishes with long-term use of this medication [40–43].

5.1 Potential Impact of Findings on the Use and Interpretation of the ISWT in Cardiac Rehabilitation Patients

It is clear that the ACSM [9] equations should not be used to estimate oxygen cost of the ISWT, and this recommendation also looks likely to be extended to walking speed in all adult populations. The acceptance of linear predictions of oxygen costs means the estimates of improvement in VO_2 in patients attending cardiac rehabilitation following an ISWT could be underestimated.

6 Conclusions

In light of historical studies on the oxygen costs of walking, and then comparing and critiquing the current results and those of previous similar studies on the ISWT, there is further confirmation of the curvilinear nature of VO_2 as a function of walking speed. During the ISWT, it appears that cardiac rehabilitation participants have a VO_2 up to 30 % higher than age-matched controls. Together, these findings suggest studies may have underestimated the VO_2 of cardiac patients as well as improvements in VO_2 following a programme of exercise-based cardiac rehabilitation. Furthermore, the application of the ACSM's 'linear' regression for either healthy or cardiac populations, based on only a few participants from studies in the 1960s, does not respect the consistently demonstrated curvilinear VO_2 response to incremented walking speeds on flat ground, and thus in all cases greatly underestimates VO_2. We recommend that in estimating VO_2 from the walking speeds of the ISWT in CHD cardiac rehabilitation participants, the following equation should be used: $VO_2 = 4.4e^{0.23 \times \text{walkingspeed (km/h)}}$. For healthy participants (Table 3), a median equation from four reports (contemporary and historical) would be $VO_2 = 4.6e^{0.22 \times \text{walkingspeed (km/h)}}$.

Future work is required to make similar evaluations in other populations that use the ISWT as an outcome measure and physical activity intensity guidance. In more accurately achieving the transposition of the relationship between walking speed and VO_2 (METs) during the ISWT to physical activity guidance, a correction factor may be required to accommodate the limited oxygen kinetics information that coincides with only 1-min stages of the ISWT.

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Compliances with Ethical standards

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Conflict of interest John P. Buckley, Fernando Cardoso, Stefan T. Birkett and Gavin G.R. Sandercock declare no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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