Effects of Exercise-Based Cardiac Rehabilitation on Cardiorespiratory Fitness: A Meta-Analysis of UK Studies.

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Abstract

Background: Exercise-based cardiac rehabilitation can promote meaningful improvements in cardiorespiratory fitness (fitness) but the magnitude of such improvements varies according to local characteristics of exercise programmes. We aimed to determine if cardiac rehabilitation, as practised in the United Kingdom (UK), could promote meaningful changes in fitness and to identify programme characteristics which may moderate these changes.

Methods: Electronic and manual searches to identify UK CR studies reporting fitness at baseline and follow up. Change in fitness (Δfitness) was expressed as mean difference (95%CI) and effect size (*ES*). A random effects model was used to calculate the mean estimate for change in Δfitness with. Between-group heterogeneity was quantified (*Q*) and investigated using planned sub-group analyses.

Results: We identified *n*=11 studies containing 16 patient groups (*n*=1578) which used the incremental shuttle walking test (ISWT) (distance walked) to assess fitness. The overall mean estimate for Δfitness showed a significant increase in distance walked (*ES*=0.48, *P*<0.001), but this estimate was highly heterogeneous (Q=77.1, P<0.001, I^2= 81%). Sub-group analyses showed significantly greater *ES* (*Q*=3.94, *P*=0.046) for Δfitness in patients prescribed *n*>12 exercise sessions compared with those receiving *n*≤12 sessions.

Conclusion: We found significant increases in fitness (based on ISWT) in patients attending exercise-based CR in the UK. UK studies provide approximately one-third of the exercise "dose", and produce gains in fitness less than half the magnitude reported in international studies.

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1. Introduction

Exercise-based cardiac rehabilitation (CR) is a therapeutic intervention that has been shown to reduce mortality and morbidity rates by 20-25%. [1-4] These estimates are strongly influenced by the positive findings of early trials [5], but more recent reviews suggest a more modest (~11%), yet still significant risk reduction. [6-8] Few data from the United Kingdom (UK) are included in the evidence-base, and the combined data from randomised controlled trials performed in the UK [5, 9, 10] provide no evidence that exercise-based CR reduces mortality or morbidity. In recent years, improvements in acute and preventative coronary care [11] have increased the pool of patients eligible for CR. Improved life expectancy results in patients living longer with established conditions including cardiovascular disease (CVD), thus, a greater emphasis on 'softer' endpoints such as enhanced quality of life[12, 13] and improved fitness has been required[12, 14].

High cardiorespiratory fitness (fitness) is an independent predictor of survival in patients with CVD [15-17]; improving fitness through structured exercise training has also been demonstrated as a method for improving survival [18-21]. The first UK study to demonstrate reduced long-term (14 year) mortality risk in patients with higher baseline fitness and those with the largest Δfitness was published recently [22]. Higher fitness reduced mortality risk threefold but the cohort design precluded the authors from determining whether CR reduced absolute mortality risk. The authors also pooled estimates of fitness from three different exercise protocols making their values difficult to compare. The 'gold-standard' assessment of fitness is via a symptom limited cardiopulmonary exercise test (CPET) to volitional exhaustion during a ramped or incremental protocol. The CPET allows for the direct quantification of expired gas allowing variables such as peak oxygen consumption ($\dot{V}O_{2peak}$) to be recorded. The majority of the evidence-base demonstrating that fitness improvements are linked to survival benefits are based on data collected using CPET methodology [15, 20, 22], however, the need for staffing expertise, plus time and cost implications have sadly precluded its use in the majority of UK CR centres [14]. Instead, submaximal surrogate measures s are used, including the six minute walking test (6MWT), Chester step test, cycle ergometry and most frequently, the Incremental Shuttle-Walking Test (ISWT) [23, 24]. Patients' ISWT performance can provide estimates of $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$ or Metabolic Equivalents [METs]) but consensus is currently lacking regarding the most appropriate method of estimation [25-27].

Treadmill exercise test data from international studies suggest CR may produce a 1.55 (1.21–1.89) METs improvement in fitness [14] but a recent UK multi-centre study pooling data from a number of test protocols reported more modest improvements (mean improvement: 0.52 METs). Changes in fitness (Δfitness) are not only associated with patient mortality, but provide an objective metric to assess the effectiveness of an exercise-based intervention. Improved fitness is associated with a myriad of physiological [3, 12] and psychological [13, 28] benefits for patients with CVD. Our aim was to systematically review and meta analyse the evidence regarding the effectiveness of UK CR programmes to improve fitness. Changes in fitness are often heterogeneous [14] so a second aim was to identify patient-level and programme-level moderators to explain any heterogeneity identified.

2. Methods

2.1. Search strategy

The search terms "shuttle walking test", "pre-", "post-", "phase III", "outpatient" and "cardiac rehabilitation" were used to identify and retrieve studies from the PubMed, Medline, Ovid and Embase databases. The reference sections of the articles were searched manually and via an internet search (Google Scholar) to identify any additional 'grey' literature.

2.2. Inclusion Criteria

Only studies written in English were included. We included studies involving patients with a diagnosis of coronary heart disease; aged ≥18 years; referred to a CR programme including a supervised exercise component lasting 4-16 weeks performed in outpatient or community settings. There was no requirement for studies to be randomised or to employ a control group as initial searches revealed only (n=2) studies that met these criteria. Studies were required to report necessary data to calculate effect sizes for Δfitness following the completion of CR. We identified only three studies reporting data from treadmill exercise [22, 29, 30]. One did not provide the necessary data to calculate Δfitness, and one reported only a pooled estimate of Δfitness from a three different treadmill and cycle ergometry protocols. Prior to this analysis we undertook a pilot investigation to compare treadmill walking with more commonly used protocols involving shuttle-walking. [27] We found that the metabolic demands of treadmill walking were fundamentally different from shuttle-walking. On this basis, we excluded such data from the remaining eligible study. [30] All remaining studies reported data from the ISWT (Figure 1.)

2.3. Review of studies for analysis

From February 2012 until February 2013, two reviewers (MA, GS) independently completed the search and data extraction according to the inclusion criteria. Initially, n=37 potential studies were identified but n=28 did not report pre- and post- exercise test data to calculate effect sizes. In total, n=10 peer-reviewed articles and one published doctoral thesis were included (Table 1). These yielded a total of n=16 groups including n=1578 patients. The reviewers extracted data pertaining to: sample size, patient age, sex and primary diagnosis. We recorded programme length (weeks), programme type, number of structured exercise training sessions. We used reported group means (SD) for distance walked during the ISWT to calculate Δfitness.

2.4. Coding of moderator variables

Moderators were selected based on their ability to influence Δfitness as reported in previous studies. The prospective moderator variables were categorised into those relating to programme design or to patient characteristics. All programme-level moderators have been reported previously. [31] We created sub-groups based on the duration of the CR programme (median split ≤7 versus >7 weeks); total exercise training dose, based on the number of supervised exercise sessions prescribed (median split: ≤12 versus >12 sessions); and according to whether the CR programme was described as 'comprehensive' or 'exercise-only'. [2] Patient level moderators were used to create sub-groups based on age (younger: ≤63 years versus older: >63 years), and primary diagnosis (post-myocardial infarction [MI], coronary artery bypass grafting [CABG], or mixed).

2.5. Calculation of change in patient fitness (Δfitness)

We first expressed overall Δfitness as the mean difference in distance walked during the ISWT (pre- versus post-CR) as this was the metric reported in the majority of the studies and is commonly used in clinical practice. We then calculated standardised effect size (*ES*) based on the (mean SD) values for distance walked in pre- and post-CR tests. We used a random effects model to calculate the mean estimate (95% CI) for *ES* of Δfitness from all groups. The Q and I^2 statistics were used to identify between-group heterogeneity with values of $Q>2$ and $I^2>50\%$ considered to indicate important levels of heterogeneity. Finally we performed planned sub-group analysis using a mixed-effects model to calculate between- and within-group Q to determine potential sources of heterogeneity.[32]

2.6. Meta-regression

Continuous moderator variables explaining significant heterogeneity were further examined by a meta-regression (random effects model) with a standardised mean difference (SMD) to evaluate their independent contribution to the variance in Δfitness. [33] Standardised *ES* (95% CI) was reported. To determine whether publication bias affected the results we constructed funnel plots of precision (1/standard error) against effect size. We calculated Egger's regression intercept of funnel plot asymmetry to evaluate the presence of publication bias and used the "trim and fill" method to determine the effects of potential imputed values.

3. Results

Figure 2 shows the mean estimate for Δfitness expressed as change in distance walked (m) calculated from all studies (*n*=1578 patients). There was a significant (*P*<0.001) improvement between pre- and post-CR measures of 84 (95%CI:74-93) m. The overall estimate of effect size (random effects model) was small (*ES*=0.48, 95%CI:0.42-0.53), statistically significant (*P*<0.0001), and highly heterogeneous (Q = 77.1; P<0.0001, I^2 = 81%).

3.1. Sub-group analysis and meta-regression

Table 2 shows the within group effect sizes and estimates of between-group heterogeneity (*Q*) from sub-group analyses. There was a trend toward a difference in Δfitness according to programme length (*Q*=2.69, *P*=0.101) but *ES* for Δfitness remained significantly heterogeneous in both sub-groups (≤7 weeks; *Q*=16.4, *P*<0.001 versus >7 weeks; *Q*=60.1, *P*<0.001). The only significant moderator of Δfitness was number of exercise sessions. The mean estimate for Δfitness in studies reporting >12 exercise sessions (*ES*=0.57) was significantly (*Q*=3.94, *P*=0.046) greater than that for studies with ≤12 sessions (*ES*=0.44).

Meta-regression showed that the number of sessions prescribed was positively associated with improved fitness (β=0.014; *SE* = 0.002; *z* = 8.61; *P*< 0.05; Figure 3). However, age (slope (β) = -0.006; *SE* = 0.007; *z* = -0.83; *P*> 0.05), and programme duration (slope (β) = -0.019; *SE* = 0.017; *z* = -1.18; *P*> 0.05) were not associated with improved fitness.

3.2. Publication bias

Figure 4 shows the funnel plot of precision (1/standard error) against *ES* which indicated evidence of significant publication bias (Egger test, *P*=0.01). However, the “trim and fill” method showed that overall effect size remained statistically significant after imputing possible missing studies (*ES*=0.43, 95%CI: 0.37-0.49).

4. DISCUSSION

We reviewed data from available studies to determine the magnitude of change in fitness (Δfitness) reported in CR studies from the UK. We aimed to determine whether the modest improvements in functional capacity reported in a recent multi-centre study [30] were indicative of fitness values reported from UK studies. The mean estimate for Δfitness expressed as distance walked from the ISWT was 84 (76-93) m which is similar to 94 m (75-116) reported elsewhere, [30] and the overall estimate of effect size (*ES*=0.48) was analogous with the value reported (*ES*=0.59). Sandercock *et al*. estimated overall *ES* from different testing modalities including graded treadmill exercise, cycle ergometry, and ISWT [30], therefore, direct comparisons between studies should be avoided. However, the results of the current study indicate that patients attending CR programmes in the UK exhibit relatively small improvements in fitness.

4.1. Comparisons with international data

Our estimate for the effect size in Δfitness (*ES*=0.48) is similar to the estimate (*ES*=0.49) reported in another systematic review and meta-analysis [34] which included a much wider range of interventions aimed predominantly at increasing physical activity in patients with CVD. The present mean estimate is, however, less than half that (*ES*=0.97) reported in a systematic review of international studies of exercise-based CR.[25] This effect size for Δfitness equates to 1.55 (95% CI:1.21-1.89) METs. We did not convert ISWT performance to METs prior to analysis due the lack of consensus over the metabolic cost of the ISWT. For the purposes of comparability with previous studies, however, two possible estimates are provided below.

Using a standard prediction based on the metabolic cost of walking [30] suggests the current change in distance walked is equivalent to a 0.4 METs increase in fitness. A less conservative estimate based on $\dot{V}O_{2peak}$ during treadmill walking [25] produces an estimate for Δfitness of 0.7 METs. Differences in the metabolic demands of treadmill [14] and shuttle walking mean estimates should be interpreted with caution [29] as should the assumption of a linear $\dot{V}O_k$ response to incremental walking speeds. Buckley *et al*.[26] reported a curvilinear $\dot{V}O_2$response during the ISWT and proposed an improved method to predict the metabolic requirements of the test. Based on this, method the improvement in ISWT performance is equivalent to a 0.76 (0.68-0.80) MET increase in fitness.

Regardless of the method of estimation, the present findings concur with previous UK data [30] and suggest that CR produces only modest improvements in fitness. Estimates of 0.4-0.8 METs are 50-70% lower the improvements in patient fitness reported in international trials. [14].

Barons et al. [20] recently reported an increase in fitness of 0.9 METs in patients from a UK centre. The pooling of data from multiple (Bruce-treadmill, Modified Bruce-treadmill, cycle ergometry) protocols precluded the inclusion of these data in the present analysis. These data [20] should be interpreted with caution as the various estimates of $\dot{V}O_2$ were derived from equations designed for use in healthy adults which may over-estimate $\dot{V}O_{2peak}$ by 30% (2.5 METs) in patients with CVD[4, 35].

The mean estimate for Δfitness showed a high degree of heterogeneity (Figure 2), some of which was explained by programme-level moderators. The length of programme was not a significant moderator, but a between-group Q value >2 may be clinically important. Sandercock *et al.* [14] found no evidence of between-group heterogeneity according to programme duration (Q=0.2, P=0.64), but it should be noted that the cut-offs used to create sub-groups differ greatly between the current study and data presented elsewhere [12]. While both used the median split, the median duration of international CR programmes was 12 weeks compared with 7 weeks determined from UK studies. The duration of most programmes included in the present study was 8 weeks; representing the minimum recommended duration under current UK guidelines, [23] and is consistent with the duration of programmes reported nationally. [23]

Heterogeneity reported within international studies (Q=3.4) was partially attributable to the total number of exercise sessions prescribed. In agreement with this finding, number of exercise sessions was the only statistically significant moderator in the present study (Q=3.9, P=0.046). Sub-group analysis is difficult to compare between studies as the median number of exercise sessions prescribed internationally (n=36) was three times greater than the number reported in UK studies (n=12). The median value of n=12 supervised exercise training sessions aligns closely with the mean value (n=11.7 sessions) reported in a national survey of CR provision [23], which indicates that CR programmes evaluated in the current study are representative of current UK provision. The impact of international CR programmes on fitness was compared in patients prescribed n<36, n=36 or n>36 structured exercise training sessions. We could not identify any UK studies in which patients were prescribed n=36 sessions (actual range was 6-26 sessions). Two of the studies included in our analysis [36, 37] assessed the effects of prescribing different exercise doses by increasing frequency of exercise training sessions over the same duration. Both studies reported no significant differences in fitness outcomes in patients exercising once versus twice per week. Arnold *et al*.[36] reported a statistically significant improvement in distance walked during the ISWT, which led the authors to conclude that once- or twice-weekly exercise training sessions were equally effective. Almodhy *et al*.[37] also reported a statistically significant improvement in distance walked in patients exercising once- or twice-weekly. However, after estimating the corresponding improvement in fitness (0.4 METs) from pre- to post-CR the authors concluded that both programmes were equally ineffective as a means to promote meaningful gains in fitness.

The cut-off of n=12 exercise training sessions to create sub-groups was arbitrary in the current study. To compensate for this limitation we used meta-regression to investigate the association between number of exercise training sessions [33]. This method demonstrated a relationship between the number of exercise training sessions and improvements in fitness within the range of values reported in UK studies. Using linear extrapolation, we were able to estimate the number of exercise training sessions that would be necessary for UK programmes to prescribe in order to elicit a similar magnitude gain in fitness as international studies. Despite between-study differences in exercise prescription and measurement of fitness, our extrapolated estimate indicates that n=36 structured exercise training sessions would elicit a change in fitness with ES= 0.97. Naturally, there are a number of assumptions underlying such an estimate. Number of exercise training sessions was the only significant moderator identified presently. We suggest the small 'dose' of supervised exercise training prescribed in UK CR centres is the likely cause of the modest improvements in fitness reported here and elsewhere. Higher baseline fitness and Δfitness values are associated with a reduction in mortality risk [20, 22]. The ‘low dose’ of exercise patients tend to receive could explain why UK trials of CR have not reported a significant impact of CR on patient mortality [5, 6].

The number of exercise sessions prescribed does not adequately describe an exercise intervention. Marked columns* in Table 1 show service-level factors identified as potential moderators of Δfitness that could not be analysed due to incomplete reporting or not being reported in a suitable format for meta-analysis. A number of these factors concern how exercise is reported in terms of the FITT (*Frequency*, *Intensity*, *Time*, *Type*) principles which are the basis of prescription. Few studies reported all four FITT principles and, in agreement with a review of international studies [14], intensity was least-often reported [36, 38, 39] despite evidence for its importance in promoting beneficial adaptations to exercise [40]. None of the studies included here reported data on exercise intensity. Instead authors provided the range of intensities prescribed at each CR centre (e.g.65-80%HRR[38]; 60-80%HRR [36, 39].

Type (modality) of exercise was identified as an important significant moderator of fitness gains in a previous review [14]. We could not form subgroups based on modality as all studies were reported as comprising either ‘aerobic exercise’, ‘circuits’ or both; with distinct overlap between descriptions provided. Proposed changes to the reporting of exercise and CR interventions are provided in supplementary Table 1.

The proportion of the prescribed CR sessions patients attend is independently associated with mortality[41], morbidity[42] and health-related quality of life (HRQoL)[43]. No study reported the number of exercise sessions patients attended, nor provided any criteria to define 'completion' of the CR programme. Similarly, few authors reported data describing how long patients attended CR; reporting instead the prescribed programme length. Omission of such basic data impact greatly on the interpretation of findings from studies (and reviews) as we cannot determine with accuracy the dose of exercise received. A delay in starting CR is associated with a decreased likelihood of uptake of CR[44]; it may also attenuate the benefits of CR for those who do attend[45]. Less than half of studies reported the time from event or surgery to start of CR [25, 30, 36, 46].

Few studies described changes in risk factors or psychosocial measures concurrent with Δfitness. Despite heterogeneity in the measures there were highly statistically significant improvements in all psychosocial measures reported in published studies. This may be further evidence for the publication bias shown in Figure 4. This that was reported showed therefore Reporting changes in such factors alongside fitness might help determine a minimum clinically important difference (MCID) for ISWT performance.

4.2. Minimum clinically importance difference (MCID)

All studies included in our analysis reported 'statistically significant' improvements in ISWT distance following CR. Only two [25, 47] discussed whether statistical significance also represented a clinically meaningful improvement in patient fitness. One challenge when interpreting changes in ISWT distance is the lack of an accepted MCID. It has been proposed recently[47] that 70 m represents a clinically important improvement in ISWT but this threshold merely represents a associated with improvements in patients own perceptions of their functional capacity. A true MCID for ISWT performance that is associated with improved HRQoL, morbidity and mortality is yet to be identified. Guyatt et al. [39] identified an MCID of 30 m in the 6MWT over 30 years ago. The 6MWT is more-often used in patients with heart failure [38] but a meta-analysis of the tests responsiveness to CR reported a 70 (67-74) m improvement in distance walked was associated with improvements in numerous clinical outcomes. We hoped to identify an MCID for the ISWT through our analysis but were unable to do so as relatively few studies (Table 1) reported concurrent changes in outcomes.

Clinical Application of Findings

Our findings that attendance of exercise-based CR is not associated with meaningful improvements in fitness will be unwelcome to CR patients and practitioners in the UK. Our aim was not to criticise current provision but to provide evidence that may lead to improvements in the delivery of CR services. By identifying a single, modifiable moderator associated with improvements in fitness i.e. number of training sessions, we hope our findings may be of practical use to inform exercise prescription guidelines within UK CR settings; an area where guidance is somewhat lacking.

Only the SIGN [24] guidelines provide specific details regarding exercise frequency and programme duration. Paragraph 3.6.2 starts by acknowledging early trials were based on: '*three exercise sessions per week for 8 weeks or longer'* yet the final recommendation is for two exercise sessions over 8 weeks including just one supervised exercise session per week. The evidence cited to support the equality of thrice weekly and once weekly supervised exercise is drawn from two small studies [48, 49]. Like many studies reviewed here, neither study addressed whether the statistically significant Δfitness observed was clinically important. Neither did these studies report long-term patient outcomes, nor even short-term changes in risk factors.

5. Limitations and Conclusions

Estimates of ($\dot{V}O_{2peak}$ derived from ISWT performance vary and evidence suggests linear equations underestimate the metabolic cost of the ISWT in cardiac patients [26]. Linear predictions suggest a difference in pre- versus post-CR $\dot{V}O_{2peak}$ (Δfitness) of 0.4-0.5 METs. Applying a curvilinear prediction model [26] to the weighted mean estimates for (Δfitness) of UK CR studies, we estimate exercise based CR promotes a Δfitness of 0.76 METs. This higher value remains less than half the mean estimate reported internationally [31]. As there was indication of significant publication bias the actual magnitude of improvement may be smaller still. After adjusting for possible bias, the magnitude of fitness improvements in in patients attending CR (*ES* = 0.43, 95% CI; 0.37-0.49) was also less than half that reported in international studies. By identifying the positive association between Δfitness and the number of exercise sessions prescribed, these data highlight the importance of prescribing an appropriate 'dose' of exercise. The methods of reporting prescribed exercise limit our conclusions as we were unable to ascertain the actual number of exercise sessions completed by any of the (*n*=1578) patients included in the analysis. Given the importance of attendance as a mediator of outcomes in CR, the practice of reporting sessions 'prescribed' should cease. Reporting the mean number of sessions attended by the study cohort should be a requirement for publication. While some studies provided an indication of exercise intensity, none provided an estimate of energy expenditure.

Due to the paucity of evidence that CR programmes in the UK reduce patient mortality and morbidity we aimed to evaluate the efficacy of exercise-based CR to determine if current provision improves fitness. Our findings show that while UK studies report statistically significant improvements in ISWT performance due to CR, the mean improvement in patients' fitness is less than half that reported internationally. The number of exercise sessions prescribed to patients was the only significant moderator of Δfitness. This finding, and our statistical extrapolation of the association between exercise "dose" and Δfintess strongly suggest the modest gains in fitness due to UK CR are due to under-prescription of exercise. I order to elicit improvements in fitness which mirror the success of international studies we should review the duration of CR programmes in the UK. Alternately, if programmes continue to work within these parameters then exercise 'dose' should be up-titrated within the time available. Alternative training strategies such as high intensity, interval training should be considered as a means of achieving this goal.

CONFLICT OF INTERESTS:

The authors report no relationships that could be construed as a conflict of interest

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Figure titles and legends.

Figure 1. Search results and selection of studies for inclusion in meta-analysis.

Figure 2. Forest plot showing change in patient fitness reported in UK studies of cardiac rehabilitation.

Legend: All studies used the Incremental Shuttle-Walking Test. Fitness is expressed as distance walked (m); Change in fitness calculated as distance walked post-cardiac rehabilitation minus distance walked pre-cardiac rehabilitation (m).

Figure 3. Meta-regression to illustrate the association between change in patient fitness and exercise sessions prescribed in UK studies of cardiac rehabilitation.

Figure 4. Estimation of publication bias in UK studies reporting Δfitness in patients attending cardiac rehabilitation.

Legend: Open circles – studies included in the meta-analysis. Closed circles – imputed studies providing evidence of significant publication bias.

Table 1. Summary of UK studies reporting change in fitness measured pre- and post-cardiac rehabilitation using the incremental shuttle-walking test

Reference	*n*=	Age (years)	Primary diagnosis	Pre-CR ISWT (m)	Post-CR ISWT (m)	Δ ISWT (m)	CR Length (weeks)	Exercise sessions (n)	Exercise Type*	Exercise Intensity*	Time to start of CR*	Programme type	Additional Outcomes
Tobin & Thow	19	61	CABG	--	--	117	12	>12	Aerobic exercise	65-85% HRR	-	Exercise only	Arrhythmia, ST-depression
Fowler et al.	11	61	CABG	409 (166)	569 (177)	82	6	≤12	Aerobic walking	-	6-8 weeks	Comprehensive	
Arnold et al. *a*	85	62	MI	469 (153)	510 (191)	101	6	≤12	Circuits & Walking	60-80% HRR	4-6 weeks	Exercise only	HADs, MQMLI
Arnold et al. *b*	121	59	MI	488 (214)	557 (171)	88	6	≤12	Circuits & Walking	60-80% HRR		Exercise only	
Sandercock *et al.*	38	66	Mixed	349 (121)	597 (235)	109	8	>12	Circuits	<70% HRmax	16 (11) weeks	Comprehensive	HADs, BP, 1 min HRR
Reardon	33	57	Mixed	327 (111)	424 (122)	74	8	>12	Aerobic intervals	Moderately hard RPE	-	Comprehensive	
Asbury et al.	28	57	Mixed	387 (186)	424 (133)	97	8	>12	Aerobic & Active Rest	60-75% HRR	<6 months	Exercise only	HADs, SF36, BP, BMI
Innes	184	66	Mixed	492 (216)	618 (165)	105	13	>12	Circuits or Aerobic	-	-	Exercise only	
Robinson *et al.*	53	59	Mixed	618 (139)	676 (176)	58	6	≤12	Circuits	60-80% HRR	-	Exercise only	SF36, MQMLI
Almodhy *et al. a*	58	71	Mixed	297 (137)	358 (161)	70	6	≤12	-	-	-	Comprehensive	
Almodhy *et al. b*	59	69	Mixed	295 (132)	370 (159)	73	6	≤12	-	-	-	Comprehensive	
Sandercock *et al. a*	104	68	Mixed	295 (139)	455 (190)	160	8	≤12	Circuits	-	11 (6) weeks	Comprehensive	
Sandercock *et al. b*	118	70	Mixed	362 (157)	420 (155)	67	8	≤12	Circuits	-		Comprehensive	
Sandercock *et al. c*	81	57	Mixed	341 (165)	503 (179)	83	6	≤12	Circuits	-		Comprehensive	
Sandercock *et al. d*	365	63	Mixed	391 (173)	411 (230)	70	8	≤12	Circuits	-		Comprehensive	
Houchen-Wolloff *et al.*	220	65	Mixed	487 (147)	456 (186)	65	6	≤12	-	-	-	Exercise only	Perceived capacity

Legend:CR-cardiac rehabiliation. CABG- coronary artery bypass grafting, MI – Myocardial infraction; ISWT – Incremental shuttle-walking test; HRR – Heart rate reserve; ΔISWT = post-CR ISWT – pre-CR ISWT. All values shown are means (standard deviation) *Indicates variables which not included in subgroup analysis due to lack or information or methods of reporting.

Table 2. Sub-group analysis to determine potential moderators of change in fitness in UK cardiac rehabilitation patients.

Moderator	Sub-Group	Groups (*n*=)	Standardised mean difference (*ES*)	95% CI	*P*-value	Within-Group Q	Within-Group *P*	Between-Group Q	Between-Group *P*
Programme length (weeks)	≤ 7	8	0.43	0.351 - 0.510	< 0.001	16.4	<0.001	2.69	0.101
	> 7	8	0.53	0.441 - 0.619	< 0.001	60.1	<0.001		
Programme type	Comprehensive	9	0.46	0.386 - 0.540	< 0.001	45.5	<0.001	0.19	0.657
	Exercise-only	7	0.49	0.399 - 0.581	< 0.001	29.8	<0.001		
Number of exercise sessions	≤12	11	0.44	0.381 - 0.500	< 0.001	55.1	<0.001	3.942	0.046
	>12	5	0.57	0.457 - 0.677	< 0.001	6.14	0.089		
Patient Age	Old	7	0.47	0.386 - 0.552	< 0.001	35.4	<0.001	0.038	0.846
	Young	9	0.48	0.396 - 0.565	< 0.001	41.8	<0.001		
Primary Diagnosis	CABG	2	0.66	0.133 - 1.188	< 0.014	0.01	0. 990	0.746	0.689
	Post-MI	2	0.49	0.372 - 0.624	< 0.001	2.86	0.239		
	Mixed	12	0.46	0.401 - 0.524	< 0.001	66.5	<0.001		

Legend: *ES* – Effect Size, 95%CI – 95% confidence intervals; Q>2 indicates heterogeneity within groups. CABG- coronary artery bypass grafting, Post-MI – Myocardial infraction. All groups are patients attending outpatient cardiac rehabilitation. Comprehensive – supervised exercise sessions plus formal educational component. Exercise only – supervised exercise sessions. Age: young: ≤63 years, old >63 years (based on median split) Subgroups for Programme Length and Number of Exercise Sessions also based on median split. Mixed subgroup includes: post-MI, recipients of CABG and other revascularisation procedures and valvuloplasty.

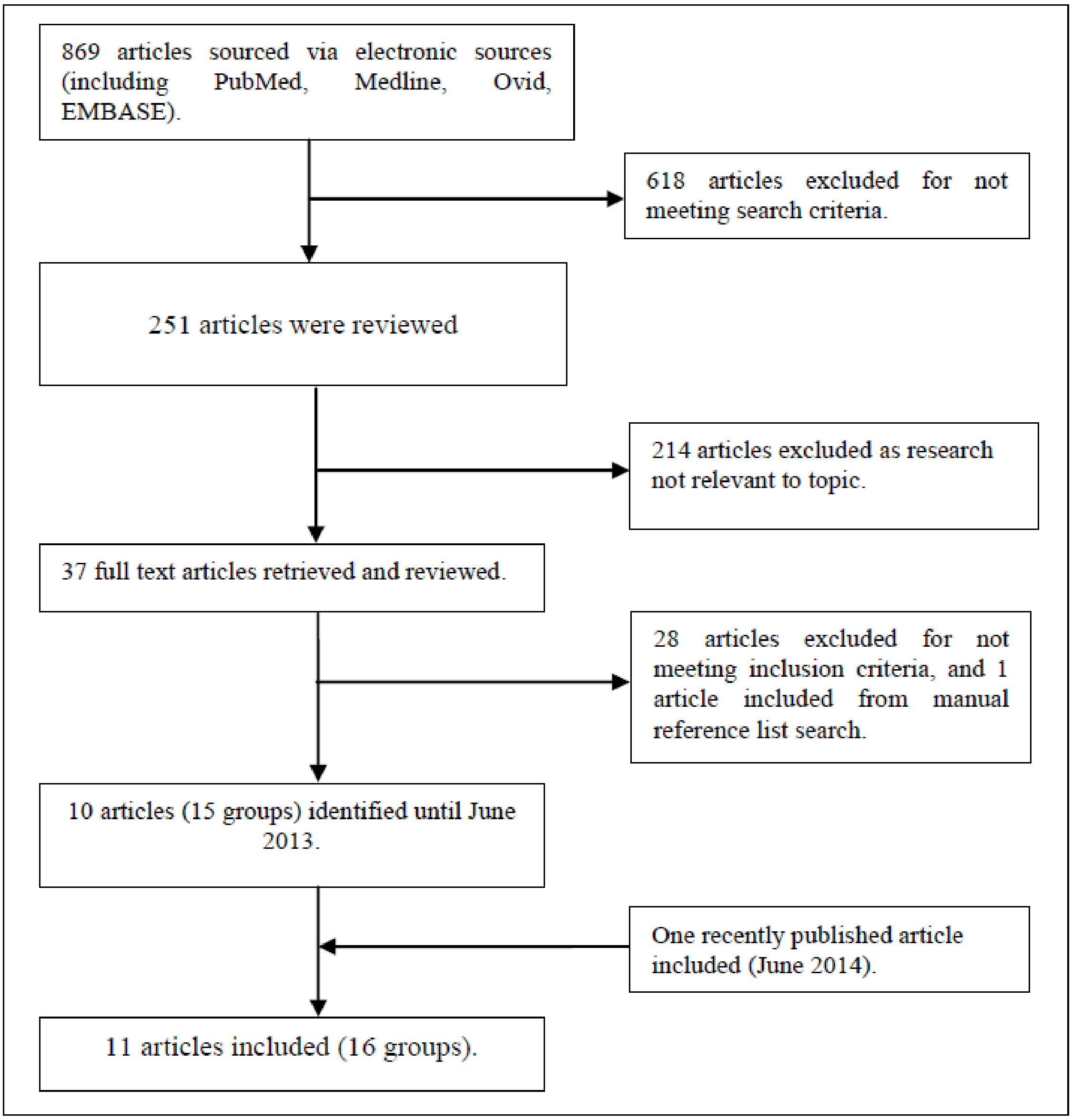
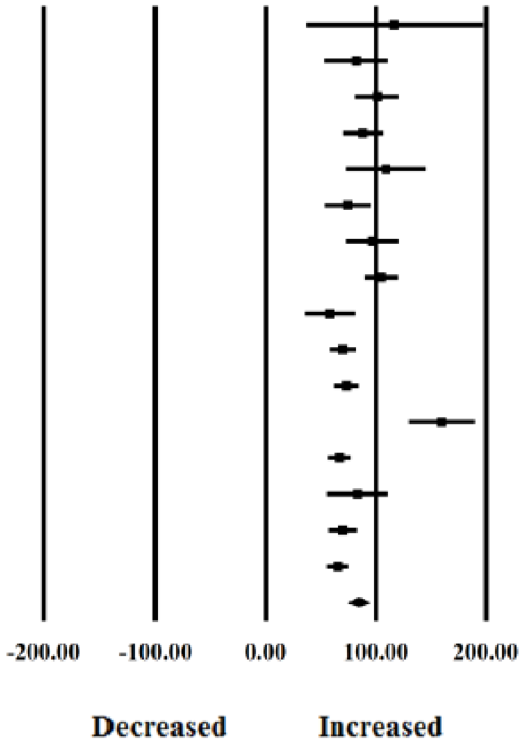

869 articles sourced via electronic sources (including PubMed, Medline, Ovid, EMBASE).
618 articles excluded for not meeting search criteria.
251 articles were reviewed
214 articles excluded as research not relevant to topic.
37 full text articles retrieved and reviewed.
28 articles excluded for not meeting inclusion criteria, and 1 article included from manual reference list search.
10 articles (15 groups) identified until June 2013.
One recently published article included (June 2014).
11 articles included (16 groups).

Figure 1.

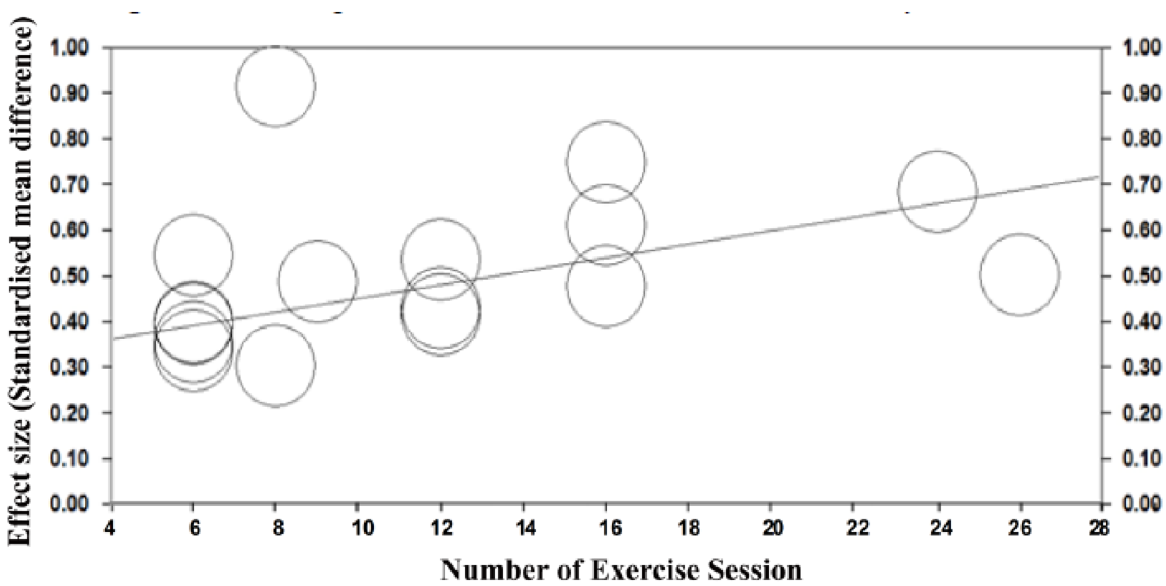
Study name		Statistics for each study		
		Difference in means	Standard error	p-Value
Tobin and Thow	(1999)	117.00	40.64	0.00
Fowler et al.	(2005)	81.80	14.51	0.00
Arnold et al. (A)	(2007)	101.00	9.91	0.00
Arnold et al. (B)	(2007)	88.00	8.97	0.00
Sandercock et al.	(2007)	109.00	18.29	0.00
Reardon	(2008)	74.30	10.46	0.00
Asbury et al.	(2008)	96.80	12.10	0.00
Innes	(2009)	105.00	7.62	0.00
Robinson et al.	(2009)	58.22	11.59	0.00
Almodhy et al. (A)	(2012)	70.00	5.40	0.00
Almodhy et al. (B)	(2012)	73.00	5.30	0.00
Sandercock et al. (A)	(2012)	160.00	15.00	0.00
Sandercock et al. (B)	(2012)	67.00	4.40	0.00
Sandercock et al. (C)	(2012)	83.00	13.90	0.00
Sandercock et al. (D)	(2012)	70.00	6.37	0.00
Houchen-Wolloff et al.	(2014)	65.20	4.75	0.00
		84.23	4.78	0.00

Difference in means and 95% CI



Forest plot for mean point estimate of change in ISWT distance walked due to cardiac rehabilitation. Points are mean points estimate (squares) with upper and lower 95% CI for the ISWT distance difference between pre- and post-cardiac rehabilitation measures. The overall mean point estimate (±95% CI) is based on a random effects model. Tobin and Thow (1999); Fowler *et al,*(2005); Arnold *et al.*(2007); Sandercock *et al.*(2007a); Asbury *et al.* (2008); Reardon (2008); Innes (2009); Robinson *et al.* (2011); Almodhy *et al.* (2012); Sandercock *et al.* (2012); Houchen-Wolloff *et al.* (2014).

Figure 2.


Effect size (Standardised mean difference)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
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4
6
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12
14
16
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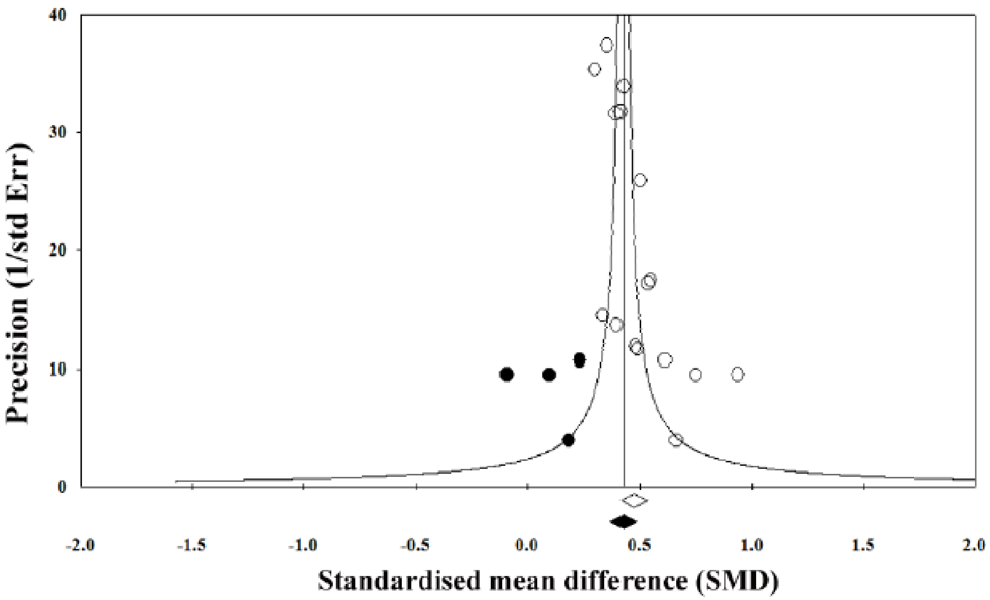
22
24
26
28
Number of Exercise Session

Figure 3.



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

Figure 4.