Utilising Observational Data For Cardiac Rehabilitation:

Impacting Care Using Registry Data

Jennifer Susan Sumner

PhD
University of York
Health Sciences

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Abstract

Cardiac rehabilitation (CR) is an established evidence-based intervention which reduces the risk of mortality, morbidity and can improve health related quality of life (HRQOL). In the UK CR service delivery and outcome are routinely evaluated through the National Audit of Cardiac Rehabilitation (NACR); a patient registry of those eligible for CR. Auditing of services facilitates the identification of practice inconsistency and inequalities or inequities that may otherwise go unnoticed. Several have been reported in the NACR annual statistical report, but what remains unknown is how this may impact patient outcome, a question which forms the basis for this programme of research. The overarching aim is to identify and better understand determinants of quality delivery and outcome and, where evident, promote positive service change for patient benefit. Specifically, I investigated how CR is currently utilised and what predicts initiation, how clinically effective current day CR is and what impact does CR timing and employment status have on patient outcome. A series of quantitative investigations were undertaken, including one systematic review and four separate data analyses using data from the NACR registry, each of which is presented in this thesis.

The research highlights the importance of adhering to clinical guidelines on service timing and the need to conduct and use information from rigorous pre-CR patient assessment. Aspects of this work have also fed into the NACR_British Association for Cardiovascular Prevention and Rehabilitation (BACPR) certification programme; a national initiative to drive service improvement. Overall this thesis serves as an exemplar of work on the utility of observational data i.e. registry-based analysis.
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Author’s Declaration

I declare that this thesis is the product of my own work other than that duly acknowledged to others. The material contained in this thesis has not been submitted for a degree in this or any other awarding institution. All sources are acknowledged as references.

The following publications arose from this thesis (my maiden name was Fell):

Predictors of cardiac rehabilitation utilisation in England: results from the national audit. Journal of the American Heart Association. Doi:10.1161/JAHA.116.003903 (Sumner, 2016)
[The candidate conceived the idea for the paper, conducted the analyses and prepared the first draft and subsequent revisions. The candidate jointly developed the study methodology and critical revisions to the paper following reviewer comments.]

[The candidate jointly conceived the idea for the paper, developed the study methodology, screened the identified literature and conducted the critical revisions to the paper following reviewer comments. The candidate developed and conducted the literature review, conducted the meta-analyses and prepared the first draft and subsequent revisions.]

Does the timing of cardiac rehabilitation impact fitness outcomes? An observational analysis Open Heart. Doi:10.1136/openhrt-2015-000369 (Fell, 2016)
[The candidate was jointly responsible for the study conception, methodology development and critical revisions to the paper following reviewer comments. The candidate conducted the analyses and prepared the first draft and subsequent revisions.]
[The candidate conceived the idea for the paper, conducted the analyses and prepared the first draft and subsequent revisions. The candidate jointly developed the study methodology and critical revisions to the paper following reviewer comments.]

Relationship between employment and mental health outcomes following cardiac rehabilitation: an observational analysis from the national audit of cardiac rehabilitation. International Journal of Cardiology. Doi:10.106/j.ijcard.2016.06.142 (Harrison, 2016) 
[The candidate jointly developed the idea for the paper, the study methodology and contributed substantially to the preparation of the manuscript and critical revisions to the paper following reviewer comments.]

Research underpinning this thesis occurred within the Cardiovascular Health Research Group at the University of York which is funded by the British Heart Foundation.
Chapter 1 Introduction and Aims of Thesis

This integrative thesis forms a coherent body of research around the subject of cardiac rehabilitation (CR). The thesis begins by defining the condition and intervention, namely coronary heart disease treated through CR. A rationale for the type of research design and methods used to address the primary research questions is then set out. Subsequently the aims of the thesis are outlined, and three research chapters are presented each with an overview of their respective papers. The research chapters start with explorations into how ‘modern’ CR is utilised, how effective routine CR is and subsequently how use and effectiveness may be impacted by patient characteristics and service delivery. The final two chapters conclude the findings of the research chapters, examine the limitations of the work, make recommendations for clinical practice and discuss future research opportunities.

Cardiovascular Disease

Cardiovascular disease covers a multitude of conditions which affect the heart and blood vessels including coronary heart disease, cerebrovascular disease, peripheral artery disease, congenital heart conditions, deep vein thrombosis and pulmonary embolism (WHO, 2017a). The global economic and societal burden of cardiovascular disease is vast; an estimated 85 million people in Europe live with cardiovascular disease (European Heart Network, 2017) (7 million in the United Kingdom (UK) alone) (Centre for Economics and Business Research, 2014; British Heart Foundation, 2018). In 2015 31% (17.7 million) of all deaths were due to cardiovascular disease (WHO, 2017a) and by 2020 the cost (direct healthcare and indirect loss of productivity) is projected to approach €122.6 billion across six major European economies (Centre for Economics and Business Research, 2014). To reduce the burden of this disease effective healthcare and prevention strategies are integral.

Cardiovascular disease is often, but not always, the product of atherosclerosis i.e. the build-up of fatty material inside the arteries which can occur anywhere in the body. Coronary Heart Disease (CHD), or ischaemic heart disease, refers specifically to atherosclerosis of the arteries which feed the heart muscle. Occlusion of these vessels reduces blood flow depriving the heart muscle of nutrients and oxygen which can lead to chest pain called angina. In extreme cases severe or complete blockage of the blood vessel leads to tissue death and heart attack (acute myocardial infarction (AMI)) (NHS Choices, 2017). AMI alone accounts for nearly 200,000 hospital episodes each year in the UK (British Heart Foundation, 2018).
CHD does not occur immediately but rather develops gradually over time. Several risk factors of CHD have been identified including smoking, poor diet (i.e. high salt, saturated fat), obesity, inactivity and high cholesterol. Hereditary factors including a family history of CHD, particular ethnic backgrounds or the presence of specific comorbid conditions i.e. high blood pressure and diabetes are also risk factors (NHS Choices, 2017; WHO, 2017a). The risk from many of these factors can be reduced through lifestyle change and as such lifestyle modification is often recommended to prevent the worsening of CHD and to reduce the risk of primary AMI (NICE, 2016). In cases where AMI occurs the treatment approach is often multifaceted. Treatment may include drugs to reduce clot formation, lower blood pressure and manage lipids as well as surgery to widen narrowed vessels improving blood flow (Percutaneous Coronary Intervention (PCI)) or bypassing the narrowed or blocked blood vessel (Coronary Artery Bypass Surgery (CABG)) and finally rehabilitation, including lifestyle management, formally known as CR (NICE, 2013b).

**Cardiovascular Care and Cardiac Rehabilitation**

The care of cardiovascular patients has evolved substantially over time. As reported in reviews by Mampuya (2012); Pashkow (1993) and Certo (1985) the benefits and implementation of early mobilisation and exercise were not recognised for a protracted period historically. Despite early reports in the 17th century of exercise prescriptions benefiting those with angina, bed rest for up to eight weeks was commonly practised in cases of acute cardiac events (Certo, 1985; Pashkow, 1993; Mampuya, 2012). The notion of bed rest was again reinforced by Herrick in 1912, who wrote a landmark article on coronary vessel occlusion and again in 1930 by White, Mallory and Salcedo who described the myocardium healing period after AMI (Herrick, 1912; White, 1936). Not until the 1940’s were light exercise therapies introduced (Certo, 1985; Pashkow, 1993; Mampuya, 2012). Levin and Lown’s chair therapy was one of the first examples of early mobilisation (Levine and Lown, 1952). Alongside pioneering work on early mobilisation, separate studies documenting the adverse effects of prolonged bed rest (Saltin, 1968) gradually led to a change in practice. Around this time the first examples CR emerged, such as the multi-disciplinary CR programme developed by Hellerstein (Hellerstein and Ford, 1957).

Aside from the development of rehabilitation a succession of cardiovascular care developments also occurred during the same period. The advent of the coronary care unit, an approach proposed in the early 60’s to improve monitoring and resuscitation access in high risk AMI patients. The units worked by assigning patients, trained staff and equipment to a single designated location within a
hospital (Julian, 1961; Wilburne and Fields, 1963). The development and use of thrombolytics, angioplasty, stenting and CABG, which all serve to reperfuse heart tissue, have also reduced mortality and morbidity as reviewed extensively in the literature (Sherry, 1989; Berry, 2009; Roguin, 2011; Head, 2013). Subsequently systematic reviews and meta-analysis comparing the effectiveness of AMI therapies (Zhu, 2001; Keeley, 2003; Deb, 2013) and the effect of CR (Jolliffe, 2001; Heran, 2011; Anderson, 2016) have paved the way to current care guidelines (NICE, 2013a; NICE, 2013b).

Today CR is defined as:

“The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease” (BACPR, 2017)

The UK Department of Health defines six stages of care for cardiac rehabilitation patients, from identification through to long term patient management (Figure 1).
CR is expected to be multi-component, multi-disciplinary and menu-driven i.e. treatment provided in accordance with the needs of the patient, including structured exercise two to three times a week over a minimum of eight weeks duration (BACPR, 2017). An abundance of national and international guidance now exists detailing standards of care (Department of Health, 2000; Giannuzzi, 2003; Balady, 2007; Piepoli, 2012; Department of Health, 2013; BACPR, 2017), however questions remain as to the extent of implementation and routine clinical practices (Kotseva, 2013; NACR, 2017).
Quality Assurance in Cardiac Rehabilitation

The National Audit of Cardiac Rehabilitation (NACR) was set up in 2005, funded by the British Heart Foundation, with an aim to improve and prevent inequalities in care and identify issues of inequity. The NACR has evolved into a world-leading audit which collects information on CR service delivery, patient use and patient outcome. It supports CR clinical teams to improve the quality of the services they deliver. In 2017 out of the 303 CR programmes, which existed at the time of the report, an estimated 74% provided data to the NACR capturing 87,827 patients starting CR (NACR, 2017). The 2017 British Association for Cardiovascular Prevention and Rehabilitation (BACPR) guidelines reiterate the importance of audit for the purposes of performance review (BACPR, 2017). Figure 2, extracted from the BACPR 2017 guidelines, details how the patient pathway and NACR data entry points align.

![CR patient journey aligned with NACR data entry pathway](image)

**Figure 2 CR patient pathway and NACR data entry points**

*Extracted from the 2017 BACPR standards and core components guideline (BACPR, 2017)*

Since the implementation of the 2012 BACPR minimum standards (BACPR, 2012) and prior to the updated 2017 guideline (BACPR, 2017), a national CR certification programme was developed.
collaboratively between the NACR and the BACPR (Furze, 2016). The aim of the scheme is to evaluate and grade CR performance promoting the continuous improvement of service quality. Launched in 2015 the pilot evaluated six standards deemed key to successful high-quality CR:

- Access of CR to all priority groups (MI, PCI, CABG, heart failure (HF))
- ≥69% with recorded assessment before starting formal CR programme
- ≥49% of core CR patients with recorded assessment after completing CR programme
- A median waiting time from referral to start within 40 days for MI/PCI and HF patients and 54 days for CABG
- A median duration of CR of 54 days for conventional delivery or 42 days where the Heart Manual (an evidence-based six-week facilitated self-management programme) was the sole method of delivery.

In the first year of assessment using data from 2013-2014 31% of programmes met five or six of these criteria, 46% met three or four of these criteria and 23% met zero or two criteria (Doherty, 2017). To this date the certification scheme continues to roll out across the UK with a view to continually re-evaluate assessment criteria to drive service improvement.

Despite established guidelines on care and schemes such as the NACR_BACPR certification programme, in recent years the efficacy of modern CR has been scrutinised. For the purposes of this thesis ‘modern’ CR is defined as the period following the introduction of major cardiovascular developments including statins (Johannesson, 1997), surgical advancements (Montalescot, 2004) and publication of multiple international guidelines on modern standards of care between 1994 and 2003 (Balady, 1994; Department of Health, 2000; Jolliffe, 2001; Giannuzzi, 2003; Balady, 2007). CR evidence accumulated in systematic reviews and meta-analyses is largely aged and arguably a poor reflection of modern-day practices. This opinion led to the commission, by the National Health Service (NHS) Research & Design programme, of a new multi-centre pragmatic Randomised Controlled Trial (RCT) in the late 1990’s known as the RAMIT trial. The study was designed to ascertain the effect of modern CR on mortality, morbidity, health-related quality of life and activity. However, the results of the RAMIT trial became the subject of much debate after the results found no evidence of benefit from CR (West, 2012). Regardless of the trial’s findings, national guidance did not change as a consequence, likely due to heavy criticism of the trial’s execution, which many argued undermined the validity of the study findings (Doherty and Lewin, 2012; Rashid and Wood,
2012; Taylor, 2012; Wood, 2012). However, more recent articles continue to challenge CR such as the systematic review by Powell (2018) which compared exercise and non exercise-based CR and found no effect on all-cause and cardiovascular mortality and a significant but clinically irrelevant effect on hospital re-admission (Powell, 2018). However, such evidence should be interpreted with caution as the study included a poor definition of CR, including articles which do not meet national guidelines on the composition of CR (BACPR, 2017). In addition, although the study purported to be a review of current CR evidence (year ≥2000), they included studies with no clear recruitment date. Thus, to date the question of modern CR efficacy remains unanswered and still important. While RCTs remain the gold standard in determining interventional efficacy, a different approach should be considered to address the unanswered question of modern-day CR effectiveness, i.e. an observational approach.

**Observational and Experimental Studies**

Broadly speaking quantitative research falls into two categories; observational and experimental. Experimental studies, such as RCTs, investigate the effect of an exposure (i.e. an intervention) by randomly allocating participants to the exposure or not and determining the effect in each group. Conversely observational research investigates exposure and effect without allocating participants but rather through identification and observation of those exposed or not (Bowers, 2008).

Notwithstanding the higher ranking of RCTs in the evidence hierarchy (Murad, 2016), a major criticism of experimental research rather than observational is bias sampling i.e. the representativeness of the data. RCTs apply strict recruitment criteria, which can often lead to a population sample which is not reflective of those in, or those that will access, routine care. For example, the mean age of RCT participants, reported in the most recent Cochrane review of CR effectiveness (Anderson, 2016), was 56 years (range 49.3-71.0 years) compared to a mean age of 67 years (range 18-108 years) in the most recent NACR statistical report (NACR, 2017). Pragmatic randomised trials attempt to overcome such issues in generalisability by more closely reflecting routine practice, from the participants recruited, the study setting used and the operationalisation of the intervention (Roland and Torgerson, 1998). However, pragmatism in trials is not a dichotomy, rather there is a spectrum between optimal trial conditions (explanatory) and routine practice (pragmatic). Consequently, tools such as the pragmatic-explanatory continuum indicator summary (PRECIS) have even been developed to assist researchers in RCT design and interpretation (Thorpe, 2009).
The availability of the pragmatic trial design does not negate the need for observational methods. Barnish and Turner (2017) commented that registries are distinct from pragmatic trials in that they can be used for real world evaluation of an intervention as it is routinely delivered rather than a ‘realistic simulation’ (Barnish and Turner, 2017). The NACR is the largest and most comprehensive registry of CR in the UK, collecting patient data from approximately 74% of CR programmes in the UK (NACR, 2017). Ethics may also play in role in the choice of design i.e. in certain instances RCT’s may be inappropriate. For example, the poor recruitment to the RAMIT trial, which was well funded, highlighted the reluctance to randomise patients to a form of usual care (no CR) that goes against the evidence base and routine practice at that time (West, 2012). The programmes which enlisted on the RAMIT trial and recruited may not have been representative of UK CR leading to selection bias, which is counter to the purpose of pragmatic trial designs (Oude Rengerink, 2017). There may also be topics which are less suitable for study with an RCT approach. For example, paper 3 aimed to explore the impact of start time on outcome. Not only is it ethically impossible to randomise patients to late starting CR, when guidelines on timing exist, but practically the size of the study and infrastructure to answer such a question is infeasible. Indeed, the cost as well as the convenience of accessing existing data are often cited as advantages of using registry data (Gliklich, 2014). Similarly, rare and very long-term outcomes are often only feasibly investigated using observational approaches (Gliklich, 2014).

As outlined, there are clear advantages and potentially ethical reasons for choosing an observational approach, but that is not to say there are no drawbacks. Confounding is a major limitation of observational research (Bowers, 2008). This is unlike RCTs which randomly allocate participants to the exposure and control, a technique which balances known and unknown confounders generating equitable groups (Roberts and Torgerson, 1998). As such care must be taken to account for underlying differences between two or more groups when exploring cause and effect relationships in observational studies. For example, observational data could be used to compare the number of deaths in those exposed to drug X (group A) to those not exposed to drug X (group B) (Figure 3). In this example a lower number of deaths are reported in those taking drug X, therefore you could conclude that drug X reduces mortality. However, the effect may also be explained by underlying differences between the groups. In this example group B are substantially older than group A and are therefore more likely to die. This is known as a confounder. Substantial work has gone into developing statistical techniques to manage confounding i.e. adjusted regression analyses,
propensity-based analyses and matching techniques, which has greatly improved the rigour of observational findings (Kahlert, 2017).

To date there continues to be much debate regarding the strength of observational data. Studies comparing the results of RCT and observational based research have reported bias in observational findings, whilst others identify no substantial differences between the results from the respective methodological approaches (Doherty and Rauch, 2013). One systematic review compared long and short-term mortality outcomes from CR in RCTs and observational studies using propensity methods; a statistical technique used to manage confounding (Dahabreh, 2012). A greater magnitude of effect was found in the observational research compared to RCTs, however the difference was rarely statistically significantly different. Limited effect differences were also reported in a Cochrane review of reviews comparing outcomes from observational and RCTs addressing the same question (Anglemyer, 2014). Overall, the evidence supports the use of observational data where appropriate methods have been employed.

For the purposes of this programme of research an observational approach was i) more appropriate for the aims of the studies and ii) generated findings which were derived from a more representative population accessing CR than a RCT could achieve.

Figure 3 Example of the impact of confounding
Thesis Aims

Healthcare audits seek to improve patient care and outcome through the review of service and patient level data against set criteria. The NACR annually reports on the delivery, patient use and outcome of those using CR services across the UK. Through analysis of routine data the audit can be used to observe and report on inequalities and inconsistencies in practice and identify instances of inequity, i.e. lack fairness, that may otherwise go unnoticed. With the inclusion of patient outcomes in the NACR dataset it also provides a unique opportunity to go beyond audit level reporting and investigate what inequality and inequity may mean in terms of patient outcome.

This thesis utilises the strengths and availability of routine patient data to investigate how service delivery and patient level factors can influence the outcome of CR. The overarching aim of this programme of research was to identify and better understand determinants of quality delivery and outcome and, where evident, promote positive service change for patient benefit.

To achieve the aims of this thesis the programme of research consisted of three phases (Figure 4), which are outlined in greater detail as follows.

![Figure 4 Alignment of CR patient pathway to research phase and main research methodology applied](image)
**Phase 1: CR utilisation and prediction of use**

Research question: How is CR utilised and what predicts initiation of use in the UK?

To provide context for the main aim of this thesis this first study explored how: i) CR is utilised expanding beyond routinely reported metrics in the NACR annual report and in the absence of current UK literature ii) what patient level factors predict use. (Chapter 2, Paper 1 (Sumner, 2016)).

**Phase 2: Effectiveness of current CR programmes**

Research question: How effective are modern day CR programmes?

To evaluate what influences the outcome of CR an understanding of the current benefits of CR programmes must first be sought. This research investigated effectiveness of modern-day CR using data from routine practice (non-RCT) drawing comparisons to RCT data. (Chapter 3, Paper 2 (Sumner, 2017)).

**Phase 3: Factors associated with the effectiveness of CR**

Research question 1: Does CR timing impact fitness-related outcomes?
Research question 2: Does CR timing impact psychological outcomes?
Research question 3: Does employment status impact patient outcome?

In the context of the research conducted in phase 1 and 2 a number of projects were undertaken to investigate the association between service practice and patient level factors and patient outcome. Given the volume of potential research questions and the indefinite number of factors collected by the NACR two themes were chosen; CR timing and mental health, the justification for such is presented in Chapter 4. (Chapter 4, Paper 3 (Fell, 2016), Paper 4 (Sumner, 2018), Paper 5 (Harrison, 2016)).
Chapter 2 Utilisation of Cardiac Rehabilitation Services

This section focusses on phase 1: providing the contextual background for the programme of research by investigating how current UK CR is used and what patient level factors predict such use.

Background

The proportion of eligible patients accessing CR varies greatly across Europe; from 3% reported in Spain and up to 90% in Lithuania (Bjarnason-Wehrens, 2010). Barriers to participation have long been explored and many factors have been identified (Figure 5) (Melville, 1999; Lane, 2001; Bethell, 2008; Cupples, 2010; Clark, 2012; Gaalema, 2014; McKee, 2014; Menezes, 2014), which have provided some opportunities to intervene and improve rates in recent years (Karmali, 2014). However, CR still remains grossly under-used.

In 2017 the overall rate of uptake for UK CR was estimated at 51% based on all eligible patients identified through HES data and programme verified attendance (NACR, 2017). Uptake in the UK has improved gradually over time (NACR, 2015; NACR, 2016; NACR, 2017) and exceeds the average European recruitment rate of 40% (Bjarnason-Wehrens, 2010), but the two most recent NACR reports note that women and older adults are under-represented in recruitment figures (NACR, 2016; NACR, 2017). It is therefore important that uptake rates not only increase but are also equitable in terms of the population accessing CR to avoid inequities in care. Since the NACR collects

Figure 5 Factors impacting participation in CR
information on patients and service use the audit dataset can be used to address the question: What determines initiation to CR in the UK? To date an abundance of literature has been published on this topic (Mazzini, 2008; Clark, 2012; Parashar, 2012; Kotseva, 2013; Gaalema, 2014; Barnard, 2015; Thorne, 2015), however there remains a distinct absence of a current, large-scale predictive analyses from the UK. Current and country specific data in the context of CR is important for two main reasons:

i) Changes to service delivery occur over time: Development of home-based programmes (Anderson, 2017) and the National Institute for Health and Care Excellence (NICE) guidance published in 2010 recommending the inclusion of heart failure patients in UK CR (NICE, 2010)

ii) CR delivery varies by country: Inpatient versus outpatient, length of programme and cost to attend programmes

A small number of English and UK cohort studies have previously explored the determinants of CR attendance through multi-variable analyses (Melville, 1999; Lane, 2001; McKee, 2014). In these studies significant predictors of non-attendance were older age, higher social deprivation, being unemployed/retired, history of poor exercise behaviours, not receiving thrombolysis treatment, prior history of MI or revascularisation and not receiving an outpatient appointment. However, these studies were limited by their sample size and/or number of study sites, the limited number of factors explored and age of the data. These limitations form the justification for a more extensive and current exploration into English factors which influence attendance at CR.

**Paper 1: Predictors Of Cardiac Rehabilitation Utilisation In England: Results From The National Audit**

Published in the Journal of the American Heart Association (Sumner, 2016)

The aims of this study were to:

i) Investigate CR utilisation rates in England expanding beyond the NACR report metrics;

ii) Determine sociodemographic and clinical characteristics associated with CR initiation
The NACR is the most comprehensive UK dataset on real-life CR provision, utilisation, and patient outcome. The NACR dataset can also distinguish between different stages of CR utilisation, thus it was ideal for the purposes of this project. As not all metrics for CR usage are routinely reported in the NACR annual statistical report an overview of CR utilisation contributes to the existing literature (aim one). For this paper four levels of CR utilisation were defined and explored:

- **Referral:** Completion of a referral form with receipt at the CR programme
- **Enrolment:** Attendance at the pre-CR assessment
- **Initiation:** Commencement of CR following the pre-CR assessment
- **Completion:** Receiving CR for ≥ eight weeks as per UK minimum standards

Analysis found that despite initial engagement with a CR programme there is a substantial drop in participating patients between referral and initiation of CR. For the second aim of this paper I was interested in what predicts initiation of CR following referral and the pre-CR assessment.

Existing research has identified a great breadth of factors associated with CR use (Figure 5). In particular, sociodemographic and clinical factors have been identified as key predictors of CR use and as such were investigated in this large-scale English cohort. This data is also collected in sufficient detail in the NACR dataset to make the analysis feasible. Efforts were made to include all pertinent factors previously identified from the English and UK cohort studies predicting attendance (Melville, 1999; Lane, 2001; McKee, 2014) and from other countries (Mazzini, 2008; Clark, 2012; Parashar, 2012; Kotseva, 2013; Gaalema, 2014; Barnard, 2015; Thorne, 2015) where available in the NACR dataset.

Measures of deprivation are almost consistently reported as key determinants of CR use regardless of country (Melville, 1999; Lane, 2001; Gaalema, 2014; Barnard, 2015; Thorne, 2015). Measurement of deprivation is extremely important as where someone lives, how they live as well as the social and economic conditions have been identified as determinants of health (Marmot, 2008; Marmot, 2012; Buck and Maguire, 2015). Dahlgren and Whitehead’s (1991) rainbow model sums up this relationship as layers of influence surrounding individuals, which can positively or negatively affect risk of ill health, prevention of disease and access to treatment (Dahlgren and Whitehead, 1991). Various indices have been developed to measure deprivation in an attempt to quantify the many social and economic factors within a given area and are often used by governments to indicate where support and resource allocation may be required (Government Department for Communities...
Examples such as the Townsend (Townsend, 1988) and Carstairs scores (Carstairs and Morris, 1990) focus on the material aspects of deprivation, whilst the Index of Multiple Deprivation (IMD) (Government Department for Communities and Local Government, 2015) attempts to factor both material and social dimensions of deprivation. A limitation of each of these tools is the assumption that deprivation is consistent within the area of assessment, however the alternative, individual grading of deprivation, is impractical on a large scale.

In this analysis we included individual measures of deprivation such as employment status as well as an aggregate measure; the IMD. For the latter the NACR dataset was linked to the English Indices of Deprivation, specifically the IMD at the Clinical Commissioning Group (CCG) level (Government Department for Communities and Local Government, 2015). Each individual patient was assigned an IMD score according to the CCG in which their general practitioner was located. The application of IMD by lower-layer super output areas (i.e. deprivation score by small neighbourhood areas) would have provided greater accuracy, however access to patient level postal codes was limited at the time of this study.

To achieve the second aim of this study a multi-variate regression design was applied to the dataset. Regression models are able to predict an outcome from a predictor variable(s) (Field, 2000), in this case CR commencement predicted by socio-demographic and clinical factors. CR commencement is a categorical binary outcome; therefore a logistic model was most appropriate in this instance. To consider the nested nature of the data (i.e. patients treated within CR centres) the Huber-White-Sandwich estimator was used, which generates robust standard errors.

The patient flow and CR utilisation is reported in Figure 6. Enrolment figures (49%) were short of the National Health Service target of 65% (Department of Health, 2013) but comparable to global rates (Samayoa, 2014). Only 37.2% of those who initiated CR completed at least eight weeks of CR. Enrolment and completion figures were attenuated by the degree of social deprivation with less deprived patients utilising CR to a greater degree compared to more deprived patients (p<0.001).
Significant factors associated with CR initiation were: Younger age, having a partner, not being employed, not having diabetes mellitus (type I or type II), having greater anxiety, not having a post-MI referral indication or having CABG as a referral indication (Figure 7). In line with existing literature being of younger age, having a partner, not having diabetes and undergoing a more invasive treatment approach (i.e. CABG) have consistently been associated with higher CR initiation (Cooper, 2002; Grace, 2008; Strens, 2013; Turk-Adawi, 2014; Chamosa, 2015). The effect of age is often attributed to lower referral rates among older patients, whilst social support is likely to increase enrolment for those in a relationship (Grace, 2008). Lower CR initiation rates by diabetics is consistently reported in the literature (Dunlay, 2009; Harrison, 2017). Treatment burden may offer one explanation for lower uptake. For example, travel and financial constraints are known treatment barriers in multi-morbidity (Rosbach and Andersen, 2017), therefore the requirement to travel to a CR centre may be a barrier to participation. Low motivation to change and tackle lifestyle risk factors may also explain lower uptake. One study in newly diagnosed diabetics reported engagement with exercise was dependent on disease severity (van Puffelen, 2015) whilst another study in diabetics reported patients tended to over-estimate their level of physical activity (Linmans, 2015), which may mean participants perceive less of a need to attend CR. Further study is warranted to explore the experiences and perceptions of diabetics offered CR. Conversely, patients with more intensive/invasive acute cardiac intervention perceive greater mortality risk, and hence are motivated to reduce this risk via CR participation.
Contrary to the existing literature the IMD was not a significant predictor of CR initiation in this study, despite social deprivation being identified as an important factor previously (Gaalema, 2014; Barnard, 2015; Thorne, 2015). This may be explained by differences in the social deprivation measure used in this study compared to others. Another explanation may be that only particular component measures of social deprivation are associated but the effect is lost in the composite IMD score. For example, in this analysis employment status, one frequently used measure of socioeconomic status, was a significant predictor of CR initiation. Studies exploring employment as a predictor of CR use have however, reported both improvements in attendance (Cooper, 2002) perhaps a product of higher socioeconomic status, as well as lower participation (Clark, 2012; McKee, 2014), which may be attributed to work competing with time for CR. Prior data from the UK alone has reported both employment (Lane, 2001) and unemployment/retired (McKee, 2014) are both detrimental to CR attendance. Reasons for the differences in findings regarding employment status are uncertain; perhaps greater detail on the employment history would elucidate a greater understanding. Sex was also not a significant predictor, although evidence from a recent systematic review showed enrolment may be predicted by sex (Samayoa, 2014). Lastly symptoms of anxiety, but not depression, were associated with a small increase in the likelihood of CR initiation. The higher burden of anxiety compared to depression may explain these results.

To conclude, successful strategies to increase participation, such as self-monitoring, action planning and tailored counselling (Karmali, 2014), should be targeted to patients with the aforementioned factors. Further work is also needed to understand and improve rates of CR completion, which was low at 37% (of those initiating CR).
Figure 7 Predictors of CR initiation, odds ratio with 95% confidence intervals

White ethnicity, IMD group three, retired and ‘other’ referral indication used as reference categories in regression. IMD: Index of Multiple Deprivation; BMI: Body Mass Index; BP: Blood Pressure; post-MI: post-myocardial infarction; MI-PCI: myocardial infarction with Percutaneous Coronary Intervention; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Surgery
Chapter 3 The Effectiveness of Cardiac Rehabilitation in Routine Practice

This section focuses on phase 2: Providing the contextual background for the programme of research by investigating how effective routinely practiced CR in the modern era is.

Background

Despite clear national guidance (NICE, 2013b) the benefits of CR have been challenged. In 1997 growing uncertainties around CR led to the commissioning of a new RCT; the RAMIT trial (West, 2012). Although the results were damning, methodological issues in the trial led to questions around the validity of the study findings (Doherty and Lewin, 2012; Rashid and Wood, 2012; Taylor, 2012; Wood, 2012) and guidance remained unchanged. The emergence of the CR efficacy debate is unsurprising given almost half the trial evidence supporting CR synthesised in the most recent Cochrane review pre-dates the ‘statin era’ (Anderson, 2016). In addition to advances in pharmaceuticals programmes have diversified in their content, including education and psychological support, as well as the types of patient eligible for CR e.g. inclusion of heart failure patients (NICE, 2010). Thus, RAMIT was sorely needed.

Since the RAMIT RCT the most recent 2016 Cochrane review on CR effectiveness identified no current RCTs with sufficient sample sizes to investigate the efficacy of modern standard CR care (Anderson, 2016). In an effort to overcome the aforementioned challenge and extend the external validity of trials, to determine the benefit of current day CR in routine practice, a recently published systematic review (the CROS review) included non-randomised studies from the statin era onwards (Rauch, 2016). The primary outcome, total mortality following CR, was confirmed although the secondary outcomes of cardiac mortality and re-hospitalisation were not evident contrary to the most recent Cochrane review of RCT evidence (Anderson, 2016).

The CROS review provided valuable information on modern day routine CR effectiveness, however it included a mixed CR population and did not consider HRQOL. To understand whether the effects were similar within a homogenous sub-population and investigate reoccurrence of AMI and HRQOL, which were not considered in the CROS review, I conducted a separate systematic review in AMI patients. Specifically, observational studies recruiting AMI patients from ≥2000 onwards, which compared the effectiveness of CR versus no CR, were included.
The aims of this study were to understand the effect of CR:

i) Outside the confines of a RCT;
ii) Identify and synthesise ‘current’ effectiveness data on routine CR practice;
iii) Extend knowledge from existing systematic reviews of observational and RCT data

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher, 2009) and the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) (Stroup, 2000) guidelines were used in the conduct and write up of this study. The study protocol was prospectively registered on PROSPERO; a database of systematic review protocols (registration number: CRD42015024021).

The PICOS criteria i.e. participants, intervention, control, outcomes and study type and justification for selection criteria for this systematic review are defined in Table 1. The process of identifying and synthesising observational data is similar to that when using RCT data. The research question and selection criteria were defined, a search strategy was developed and implemented, data quality was assessed, and data synthesis conducted. However, a few points warrant discussion. Firstly, the indexing of observational studies is not as established or consistent as RCTs (Higgins and Green, 2011). As such study design terms were not incorporated in the search strategy for this review to avoid missing publications. Instead combinations of medical subject headings and keywords around four themes were used: Cardiac population descriptors, CR intervention, CR use and patient outcomes. Search strings, similar to the standardised Cochrane search string for RCT’s (Higgins and Green, 2011), are currently under development by the Cochrane collaboration to improve observational search strategies (Belisario, 2013).

A further point to raise is on the quality appraisal of observational data. For this study an appraisal checklist developed recently by the Cochrane collaboration was used (Wells, 2013). A major limitation of this appraisal tool was the inclusion of questions relating to pre-published study protocols. The practice of protocol publication has been slow to adopt to observational research
(Loder, 2010; Williams, 2010). As no pre-published protocols were identified for the included studies all questions relating to this topic had to be removed from the appraisal checklist.

Lastly, this review limited the inclusion criteria to studies which recruited participants from the year 2000 onwards. The purpose of this study was to systematically review current evidence on the effectiveness of CR in current routine practice. Cardiovascular care has evolved substantially over the last two decades; the introduction of statins (Johannesson, 1997), surgical advancements such as stenting for reperfusion (Montalescot, 2004) as well as the publication of multiple international guidelines on modern standards of care between 1994 and 2003 (Balady, 1994; Department of Health, 2000; Jolliffe, 2001; Giannuzzi, 2003; Balady, 2007). Historical data, which is often included in existing systematic reviews on CR, is arguably a poor reflection of modern-day practices. On this basis and so the conclusions of this review are applicable to modern care standards the date restriction was imposed and this period is considered as the ‘modern CR’ era as outlined in Chapter one.
### Table 1 PICOS screening criteria

| **Participants** | Male or female adults diagnosed with AMI; either ST-elevated (STEMI) or non-ST-elevated (nSTEMI) were included. Both medically managed (i.e. drug therapies) or re-vascularised (CABG or PCI) AMI patients were included. The AMI population was chosen as the predominant cause of CHD related death and to minimise heterogeneity in the analyses population i.e. by factoring the impact of different care pathways. |
| **Intervention** | CR delivered as a structured, multi-component programme which included exercise and/or structured physical activity in addition to at least one of the following: information provision, education, health behaviour change, psychological support or intervention and social support. CR programmes using a mixture of supervised or unsupervised approaches conducted in any setting (inpatient, outpatient, community, home based) were included. |
| **Control** | Patients, as defined previously, who did not participate in CR. It was anticipated that patients in the control group were only medically supervised, usually by a general practitioner or equivalent, but may have also attended unstructured prevention programmes. |
| **Outcomes** | All cause- and cardiac-related mortality. Secondary outcomes included all cause and cardiac-related hospital re-admission, re-occurrence of AMI, re-vascularisation and HRQOL. The outcomes were based on the criteria typically assessed in the Cochrane systematic reviews of CR effectiveness (Anderson, 2016). |
| **Study type** | Observational studies (prospective or retrospective cohort, case-control data from routine practice) comparing CR attenders to non-attenders were included. |
| **Other criteria** | As a review of modern CR practice the search strategy and population inclusion was date limited from 2000 to present day. This is in line with the period of time when major cardiovascular treatment developments (Johannesson, 1997; Montalescot, 2004) and multiple international guidelines on modern standards of care, including CR service were introduced (Balady, 1994; Department of Health, 2000; Jolliffe, 2001; Giannuzzi, 2003; Balady, 2007). Foreign language papers were included and translated where possible. |
Lastly, statistical analyses of observational research require appropriate confounding management in the absence of randomisation to study groups. Outcomes reported from observational research may therefore be ‘adjusted’ or ‘unadjusted’ according to whether confounding was addressed. Given the inherent differences in bias between adjusted and unadjusted outcomes forest plots were generated with subgroups by adjustment status. This also meant the potential impact of adjustment on the study findings could be visually examined (Figure 8).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1 Unadjusted outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim C 2011</td>
<td>0.0432</td>
<td>1.4244</td>
<td>2.5%</td>
<td>1.04 [0.06, 17.03]</td>
<td></td>
</tr>
<tr>
<td>Coll-Fernandez R 2014</td>
<td>-3.9666</td>
<td>1.0121</td>
<td>4.7%</td>
<td>0.02 [0.00, 0.13]</td>
<td></td>
</tr>
<tr>
<td>Rauch B 2014</td>
<td>-1.3129</td>
<td>0.2468</td>
<td>27.5%</td>
<td>0.27 [0.17, 0.44]</td>
<td></td>
</tr>
<tr>
<td>Junger C 2010 STEMI</td>
<td>-1.5256</td>
<td>0.1784</td>
<td>32.4%</td>
<td>0.22 [0.15, 0.31]</td>
<td></td>
</tr>
<tr>
<td>Junger C 2010 NSTEMI</td>
<td>-1.0532</td>
<td>0.1698</td>
<td>32.8%</td>
<td>0.35 [0.25, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>0.25 [0.16, 0.40]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.14; Chi² = 11.68, df = 4 (P = 0.02); P² = 66%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.91 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 2.1.2 Adjusted outcome |
| Rauch B 2014 | -0.7765 | 0.2718 | 18.1% | 0.46 [0.27, 0.78] |
| Junger C 2010 STEMI | -0.8516 | 0.1946 | 35.4% | 0.41 [0.28, 0.56] |
| Junger C 2010 NSTEMI | -0.6349 | 0.1698 | 48.5% | 0.53 [0.38, 0.74] |
| Subtotal (95% CI) | 100.0% | 0.47 [0.38, 0.59] |
| Heterogeneity: | Tau² = 0.00; Chi² = 1.00, df = 2 (P = 0.61); P² = 0% |
| Test for overall effect: Z = 6.49 (P = 0.00001) |

Test for subgroup differences: Chi² = 5.93, df = 1 (P = 0.01), P² = 83.1%

Figure 8 All-cause mortality forest plot: CR attenders versus non-attenders presented by adjusted and unadjusted outcome subgroups

This systematic review identified 2,382 unique articles leading to eight papers meeting the inclusion criteria following screening. Reductions in mortality risk (Figure 8) and improvements in HRQOL were observed. Conversely CR had no effect on re-vascularisation or re-hospitalisation in this study. Overall, systematic reviews of RCT (Lawler, 2011; Anderson, 2016; Powell, 2018) and observational evidence (Rauch, 2016; Sumner, 2017) appear to draw differing conclusions. Specifically, no effect on total mortality (Lawler, 2011; Anderson, 2016; Powell, 2018), cardiac mortality (Powell, 2018) or re-admission (Lawler, 2011; Anderson, 2016; Powell, 2018) were observed in trial-based evidence synthesis contrary to observational evidence synthesis (Rauch, 2016; Sumner, 2017). This may reflect differences in the populations studied and intervention delivered where RCTS are frequently argued to be unrepresentative of routine practice. For example, the Cochrane reviews of trial-based
CR evidence include exercise-only formats as well as historical studies which pre-date treatment advancements and changes to service delivery, as outlined in Chapter one (Heran, 2011; Anderson, 2016). Poor execution of systematic reviews can also lead to erroneous results, as is the case with the Powell (2018) review, which included a poorly defined intervention criteria as well as not rigorously adhering to their inclusion criteria of year ≥2000 onwards (Powell, 2018). Where similarities between trial and observational evidence did arise, meta-analysis was not conducted e.g. HRQOL, due to limited available evidence or meta-analysis were based on unadjusted analyses (Sumner, 2017) which are prone to bias (Bowers, 2008). Thus, with respect to unadjusted analyses, the conclusions should be interpreted with caution.

In conclusion, there is divergence between the conclusions of current observational evidence synthesis and trial-based reviews with respect to total and cardiac mortality and re-hospitalisation. These differences may be expected when analyses of registry data will reflect routine practices and other reviews have included outdated evidence which does not reflect current day practices or the populations receiving care. There is also a need to obtain and analyse routine data on UK CR to determine the current day effects within local context and explore which patient and service level factors determine the greatest benefit.
Chapter 4 Factors Associated with Cardiac Rehabilitation Effectiveness

This section focuses on phase 3: Investigating whether service practice and patient factors are associated with patient outcome.

Background

The benefits of CR have been demonstrated in both RCT (Lawler, 2011; Anderson, 2016) and observational studies (Rauch, 2016; Sumner, 2017) hence national and international guidelines continue to recommend CR (Department of Health, 2000; Giannuzzi, 2003; Balady, 2007; Piepoli, 2012; Department of Health, 2013; NICE, 2013b; BACPR, 2017). For the purposes of maintaining best practice, once an intervention is implemented, it should be continually reviewed and refined. The NACR serves as a platform from which national CR programmes can be evaluated. Indeed, national inequalities and inequities in CR practice and service use are clearly evident in the annual reports (NACR, 2016; NACR, 2017). For example, Figure 9 displays the median wait time between referral and programme start by each CR programme for MI/PCI and CABG patients. There is clear variation in wait-time by CR programme and referral indication.
Identifying programme differences is important especially if practice falls outside evidence-based guidelines, however the impact of variation on outcome is not understood or addressed in routine audit reporting and requires in-depth analysis. With this in mind, Chapter 3 summarises three papers which have used the NACR audit to address key research questions about the extent of service and patient variation and what this variation means in terms of patient outcome. Paper 3 and 4 consider the influence of CR timing and paper 5 the influence of employment status on patient outcome.
Paper 3: Does The Timing Of Cardiac Rehabilitation Impact Fitness Outcomes? An Observational Analysis

Published in Open Heart (Fell, 2016)

The aims of this study were to explore:

i) the characteristics of patients starting CR late;

ii) to determine if an association between CR timing and fitness related outcomes exist

National deviations in CR practice exist, of which CR timing is one example. CR timing in this context denotes the time between a patient’s referral to a CR programme and commencement of the core CR programme. At the time of this paper national guidelines and evidence indicated patients should be seen promptly and ideally start CR within four weeks of referral (Department of Health, 2010; NICE, 2011; BACPR, 2012; Piepoli, 2012; NICE, 2013b; BACPR, 2017); in practice not all programmes meet this target. Increasing service demands and decreasing NHS resources may account for this. There is, however, a perception that delays may not only reduce chances of enrolment but also impact the outcome of CR and emerging evidence appears to demonstrate this may be the case (Russell, 2011; Pack, 2013; Johnson, 2014), but the topic requires further exploration. To understand the impact of service variation on outcome an RCT design would not be suitable, both practically when assigning patients to different start times and ethically randomising patients to late starting CR, which goes against guideline recommendations. Instead routinely collected CR service data, such as that recorded in the NACR dataset, is required. A multi-variate logistic regression model was used to investigate how variation in CR timing, particularly outside recommended timeframes, impacts fitness-related outcomes.

The focus on fitness-related outcomes was chosen on the basis that there is an emphasis on exercise-based CR reducing mortality (Anderson, 2016). CR originated as an exercise-only format and the first RCTs dating back to the 1980’s tested and proved efficacy in exercise only programmes (Anderson, 2016). Today CR is expected to be multicomponent and more recent studies have demonstrated the benefits of including other components such as education and psychological support (Anderson, 2016). That being said, exercise remains integral to delivering an effective CR programme. To capture the patient and clinician reported perspective of fitness three outcome measures were explored and included as categorical variables:
- Patient reported physical activity (150mins/week: yes or no) - the recommended weekly moderate intensity physical activity level (WHO, 2017b)
- Physical fitness as a dimension of the Dartmouth Quality of Life scale (healthy status score one to three or non-healthy status score four to five)
- The incremental shuttle-walk test (ISWT) (< 70 m improvement in distance or ≥ 70 m distance improvement pre- to post-CR) - a clinical measure of physical fitness

CR timing was included as a continuous variable to test the impact on outcome of each day increase in wait time. In addition, in a separate analysis, CR timing was categorised as ‘on time’ (zero-28 days) or delayed (29-365 days). This cut point was based on recommendations that patients should be seen early, ideally within four weeks of referral. Adjusted cut points were set for CABG patients as this group must recover from surgery (sternotomy) before CR can commence. For CABG patients ‘on time’ was defined as zero-42 days. Data were extracted between 2012 and 2015 and multivariate logistic regression analyses were run accounting for age, sex, number of comorbidities, duration of CR, BMI at baseline, systolic and diastolic blood pressure, smoking status, ethnicity, treatment and baseline activity level. The Huber-White-Sandwich estimator was used, which generates robust standard errors, to manage the nested nature of the data.

A total of 32,899 participants were included in the analyses. Overall 63% of the study population were classified as attending CR late. Significant predictors of late CR were being older, female, non-British, having a lower BMI, having at least one comorbidity, having higher systolic and lower diastolic blood pressure, being a current smoker, being less likely to achieve 150mins/week of physical activity and achieving a shorter ISWT distance. Reasons for late CR were not explored in this paper but variation in practice may be a product of increasing service demands and decreasing NHS resources. Case mix may also play a role; of late attenders 73% had at least one comorbidity compared with 69% in early attenders. Case complexity could certainly delay the start of rehabilitation. Referral indication also seems to play a role with post-MI patients experiencing the longest delays to starting CR (a median of 12 days longer than the maximum recommended wait time) despite these patients undergoing no revascularisation surgery, which might delay the start of CR.
The results from regression analyses are reported in Table 2. Significant associations between CR timing and fitness related outcomes were found, that is delayed timing is detrimental to fitness related outcomes. For every one-day increase in CR wait time patients were 1% less likely to improve across all fitness-related measures (p<0.05). This seems to fit with a recent study of 1241 CR patients which concluded delayed enrolment is directly related to patient outcome (metabolic equivalent of tasks (METs) and weight improvement) (Johnson, 2014). A further analysis in 6497 CABG patients also found an association between longer wait time in CR commencement and less improvement in cardiopulmonary fitness (Marzolini, 2015). Chow et al (2010) also reported that peak changes in lifestyle, in those attending lifestyle and exercise programmes, occur within the first six months after acute coronary syndrome (Chow, 2010). Overall the notion that timing is important in optimising treatment response is supported by the evidence.
Table 2 Results from logistic regression: association between fitness-related outcomes and CR timing

<table>
<thead>
<tr>
<th>CR wait time (days)(^a)</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 minutes physical activity/week achieved</td>
<td>0.997</td>
<td>0.005</td>
<td>0.995, 0.999</td>
</tr>
<tr>
<td>Healthy QOL relating to physical fitness reported</td>
<td>0.996</td>
<td>&lt;0.001</td>
<td>0.995, 0.998</td>
</tr>
<tr>
<td>Meaningful improvement in shuttle walk test distance achieved</td>
<td>0.997</td>
<td>0.003</td>
<td>0.995, 0.999</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late CR(^b)</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 minutes physical activity/week achieved</td>
<td>0.863</td>
<td>0.051</td>
<td>0.744, 1.000</td>
</tr>
<tr>
<td>Healthy QOL related physical fitness reported</td>
<td>0.773</td>
<td>0.001</td>
<td>0.668, 0.893</td>
</tr>
<tr>
<td>Meaningful improvement in shuttle walk test distance achieved</td>
<td>0.793</td>
<td>0.008</td>
<td>0.669, 0.941</td>
</tr>
</tbody>
</table>

CR: Cardiac Rehabilitation, QOL: Quality of Life, CI: Confidence Interval. Analyses were adjusted for age, sex, number of comorbidities, duration of CR, BMI at baseline, systolic and diastolic blood pressure, smoking status, ethnicity, treatment and baseline activity level. Data were clustered with centres using cluster robust standard errors.

\(^a\) Number of days between referral to CR and start of core CR

\(^b\) Late CR was defined as the time between referral to CR and start of core CR 29-365 days for post-MI, PCI, MI-PCI patients or 43-365 days for CABG patients.

The paper concludes that CR timing is an important determinant of post CR fitness-related measures. With many programmes not meeting recommendations for timely CR it is important that barriers to timely commencement of CR are identified and strategies are developed to overcome avoidable delays. A mixed method design, which refers to the use of quantitative and qualitative methods in one or a series of studies, could be one approach to investigate this question further. The approach is more holistic in that different dimensions are considered and a greater depth of understanding is achieved. For instance, in paper three quantitative analysis was used to predict clinical outcome according to wait-time. A qualitative study such as a focus group discussion or
individual interviews could be conducted with health care professionals and patients at CR centres with long delays to explore reasons for delay. The information gathered from qualitative work would provide context and greater meaning to the numeral data, leading to appropriate solutions being developed.

Overall the impact of the paper has been such that CR timing has been included as one of the quality criteria in the recent NACR_BACPR CR certification programme and discussed in the most recent NACR statistical reports (NACR, 2016; NACR, 2017).
Paper 4: Does Service Timing Matter For Psychological Outcomes In Cardiac Rehabilitation? Insights From The National Audit Of Cardiac Rehabilitation.

Published in the European Journal of Preventative Cardiology (Sumner, 2018)

The specific aims of this study were to:

i) To investigate participation of patients eligible for CR with and without symptoms of anxiety and depression;

ii) to determine if an association between CR timing and mental health outcomes exists.

Increasingly patients attending CR are multi-morbid (NACR, 2017). Frequently those with chronic conditions experience mental health problems such as depression and anxiety (Naylor, 2012); cardiology is no different. In a systematic review the prevalence of major depression was reported as 19.8% and the proportion with symptoms of depression ranged from 15-31% depending on which screening instrument was used in acute myocardial infarction (AMI) survivors (Thombs, 2006). As part of modern CR practices in the UK symptoms of depression and anxiety are assessed during baseline assessment. Several screening tools exist and are used commonly in clinical practice: The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Snaith, 2003), Patient Health Questionnaire (PHQ-9) (Spitzer, 1994), Becks Depression Inventory (BDI) (Beck, 1961) and the Generalized Anxiety Disorder tool (GAD-7) (Spitzer, 1994) are just a few examples. The comparative utility of such tools has been previously critiqued in CHD and coronary arterial disease populations (Bunevicius, 2013; Haddad, 2013; Ceccarini, 2014). PHQ-9 and BDI have been reported as the preferred instruments for depression screening due to their ease of use and accuracy, whilst HADS maybe preferred for anxiety screening. Although HADS is advantageous in that it evaluates depression and anxiety together, a systematic review of HADS data reported inconsistencies across studies, specifically its ability to distinguish between the constructs of anxiety of depression have been questioned (Cosco, 2012). This has led to the development of a further study investigating the diagnostic accuracy of HADS, through analysis of patient-level HADS data, which is currently underway (Thombs, 2016). Despite this ongoing debate the 2017 BACPR guidelines continue to recommend the use of HADS in clinical practice (BACPR, 2017). Based on the BACPR recommendation and the limited data collected on other screening tools in the NACR dataset, HADS was included in this analysis.
There are several reasons why screening for mental health conditions is important. Existing evidence has shown poor adherence to CR, reduced access of health services and an increased interest in unhealthy behaviours (McGrady, 2009; Naylor, 2012). Mortality and re-AMI have also been adversely linked to mental health (Frasure-Smith, 1993; Bush, 2001; Rutledge, 2009; Batelaan, 2016). A position paper by the European Association of Cardiovascular Prevention and Rehabilitation (EACPR) concludes that the success of CR depends on managing underlying mental health conditions (Pogosova, 2015).

Although the treatment of co-morbid mental health conditions should take precedence, it is also important to understand if service practices are related to mental health to encourage best practice. Service variation, specifically timing of CR, has previously been implicated in impacting patient outcome (Fell, 2016). This project therefore set out to explore if mental health outcomes are associated with CR timing. As the NACR collects routine service delivery and mental health outcomes its use was deemed ideal to investigate this question. Timing i.e. time between referral and core CR start, was defined as per paper 3, however there were a number of differences between paper 3 and this project as I shall outline. Unlike paper 3 this study also considered change in outcome pre-to post-CR in addition to outcome at follow-up. In brief, post-CR hospital anxiety and depression scale (HADS) scores were included in the analyses as a categorical variable (no symptoms/ symptoms present) with scores less than eight representing low or no symptoms of anxiety or depression (Zigmond and Snaith, 1983; Snaith, 2003). Change in HADS category between pre- and post-CR were also derived and categorised as:

- Symptomatic to non-symptomatic
- No change in symptomatic patients
- Non-symptomatic to symptomatic
- No change in non-symptomatic patients

Three different statistical techniques were applied to analyse the data. Firstly, I explored the marginal probabilities of the outcome occurring over time i.e. the percentage probability of being classed as symptomatic over wait-time. Secondly, the amount of variance due to data clustering by centre was investigated using intra-class correlations (ICC) for HADS scores, wait-time and CR duration i.e. does the average HADS score vary by centre. Thirdly, I considered the impact of missing data on the results through multiple imputation.
Multi-variate logistic regression analyses were performed to investigate the relationship between CR wait-time and post-CR outcome (HADS category). Multinomial logistic regression models were used to investigate the relationship in change in anxiety and depression between pre- to post-CR and wait-time. ‘Non-symptomatic to symptomatic’ was used as the reference category as I was most interested in reporting the effect of wait time on achieving a positive outcome i.e. symptomatic to non-symptomatic. All analyses were adjusted for age, sex, number of comorbidities, CR duration, ethnicity, relationship status, employment status, history of previous cardiac event, treatment received, year of initiating event and baseline anxiety and depression score (baseline scores included in the CR wait-time and post-CR outcome analyses only). To consider the nested nature of the data (i.e. multiple patients treated within the same CR centre) the Huber-White-Sandwich estimator was used, which generates robust standard errors. Logistic and multinomial regressions were also run in sensitivity analyses using imputed data. Missing data were imputed using the multiple imputation chained equations (MICE) method (Azur, 2011). Age, sex, ethnicity, number of comorbidities, employment status, relationship status, CR duration, history of previous cardiac event, treatment received, year of event, and baseline and post-CR HADS scores were included in the imputation model.

In the analysis sample 39,588 patients completed CR and had a complete pre and post HADS assessment (approximately 70% of those who completed CR and had a baseline HADS). Participants were primarily male, British and had a mean age of 65 years. Symptoms of anxiety and depression at baseline were identified in 28% and 17% of patients respectively decreasing to 21% and 12% post CR. ICCs demonstrated roughly similar HADS distributions across CR programmes, however variation in the wait-time to start CR and duration of CR were observed.

In those without and without symptoms of anxiety and depression wait-time did not vary substantially (range 36-37 days). This was similar for most HADS change categories (range 35-37), except for those who remained symptomatic who waited the longest (40 days). The duration of CR did not substantially vary for those with and without anxiety symptoms (one day difference) but was significantly longer for those with depression compared to those without (four days longer p<0.001). For change in HADS category those who remained non-symptomatic had the shortest CR duration (58 days) and those who went from non-symptomatic to symptomatic had the longest at 63 days. Non-completion of CR was higher in those with symptoms of anxiety (28%) and depression (31%) compared to those without, 5% and 8% difference respectively (both p<0.001).
Statistically significant associations were observed between CR wait-time and symptoms of anxiety and depression (Table 3). The associations largely remained significant in sensitivity analysis with imputed data. In other words, delayed CR or increasing wait-time increases the likelihood of being symptomatic post-CR. Analysis by change in HADS category also identified a number of similar significant associations (Table 4). Overall the symptomatic to non-symptomatic HADS change category had the most consistent significant association with wait-time, however in sensitivity analysis with imputed data none of these effects remained statistically significant (Table 5).
Table 3 Results from logistic regression: CR wait-time (late CR or CR wait-time in days) and likelihood of having symptomatic anxiety or depression scores following CR

<table>
<thead>
<tr>
<th></th>
<th>Observed data</th>
<th>Imputed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptoms of anxiety</td>
<td>Symptoms of depression</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>CR wait-time (days)</strong> a</td>
<td>OR 1.001 p=0.001 (1.0008, 1.003)</td>
<td>OR 1.002 p&lt;0.001 (1.001, 1.003)</td>
</tr>
<tr>
<td><strong>Late CR</strong> b</td>
<td>OR 1.13 p=0.002 (1.04, 1.23)</td>
<td>OR 1.24 p&lt;0.001 (1.12, 1.38)</td>
</tr>
</tbody>
</table>

CR: Cardiac Rehabilitation, OR: Odds Ratio, CI: Confidence Interval. Analyses adjusted for age, sex, comorbidity, CR duration, ethnicity, relationship status, employment, history of previous cardiac event, treatment received, baseline anxiety and depression score and year of initiating event. Data were clustered with CR centres using cluster robust standard errors.

a Number of days between referral to CR and start of core CR

b Late CR was defined as the time between referral to CR and start of core CR 29-365 days for post-MI, PCI, MI-PCI patients or 43-365 days for CABG patients.

Symptoms present defined as score ≥ eight
Table 4 Results from multinomial logistic regression: CR wait-time (late CR or CR wait-time in days) and change in anxiety and depression category (Observed data)

<table>
<thead>
<tr>
<th>Observed data</th>
<th>Change in anxiety category RR (95% CI)</th>
<th>Change in depression category RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Late CR b</td>
<td>Late CR b</td>
</tr>
<tr>
<td></td>
<td>CR wait-time (days) a</td>
<td>CR wait-time</td>
</tr>
<tr>
<td>Non-symptomatic to symptomatic</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Symptomatic to non-symptomatic</td>
<td>0.85 p=0.04</td>
<td>0.81 p=0.01</td>
</tr>
<tr>
<td></td>
<td>(0.74, 0.99)</td>
<td>(0.68, 0.95)</td>
</tr>
<tr>
<td></td>
<td>0.99 p=0.006</td>
<td>0.99 p=0.46</td>
</tr>
<tr>
<td></td>
<td>(0.994, 0.9991)</td>
<td>(0.997, 1.001)</td>
</tr>
<tr>
<td>No change: symptomatic</td>
<td>1.04 p=0.58</td>
<td>1.06 p=0.42</td>
</tr>
<tr>
<td></td>
<td>(0.89, 1.21)</td>
<td>(0.90, 1.24)</td>
</tr>
<tr>
<td></td>
<td>1.002 p=0.004</td>
<td>(1.0008, 1.004)</td>
</tr>
<tr>
<td></td>
<td>(0.997, 1.001)</td>
<td></td>
</tr>
<tr>
<td>No change: non-symptomatic</td>
<td>0.93 p=0.26</td>
<td>0.85 p=0.01</td>
</tr>
<tr>
<td></td>
<td>(0.82, 1.05)</td>
<td>(0.74, 0.97)</td>
</tr>
<tr>
<td></td>
<td>0.99 p=0.03</td>
<td>0.99 p=0.09</td>
</tr>
<tr>
<td></td>
<td>(0.996, 0.9998)</td>
<td>(0.997, 1.0002)</td>
</tr>
</tbody>
</table>

RR: Relative Risk, CI: Confidence Interval, CR: Cardiac Rehabilitation, HADS: Hospital Anxiety Depression Scale. Analyses adjusted for age, sex, comorbidity, CR duration, ethnicity, relationship status, employment, history of previous cardiac event, treatment received and year of initiating event.

Data were clustered with CR centres using cluster robust standard errors.

\(^a\) Number of days between referral to CR and start of core CR

\(^b\) Late CR was defined as the time between referral to CR and start of core CR 29-365 days for post-MI, PCI, MI-PCI patients or 43-365 days for CABG patients.

Symptoms present defined as score ≥eight
Table 5 Results from multinomial logistic regression: CR wait-time (late CR or CR wait-time in days) and change in anxiety and depression category (Imputed data)

<table>
<thead>
<tr>
<th>Change in HADS category</th>
<th>Imputed data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in anxiety category RR (95% CI)</td>
<td>Change in depression category RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Late CR (^b)</td>
<td>CR wait-time (days) (^a)</td>
</tr>
<tr>
<td>Non-symptomatic to symptomatic</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Symptomatic to non-symptomatic</td>
<td>0.95 p=0.37 (0.86, 1.05)</td>
<td>0.99 p=0.16 (0.99, 1.00)</td>
</tr>
<tr>
<td>No change: symptomatic</td>
<td>1.02 p=0.58 (0.93, 1.13)</td>
<td>0.99 p=0.96 (0.99, 1.00)</td>
</tr>
<tr>
<td>No change: non-symptomatic</td>
<td>0.98 p=0.78 (0.90, 1.07)</td>
<td>0.99 p=0.29 (0.99, 1.00)</td>
</tr>
</tbody>
</table>

**RR**: Relative Risk, **CI**: Confidence Interval, **CR**: Cardiac Rehabilitation, **HADS**: Hospital Anxiety Depression Scale. Analyses adjusted for age, sex, comorbidity, CR duration, ethnicity, relationship status, employment, history of previous cardiac event, treatment received and year of initiating event.

Data were clustered with CR centres using cluster robust standard errors.

\(^a\) Number of days between referral to CR and start of core CR

\(^b\) Late CR was defined as the time between referral to CR and start of core CR 29-365 days for post-MI, PCI, MI-PCI patients or 43-365 days for CABG patients.

Symptoms present defined as score \(\geq 8\).

Variations in the timing of CR have been reported in the NACR annual report and in some instances programmes fall outside of recommended practice. CR wait-time was found to be a significant predictor of psychological outcomes, to the effect that delays are detrimental. Overall, baseline assessment, in particular mental health status, is important so a patient’s programme can be tailored to the patient and co-morbidity is managed. Programmes falling outside recommendations must also strive towards timely delivery of CR.
The aims of this study were to:

i) determine the characteristics of patients attending CR by employment status;
ii) determine if and to what extent an association between employment status, mental health and QOL exists.

CR is a well evidenced and established intervention (NICE, 2013b). National and international evidenced-based guidelines acknowledge CR can be beneficial to HRQOL among other benefits (Department of Health, 2000; Giannuzzi, 2003; Balady, 2007; Piepoli, 2012; Department of Health, 2013; NICE, 2013b; BACPR, 2017). Baseline assessment of participants allows for tailoring of care as per the ‘menu-driven’ approach recommended by the BACPR (BACPR, 2017). Baseline assessment also provides opportunities to more specifically target and tailor an intervention for those at risk of poorer outcome. Employment status has been identified as a factor which influences service use and outcome. For example, paper 1 in this thesis identified that being employed significantly decreased the likelihood of CR participation (OR 0.86, 95% CI 0.77-0.96) (Sumner, 2016). Evidence has also associated unemployment with worse health outcomes, including mental health and well-being (Fryers, 2003; Bambra and Eikemo, 2009). However, the link between employment and health has scarcely been studied in CR populations. One study in PCI patients found lower QOL at baseline and 12 months after treatment in unemployed patients (Leslie, 2007). To further explore the relationship between health and employment in CR populations this study set out to investigate whether employment status influences mental health and quality of life outcomes in CR participants. The NACR dataset routinely collects socio-demographic information, including employment status and mental health outcomes in those attending CR, making it an ideal dataset to achieve the aims of this project.

At the time of this study approximately two thirds of the CR population were identified as retired (NACR, 2015). Therefore, three employment status categories were used in this study; unemployed, retired and employed. Mental health was assessed using the HADS scale, which assesses symptoms.
of anxiety and depression. Participants were categorised according to established clinical cut-offs with scores less than eight representing low or no symptoms of anxiety or depression (Zigmond and Snaith, 1983; Snaith, 2003). QOL was assessed using the ‘general QOL’ and ‘feelings’ dimensions of the Dartmouth QOL Scale and scores were dichotomised to healthy (score one to three) or unhealthy (score four to five). Multi-variate logistic regression analyses were run adjusting for age, sex, number of comorbidities, duration of CR, treatment and social deprivation as determined by the IMD score. Employed working status was used as the reference category.

A total of 24,242 CR participants were included in the analyses. Those in the employment category were significantly more likely to be male and have less comorbidities than those unemployed or retired. Participants were significantly older in the ‘retirement’ group as would be expected. At baseline a significantly lower proportion of unemployed participants were categorised as healthy according to HADS or the Dartmouth scales compared to those employed or retired. Unemployed participants were also significantly more likely to change from an unhealthy to a healthy category following CR; this is likely due to the greater propensity to change.

The results from regression analyses are reported in Table 6. The investigation found an association between unemployment and depression and well-being outcomes, but not anxiety. That is, unemployed participants of CR are significantly less likely to be categorised as healthy in terms of depression and well-being following CR. Although the lack of association with anxiety may not appear to align with existing evidence, for example one meta-analysis reported higher psychological problems, including anxiety, in the unemployed (Paul and Moser, 2009), it is important to consider differences in the study population, study designs and analysis. Further investigation could also be undertaken to evaluate the moderating effects of certain variables i.e. sex, which is strongly associated with anxiety disorders (Bandelow and Michaelis, 2015).
Table 6 Results from logistic regression: association between employment status and mental health and well-being

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unemployed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms of anxiety</td>
<td>0.934</td>
<td>0.56</td>
<td>0.743, 1.175</td>
</tr>
<tr>
<td>No symptoms of depression</td>
<td>0.734</td>
<td>0.034</td>
<td>0.552, 0.977</td>
</tr>
<tr>
<td>Healthy Dartmouth feelings reported</td>
<td>0.772</td>
<td>&lt;0.001</td>
<td>0.675, 0.884</td>
</tr>
<tr>
<td>Healthy Dartmouth QOL reported</td>
<td>0.525</td>
<td>&lt;0.001</td>
<td>0.406, 0.678</td>
</tr>
<tr>
<td><strong>Retired</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms of anxiety</td>
<td>0.992</td>
<td>0.980</td>
<td>0.513, 1.915</td>
</tr>
<tr>
<td>No symptoms of depression</td>
<td>0.978</td>
<td>0.892</td>
<td>0.711, 1.346</td>
</tr>
<tr>
<td>Healthy Dartmouth feelings reported</td>
<td>0.988</td>
<td>0.872</td>
<td>0.849, 1.149</td>
</tr>
<tr>
<td>Healthy Dartmouth QOL reported</td>
<td>0.802</td>
<td>0.151</td>
<td>0.593, 1.084</td>
</tr>
</tbody>
</table>

QOL: Quality of Life, CI: Confidence Interval. Analyses adjusted for age, sex, number of comorbidities, duration of CR, treatment and social deprivation. Data were clustered with CR centres using cluster robust standard errors.

Symptoms not present defined as score < eight on Hospital Anxiety Depression Scale

Dartmouth scale healthy score one to three

To conclude, employment status is an important factor to consider when tailoring care for individuals. For example, increased monitoring of mental health in unemployed participants may be advised or tailoring of care for those identified as unemployed with poor baseline HADS and Dartmouth QOL scores. For instance, the recent Scottish Intercollegiate Guidelines Network (SIGN) CR guideline recommends the provision of a relaxation course (SIGN, 2017). Future work should seek to determine what types of intervention tailoring would enable unemployed participants to derive the same benefits from CR.
Chapter 5 Conclusion of Research Chapters

The implementation and delivery of routine services often varies in practice. In the UK the NACR has reported on several inconsistencies, however the implications of such were unknown. The overarching aim of these works were to identify and better understand determinants of quality delivery and outcome and, where evident, promote positive service change for patient benefit. On this basis a programme of research was conducted which investigated how CR is currently utilised and what predicts initiation, how clinically effective current day CR is and what variations in service delivery (CR timing) and patient profile (employment status) mean in terms of patient outcome. The results of this work led to five publications and have informed the NACR_BACPR certification programme, which was implemented to drive service improvement.

From this body of work I will summarise three key topics, which have implications for future practice: Pre-CR assessment, the use of NACR dataset and observational methods. The first topic: pre-CR assessment, refers to the baseline evaluation of a patient before they commence CR. The information gathered offers the CR team a profile of attending participants and subsequently how the offered programme can be tailored to meet the needs of each patient. This approach fits with the recommended ‘menu-driven’ approach as advised in the BACPR guidelines (BACP_R, 2017). Pre-CR assessment can also be used as a benchmark for individual participants, which can be used to track progress and provides an opportunity to consider the patients’ health service experience prior to CR i.e. wait-time and what an individual’s profile may mean in terms of outcome i.e. employment status. Tailoring of CR to this level may offer additional improvements by factoring the dimensions of equity and equality, however further work would be required to understand to what extent tailored patient care could reduce risk of poor outcome in particular patient groups. For example, could those who experience a delay to commencing CR benefit from a longer CR programme? Overall the current work identified a number of small statistically significant effects, which are clinically relevant and support the use of pre-CR assessment as outlined.

To robustly evaluate the impact of pre-assessment a post-CR assessment must be conducted. Patient progress is severely undermined if data capture is incomplete and missing data, particularly at follow-up, is evident in the NACR dataset. The NACR receives data from approximately 74% of CR in the UK (NACR, 2017) but the completeness of the data from each site is variable. Missing data prevents complete tracking of all participants and/or the inability to adjust for particular variables in analysis. Overall this leads to reductions in the analysis sample size and can cause bias in the
sample being analysed. A main advantage of observational research approaches is that they reflect routine practice, but this can be hindered if data is missing. To that end the analyses conducted have consistently reported on the challenges of missing data within the NACR dataset. This has fed into both the BACPR guidelines (BACPR, 2017) and the NACR_BACPR certification programme, which promote completion of post-CR record in the NACR dataset.

Lastly, despite advances in statistical analysis techniques, which have greatly improved the rigour of observational findings by managing confounding i.e. adjusted regression analyses, propensity-based analyses, matching techniques (Kahlert, 2017), there is still a lag in effectively applying these techniques. Paper 2; a systematic review of observational CR effectiveness studies, identified many observational studies with limited or no adjustment for confounding despite the review date limiting to current literature (≥year 2000). Pre-publication of protocols, a best practice standard, has also been slow to adopt in observational work (Loder, 2010; Williams, 2010). Adoption of best practices is needed to provide rigorous evidence for policy makers, especially in cases where RCTs are not feasible.
Chapter 6 Conclusion of Thesis

CR is an evidence-based intervention which has been shown to reduce mortality, morbidity and improve HRQOL, however it is largely unknown what impact variation in service delivery and patient profile may have on outcome. The work presented forms a coherent body of research by first exploring the utilisation and effectiveness of routine CR using data from the NACR and a systematic review of observational studies. These studies (papers 1 and 2) essentially provide valuable context as to the current status of modern-day routine CR. With this baseline in place the work continues by exploring how the heterogenous nature of patients and service delivery impacts outcome along two key themes; CR timing and mental health. The work highlights the importance of using pre-CR assessment as a tool to tailor care and/or why variation of practice needs management, the common limitations of the conducted work and potential for future investigations. This body of work has achieved its aims by identifying factors associated with CR initiation and outcome and by informing the assessment criteria for the NACR_BACPR certification programme, thus impacting practice.

Chapter one outlined why observational methods were appropriate for this programme of research. In brief, the distinction between pragmatic trials and observational work is defined; the latter can be used for real world evaluation rather than evaluation of a ‘realistic simulation’ (Barnish and Turner, 2017). There are also instances where RCT’s, pragmatic or otherwise, are unethical or impractical. For example, the effectiveness of routine CR cannot be re-evaluated in RCT as it would be unethical to withhold recommended treatment from the control participants. Likewise, you could not delay a participant’s treatment to explore the impact this has if guidelines have established timely intervention is required. Notwithstanding RCTS as the gold standard for establishing efficacy, there was a need for the observational approach in these studies. The NACR is the most comprehensive UK dataset on real-life CR provision, use and patient outcome and was thus ideal for the purposes of these projects. The research presented also supports the joint aims of the British Heart Foundation funded NACR to improve care and prevent inequalities and inequities. Overall the work serves as an exemplar of the utility and strength of observational research; through analyses of registry data and meta-analysis of published observational data.

Regarding impact, in 2015 the NACR and BACPR launched the national CR certification programme. The programme’s aim is to evaluate CR performance according to criteria deemed key to successful high-quality CR and ultimately drive service quality. Raising awareness of data completion issues,
the benefit of pre-CR assessment and more specific criteria such as CR timing have been reported on in four of the five publications presented in this thesis. The body of work is timely, largely conducted between 2014-2016, and has fed into the reporting of service delivery as part of the NACR annual report and formed one of the criteria developed for the NACR_BACPR certification programme.

Completion of these research projects has also revealed a number of avenues for future research; the most substantial being the need for an observational investigation into the effectiveness of routine CR. Paper 2 identified no current UK studies of CR effectiveness in routine practice for AMI patients (i.e. registry data). Furthermore, the effectiveness of modern CR continues to be challenged to this date. A 2018 review of RCT evidence comparing exercise and non exercise-based CR, excluding historical trial evidence (<year 2000), found no effect on all-cause and cardiovascular mortality and a significant but clinically irrelevant effect on hospital re-admission (Powell, 2018). However, this review included exercise only CR formats, which are arguably non-representative of current CR practices i.e. multi-component. To truly address the question of routine CR effectiveness an investigation of routine patient data is required; to that end I am working with the NACR research group managing an application to link the NACR dataset to HES and ONS data. The aim is to explore mortality, re-admission and re-occurrence in patients attending CR or not. This dataset will also facilitate further investigations into what service or patient factors drive mortality, re-admission and re-occurrence outcomes. In addition, papers 1, 3 and 4 also support further investigations into the effects of service variation on patient outcome. CR duration or ‘dose’ is one specific area that requires attention.

To conclude, this thesis began by providing the theoretical justification for observational research approaches. The publications presented demonstrate the practical application and utility of using observational techniques to address important issues in CR care. The body of work highlights the importance of considering service and patient variation when delivering routine CR, re-emphasising the importance of pre-CR assessment. Furthermore, this work has fed into NACR annual reporting and a national initiative to drive service improvement; the NACR_BACPR certification programme.
Appendices

Appendix I: Candidate’s Publications
Paper 1: Predictors Of Cardiac Rehabilitation Utilization In England: Results From The National Audit
Predictors of Cardiac Rehabilitation Utilization in England: Results From the National Audit

Jennifer Sumner, MSc, BSc; Sherry L. Grace, PhD; Patrick Doherty, PhD

Background—Cardiac rehabilitation (CR) is grossly underused, with major inequities in access. However, use of CR and predictors of initiation in England where CR contracting is available is unknown. The aims were (1) to investigate CR utilization rates in England, and (2) to determine sociodemographic and clinical factors associated with CR initiation including social deprivation.

Methods and Results—Data from the National Audit of CR, between January 2012 and November 2015, were used. Utilization rates overall and by deprivation quintile were derived. Logistic regression was performed to identify predictors of initiation among enrollees, using the Huber-White sandwich estimator robust standard errors method to account for the nested nature of the data. Of the 234,736 (81.5%) patients referred to CR, 141,648 enrolled, 97,406 initiated CR, and of those initiating, 37.2% completed a program of ≥6 weeks duration. The significant characteristics associated with CR initiation were younger age (odds ratio [OR] 0.98, 95% CI 0.98–0.99), having a partner (OR 1.31, 95% CI 1.17–1.48), not being employed (OR 0.86, 95% CI 0.77–0.96), not having diabetes mellitus (OR 0.84, 95% CI 0.77–0.92), not having a myocardial infarction (OR 0.57, 95% CI 0.42–0.76), and having had coronary artery bypass graft surgery (OR 1.64, 95% CI 1.09–2.47).

Conclusions—CR enrollment does not meet English National Health Service targets; however it compares with that in other countries. Evidence-based approaches increasing CR enrollment and initiation should be applied, focusing on the identified characteristics associated with CR initiation, specifically older, single, employed individuals with diabetes mellitus and those not revascularized. (J Am Heart Assoc. 2016;5:e003903 doi: 10.1161/JAHA.116.003903)

Key Words: cardiac • cardiac rehabilitation • patient compliance • patient factors • uptake • utilization

Cardiac rehabilitation (CR) is an outpatient chronic disease management program designed to optimize secondary prevention and improve quality of life.1,2 Participation in CR is associated with reduced cardiovascular mortality and hospital readmission among other benefits.1,2 Accordingly, patients in the United Kingdom and several other countries have access to preventative CR programs. However, when viewed from a global perspective, CR is grossly underused. Recent meta-analyses showed that in the last decade ~43% of patients are referred,3 40% enroll,4 and those who initiate CR adhere to an average of 67% of prescribed sessions.4 Greater participation is associated with lower mortality in a dose-response fashion,5 and hence it is imperative that CR utilization be increased to optimize outcomes at the population level.

There has been considerable research undertaken, both qualitative and quantitative, to understand factors associated with insufficient patient utilization of CR. A meta-synthesis of qualitative studies suggested that patients’ knowledge of CR services, perceptions of cardiovascular disease, as well as financial and occupational constraints are key factors influencing their utilization.6 Data from several registries in the United States and Europe have quantified sociodemographic and clinical characteristics associated with utilization. For example, data from 780 patients in the American Heart Association Get with the Guidelines database showed that nonwhite patients were much less likely to enroll than their white counterparts.7 Data from 2096 myocardial infarction (MI) patients in the Prospective Registry Evaluating outcomes after MI showed that women, patients with hypertension or peripheral artery disease, and those without health insurance were less likely to participate 1 month postdischarge. Furthermore, older, nonwhite, smokers, and those of less economic means and educational attainment were significantly less likely to participate 6 months post discharge. Patients who had a
percutaneous coronary intervention (PCI) were less likely to participate at either time-point. In Europe, data from the EUROASPIRE III survey of 13,935 patients showed older, female patients who did not have coronary artery bypass graft (CABG) surgery and those who smoked were less likely to attend. Consistent with the above findings regarding the centrality of financial/socioeconomic factors, numerous studies have also demonstrated social deprivations (e.g., income, employment, and education) as a key factor associated with both low CR utilization and higher mortality.

To date, research on the determinants of CR initiation in English cohorts has been limited, and stems only from small non-representative samples. A more thorough investigation is required to identify country-specific influencing factors that could inform targeted interventions to increase CR utilization. Accordingly, the aims of this study were to (1) investigate CR utilization rates in England, and (2) determine sociodemographic and clinical characteristics associated with CR initiation including social deprivation.

Methods
This study is reported following the guidelines: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Design and Data Source
The National Audit of CR (NACR), funded by the British Heart Foundation, is a web-based registry of CR in England, Wales, and Ireland. Information on service delivery, utilization, as well as patient characteristics and outcomes is collected. Data are entered onto NACR by practitioners involved in CR delivery, according to a data dictionary (http://www.cardiacrehabilitation.org.uk/nacr/downloads.html). Data on patients eligible for CR and those referred are entered onto NACR. Participation in NACR is high: in 2015 a total of 204/308 (66.2%) programs provided data to the NACR, in England alone 164 programs. Data were extracted retrospectively for this observational study.

At centers involved in NACR, CR-indicated patients are typically approached by the CR team. Referral to a CR program is generally completed while patients are still in the hospital or shortly after discharge by phone for day case PCI patients. For agreeing patients, a pre-CR assessment takes place, during which sociodemographic and clinical characteristics are recorded as well as attendance and outcome following CR. Across the United Kingdom, CR is delivered in accordance with the British Association of Cardiovascular Prevention and Rehabilitation's standards. This includes both center and home-based self-management approaches such as the Heart Manual. Patients in the center-based programs are typically offered 16 sessions over 8 weeks at a minimum.

Ethics
The NACR, through the Health and Social Care Information Centre, has approval from the Health Research Authority's Confidentiality Advisory Group (under Section 251 of the NHS Act 2006) to collect patient-identifiable data without explicit consent from individual patients for the purposes of audit and research. Approval is reviewed annually. Separate ethical approval was therefore not required as part of this project.

Measures
CR utilization was operationalized as referral, enrollment, initiation, and completion. CR referral was defined as completion of a written/fax or electronic/systematic referral form with receipt at the CR program. CR enrollment was defined as attendance at the pre-CR assessment. The dependent variable of CR initiation was defined as commencement of CR following the pre-CR assessment (i.e., initiate the exercise program, for at least 1 session). Patients were defined as CR-initiators and non-initiators accordingly. Finally, CR completion was defined as receiving CR for ≥8 weeks, as per UK minimum standards. This was confirmed where participants had a program end date and/or post-CR assessment entered at least 8 weeks from program initiation.

Sociodemographic characteristics assessed were age (years), sex (male/female), marital status (partnered/single), work status (employed/unemployed/retired), and ethnic background (White-British, Asian, Other). Clinical characteristics included main referral indications: post-MI (with medication management only), elective PCI, MI with PCI and CABG, prior cardiac history/event (yes/no), comorbidities including diabetes mellitus, risk factors (hypertension, physical inactivity, obesity as assessed via body mass index), as well as anxiety and depression symptoms. The latter were assessed on the Hospital Anxiety and Depression Scale (HADS), a reliable and well-validated scale, with higher scores representing worse symptoms. Wait times were also calculated based on date of initiating event, referral date, enrollment date, and CR start date.

Finally, to investigate the impact of social deprivation on CR utilization, data from the 2015 English Indices of Deprivation, specifically the Index of Multiple Deprivation (IMD) reported at the Clinical Commissioning Group (CCG) level, were linked to NACR. Individual patients were assigned an IMD score according to the CCG in which their general
practitioner was located. CCGs are clinically led bodies responsible for the planning and commissioning of healthcare services for their local area.

The IMD scores are based on 8 distinct domains of deprivation: income, employment, education, skills and training, health and disability, crime, barriers to housing and services, and living environment. These are combined, using appropriate weights, to calculate the IMD.22 For this study, IMD score was grouped into 5 equal-sized groups according to score. Quintile 1 represents most-deprived patients and quintile 5 represents least-deprived patients. In some instances, individual patient general practitioner postal code was unavailable; thus CCG-IMD could not be assigned.

Participants
To test the first objective, all adult (≥18 years) cardiac patients in England entered onto the NACR between January 1, 2012 to November 5, 2015 were included. The main referral indications MI, MI with PCI, PCI, and CABG are presented separately; other indications such as heart failure were grouped in an “other” category. There were no exclusion criteria. For the second objective examining variables associated with CR initiation, only patients who attended the pre-CR (enrolled) assessment were included, so data collected on their sociodemographic and clinical characteristics at that time were available. Data were restricted to those that had an IMD social deprivation score as well.

Statistical Analysis
All analyses were conducted using STATA version 13.1. Descriptive statistics were used to describe CR utilization, and compare characteristics of CR initiators and noninitiators. Differences in these characteristics were then compared by initiation status using t tests, χ², or Wilcoxon rank-sum tests as appropriate. For continuous variables, standardized differences were also calculated to determine the meaningfulness of group differences irrespective of sample size. Differences greater than 0.1 were considered meaningful.23

A multivariate logistic regression was computed to assess factors associated with CR initiation. Variables were chosen for the multivariate analysis based on existing evidence indicating an association with initiation.6–12 Independent variables were age, sex, ethnicity, marital status, IMD quintile, employment status, comorbidity count, prior cardiac event, diagnosis of diabetes mellitus, anxiety and depressive symptoms, risk factors, and referral indication. To take account of the nested nature of the data (ie, patients treated within CR centers), the Huber-White-sandwich estimator robust standard errors method was used.

Results
Cohort Characteristics
As shown in Figure 1, the English NACR cohort comprised almost 300,000 patients during the period of study. A total of 98,880 referred English patients completed a pre-CR assessment in the period of study (ie, enrolled) and had available deprivation data. Their characteristics are presented in Table 1. As shown, patients were primarily British, partnered, retired, males, had a comorbid condition, and were physically inactive. Other ethnic cultural backgrounds were primarily black, Chinese, and those identifying as bi- and multiracial. Other CR referral indications were heart failure, valve surgery, implantable cardioverter-defibrillator, and pacemakers. The most common cardiac history included MI, angina, and PCI.

CR Utilization
With regard to objective 1, CR utilization rates are shown in Figure 1. Over 80% of the cohort was referred to CR, 49.1% enrolled (attended pre-CR assessment), and 33.8% initiated CR. Of those who initiated CR, 37.2% completed a program of at least 8 weeks duration. The mean program duration was

![Figure 1. Patient flow in NACR and cardiac rehabilitation utilization. NACR indicates National Audit of Cardiac Rehabilitation.](image-url)
### Table 1. Sociodemographic and Clinical Characteristics of CR Initiators and Noninitiators

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall N=98,880</th>
<th>CR Initiators n=55,953 (56.6%)</th>
<th>Noninitiators n=42,927 (43.4%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>65.79 (12.36)</td>
<td>64.53 (11.69)</td>
<td>67.43 (12.99)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, n males</td>
<td>69,516 (72.0%)</td>
<td>40,510 (74.1%)</td>
<td>29,006 (69.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity, n British</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, British</td>
<td>69,059 (90.4%)</td>
<td>29,325 (91%)</td>
<td>39,779 (90%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5,231 (6.8%)</td>
<td>2,082 (6%)</td>
<td>3,149 (7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2,066 (2.7%)</td>
<td>808 (3%)</td>
<td>1,258 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marital status, n partnered</td>
<td>55,282 (74.7%)</td>
<td>32,908 (77.5%)</td>
<td>22,374 (70.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employment status, n</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unemployed</td>
<td>98,877 (15.9%)</td>
<td>64,000 (16.4%)</td>
<td>34,877 (15.1%)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>16,991 (27.4%)</td>
<td>11,405 (23.3%)</td>
<td>5,586 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>35,022 (56.5%)</td>
<td>21,114 (54.2%)</td>
<td>13,908 (60.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>English indices of deprivation quintile</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>14,269 (14.4%)</td>
<td>7,749 (13.8%)</td>
<td>6,520 (15.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18,431 (18.6%)</td>
<td>9,190 (16.4%)</td>
<td>9,241 (21.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16,048 (16.2%)</td>
<td>8,562 (15.3%)</td>
<td>7,486 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25,070 (25.3%)</td>
<td>15,519 (27.7%)</td>
<td>9,551 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>25,062 (25.3%)</td>
<td>14,933 (26.6%)</td>
<td>10,129 (23.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-MI</td>
<td>16,910 (17.2%)</td>
<td>6,985 (12.5%)</td>
<td>9,925 (23.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI-PCI</td>
<td>30,552 (31.1%)</td>
<td>18,386 (33.0%)</td>
<td>12,166 (28.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>17,783 (18.1%)</td>
<td>10,061 (18.1%)</td>
<td>7,722 (18.1%)</td>
<td>0.024</td>
</tr>
<tr>
<td>CABG</td>
<td>15,110 (15.4%)</td>
<td>10,290 (18.5%)</td>
<td>4,820 (11.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>17,758 (18.2%)</td>
<td>9,859 (17.9%)</td>
<td>7,897 (17.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary present (≤1)</td>
<td>65,560 (66.3%)</td>
<td>39,583 (68.9%)</td>
<td>26,977 (62.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic</td>
<td>15,925 (16.1%)</td>
<td>8,876 (15.8%)</td>
<td>7,049 (16.4%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Prior cardiac event or procedure</td>
<td>32,896 (33.2%)</td>
<td>19,518 (34.8%)</td>
<td>13,378 (31.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>10,004 (21.3%)</td>
<td>4,989 (17.2%)</td>
<td>5,015 (27.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physically inactive (&lt;150 minutes per week)</td>
<td>60,346 (77.8%)</td>
<td>33,733 (73.7%)</td>
<td>26,573 (83.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td>18,147 (29.6%)</td>
<td>11,814 (29.2%)</td>
<td>6,333 (30.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertensive (BP &gt;140/90 mm Hg)</td>
<td>21,934 (32.1%)</td>
<td>13,763 (32.2%)</td>
<td>8,171 (32.0%)</td>
<td>0.617</td>
</tr>
<tr>
<td>Mean Anxiety Score (SD)</td>
<td>5.73 (4.24)</td>
<td>5.78 (4.19)</td>
<td>5.61 (4.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Depression Score (SD)</td>
<td>4.61 (3.77)</td>
<td>4.60 (3.73)</td>
<td>4.62 (3.85)</td>
<td>0.286</td>
</tr>
<tr>
<td>Median time between initiating event and referral to CR, days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Median time between initiating event to prehab assessment, days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>25</td>
<td>33</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Median time between referral and CR start, days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>—</td>
<td>43</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Percentages were calculated using the denominator corresponding to the number of patients for whom the characteristic was reported. BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CR, cardiac rehabilitation; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

*Standardized difference >0.1.

<sup>1</sup>Capped at 365 days.
Figure 2. Proportion of patients (%) enrolled and completing CR by IMD quintile. CR indicates cardiac rehabilitation; IMD, Index of Multiple Deprivation. *Enrollment and completion compared in least (IMD quintile 1) vs most (IMD quintile 9) deprived group using χ². For both tests, P<0.001.

9.2 weeks or 65 days (SD 37.4; median=56 days). Wait times are shown in Table 1. Figures did not differ significantly between those with or without deprivation data (data not shown).

As shown in Figure 2, there was a gradient in CR utilization based on degree of social deprivation. For each, those with lesser deprivation utilized CR to a greater degree (P<0.001).

CR Initiators Versus Noninitiators

As shown in Table 1, 55,953 (56.6%) patients initiated CR following the pre-CR assessment. A number of significant differences in participant characteristics were observed between CR initiators and noninitiators at a bivariate level. With regard to sociodemographic characteristics, noninitiators were significantly older, more often female, non-British, single, retired, and at increased socioeconomic deprivation than CR initiators. With regard to clinical characteristics, noninitiators were more likely to have a referral indication of MI but less likely to have an indication of MI with PCI and CABG. Moreover, noninitiators had fewer comorbidities, less often had a prior cardiac event, were more physically inactive, and were more likely to be smokers than CR initiators. No meaningful differences in hypertension, anxiety or depressive symptoms, or wait times were observed. The association of age with CR initiation was particularly robust; for no other continuous variables was the standardized difference >0.1.

Predictors of CR Initiation

Table 2 presents the findings from multivariate analysis. Smoking was not included in the model due to a high degree of missing data. The significant sociodemographic characteristics associated with initiation were the following: younger age, having a partner, and unemployment. The significant clinical characteristics associated with initiation were the

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.38</td>
<td>0.98 to 0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex: female</td>
<td>0.96</td>
<td>0.89 to 1.03</td>
<td>0.294</td>
</tr>
<tr>
<td>Ethnicity (white, British as reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1.36</td>
<td>0.91 to 2.05</td>
<td>0.127</td>
</tr>
<tr>
<td>Other ethnic groups</td>
<td>1.69</td>
<td>0.95 to 2.99</td>
<td>0.070</td>
</tr>
<tr>
<td>Marital status: Partnered</td>
<td>1.31</td>
<td>1.17 to 1.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Predictors of CR Initiation From Multivariate Regression

IMD (group 3 reference)

| Quintile group 1 | 1.07 | 0.40 to 2.81 | 0.886 |
| Quintile group 2 | 0.74 | 0.40 to 1.34 | 0.323 |
| Quintile group 4 | 1.61 | 0.98 to 2.62 | 0.050 |
| Quintile group 5 | 1.21 | 0.61 to 2.41 | 0.574 |

Employment status (retired as reference)

| Employed     | 0.86 | 0.77 to 0.96 | 0.011 |
| Unemployed   | 0.95 | 0.88 to 1.13 | 0.627 |
| ≥1 Comorbidity | 1.07 | 0.72 to 1.60 | 0.716 |
| Prior cardiac event | 0.87 | 0.73 to 1.04 | 0.147 |
| Diabetic      | 0.84 | 0.77 to 0.92 | <0.001 |
| Anxiety score | 1.02 | 1.003 to 1.04 | 0.017 |
| Depression score | 0.98 | 0.96 to 1.04 | 0.141 |
| Physical inactivity | 1.14 | 0.86 to 1.52 | 0.328 |
| BMI           | 0.99 | 0.98 to 1.005 | 0.320 |
| Blood pressure | 0.98 | 0.82 to 1.16 | 0.381 |

Referral indication (other as reference)

| Post-MI       | 0.57 | 0.42 to 0.76 | <0.001 |
| MI-PCI        | 0.91 | 0.71 to 1.15 | 0.434 |
| PCI           | 0.85 | 0.69 to 1.04 | 0.133 |
| CABG surgery  | 1.64 | 1.02 to 2.47 | 0.017 |

BMI indicates body mass index; CABG, coronary artery bypass graft; CR, cardiac rehabilitation; IMD, Index of Multiple Deprivation; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

Discussion

To our knowledge, this is the largest cohort of patients in which CR utilization and predictors of CR initiation have been described. Generally CR was found to be underutilized. Factors associated with failure to initiate CR were generally consistent with what has been observed in other countries, namely, increasing age, nonpartnered status, less invasive treatment type, and the presence of comorbid diseases following: not having diabetes mellitus, greater anxiety, not having a referral indication of MI without revascularization, and CABG surgery.
mellitus; hence efforts should focus on enrolling these patient groups.

The average CR enrollment rates globally are 40%4; comparatively enrollment (defined as attendance at pre-CR assessment) was found to be 50% in this study, with 34% of the cohort starting a CR program. While these rates are comparable, this is, however, still far from the target of 65% enrollment set by the National Health Service England18 and other clinical associations.29-33 The level of completion in those who initiate CR is also worryingly low at 37.2%, and more work is needed to understand the reasons for this.

In terms of predictors of CR initiation, sociodemographic factors were partially consistent with work from other cohorts, although some differences were observed. Older age is consistently reported as a determinant of nonutilization,24-27,33 a finding reflected in this study. This is often attributed to lower referral rates among older patients, despite the fact that older patients have been shown to benefit from CR.34 Similarly, being in a relationship is often associated with increased enrollment,35 likely due to social support. Moreover, sex was not found to be significantly associated with initiation, although evidence from a recent systematic review showed enrollment may be predicted by sex.6

Interestingly, the multidimensional index of social deprivation was not a significant predictor of CR initiation in the multivariate model; however, employment alone was. This suggests that particular aspects of socioeconomic deprivation are pertinent to CR use.6 This work status is evidently complex, with some studies reporting that employed patients are more likely to attend,26 which is likely a function of their higher socioeconomic status; others have shown that work may compete with the time needed for CR session participation and may lead to dropout.6,14

Finally, other studies suggest that retired patients are more likely to attend (which is likely a function of time availability).

In relation to the clinical factors associated with noninitiation, some were consistent with existing evidence.24,27,35,36 For example, data from 6974 referred cardiac patients in the Wisconsin CR Outcomes Registry showed that patients who had undergone CABG surgery were significantly more likely to enroll than patients who had not.24 It is likely that patients with more intensive/invasive acute cardiac intervention perceive greater mortality risk, and hence subsequent motivation to reduce this risk via CR participation. Moreover, presence of diabetes mellitus has consistently been associated with lower rates of enrollment.34,32 Patients with diabetes mellitus likely have lower self-efficacy in managing their diseases, due to their long history of being unable to tackle the lifestyle risk factors that cause cardiovascular disease. In relation to mental health, depressive symptoms were not associated with CR initiation but a small effect was observed for symptoms of anxiety in this cohort. This could be due to the greater burden of anxiety observed in the cohort than depression.

Health Service Implications

Interventions to improve utilization have been recently reviewed.37 Successful strategies to increase enrollment included structured nurse- or therapist-led contacts, early CR assessment appointments after hospital discharge, and motivational letters. These approaches should in particular be targeted to older, unpartnered patients who are working, have comorbid diabetes mellitus, and do not have CABG as a referral indication. Successful strategies to increase participation were self-monitoring, action planning, and tailored counseling.

Limitations

This large, multicenter investigation retrospectively accessed routinely collected patient data from an established national audit of CR services. However, some caution is warranted in interpreting the findings. First, although CR programs are encouraged to provide complete patients records, it was expected that a proportion of patient data would be missing. As such, smoking status could not be considered in the multivariate analysis. Second, because not all indicated inpatients are approached and entered into NACR, the rate of referred patients reported herein is likely inflated. Thus, referral rates should be interpreted with caution. Yet even in this select group, the problem of low enrollment, participation, and completion persists.

Conclusions

Although the enrollment rate of ~50% observed in England is below the recommended 65% benchmark, comparatively England has utilization rates consistent with what is observed in other countries. Factors associated with CR initiation should be considered as flags for CR practitioners as part of patient identification processes and during pre-CR assessment. Evidence-based interventions to increase utilization in these patients need to be broadly applied, so that the beneficial impact of CR in reducing cardiovascular mortality and morbidity can be optimized across the country. It was also evident that work is needed to improve the proportion of enrolling patients completing the recommended duration of CR, which was low at 37.2%.

Acknowledgments

Thanks to Emeritus Professor Bob Lewin who founded the National Audit of Cardiac Rehabilitation (NACR).
Sources of Funding

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Disclosures

None.

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13. Melville MF, Pockham G, Brown N, Weston G, Gray D. Cardiac rehabilitation: socially deprived patients are less likely to attend but patients ineligible for thrombolysis are less likely to be invited. Heart. 1999;82:373-377.

The candidate conceived the idea for the paper, conducted the analyses and prepared the first draft and subsequent revisions. The candidate jointly developed the study methodology and critical revisions to the paper following reviewer comments.

Jennifer Sumner
Sherry L Grace
Patrick Doherty
Paper 2: The Effectiveness Of Modern Cardiac Rehabilitation: A Systematic Review Of Recent Observational Studies In Non-Attenders Versus Attenders
RESEARCH ARTICLE

The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders

Jennifer Sumner*, Alexander Harrison, Patrick Doherty
University of York, Department of Health Sciences, York, United Kingdom

* Jenny.sumner@york.ac.uk

Abstract

Background
The beneficial effects of cardiac rehabilitation (CR) have been challenged in recent years and there is now a need to investigate whether current CR programmes, delivered in the context of modern cardiology, still benefit patients.

Methods
A systematic review of non-randomised controlled studies was conducted. Electronic searches of Medline, Embase, CINAHL, science citation index (web of science), CIRRIE and Open Grey were undertaken. Non-randomised studies investigating the effects of CR were included when recruitment occurred from the year 2000 onwards in accordance with significant CR guidance changes from the late 1990’s. Adult patients diagnosed with acute myocardial infarction (AMI) were included. Non-English articles were considered. Two reviewers independently screened articles according to pre-defined selection criteria as reported in the PROSPERO database (CRD42015024021).

Results
Out of 2,656 articles, 8 studies involving 9,836 AMI patients were included. Studies were conducted in 6 countries. CR was found to reduce the risk of all-cause and cardiac-related mortality and improve Health-Related Quality of Life (HRQOL) significantly in at least one domain. The benefits of CR in terms of recurrent MI were inconsistent and no significant effects were found regarding re-vascularisation or re-hospitalisation following AMI.

Conclusion
Recent observational evidence draws different conclusions to the most current reviews of trial data with respect to total mortality and re-hospitalisation, questioning the representativeness of historic data in the modern cardiological era. Future work should seek to clarify
which patient and service level factors determine the likelihood of achieving improved all-cause and cardiac mortality and reduced hospital re-admissions.

Introduction

Coronary heart disease (CHD) is a huge global problem accounting for the leading cause of death worldwide [1]. Acute myocardial infarction (AMI) is the most common cause of death from CHD and is associated with 188,000 hospital episodes each year in the United Kingdom (UK) alone, representing a major cause of death and ill health [2]. Recognising this burden and the need to rehabilitate patients National, European and International guidelines recommend the provision of cardiac rehabilitation (CR) services [3–6]. In brief, CR is a multi-component intervention generally comprising of structured exercise training, psychological support and education to promote positive lifestyle changes. Improvements in risk factors, mortality, morbidity and Health-Related Quality of Life (HRQoL) have all been associated with CR attendance [4,7–9].

Despite the many documented advantages associated with CR, utilisation is highly variable and relatively low [10–12]. Across Europe an estimated 2 million eligible patients per year access CR but less than 40% uptake CR [13]. Comparatively in 2016 the National Audit of Cardiac Rehabilitation (NACR) for England, Wales and Northern Ireland reported an overall uptake to CR of 50%, placing the UK in the top 2% of countries for uptake in Europe, but there are still improvements to be made [11].

In recent years research has focused on innovations to improve referral and uptake [14]. However, the benefits of CR, as delivered in the context of the present day, have been challenged. The largest pragmatic Randomised Controlled Trial (RCT) of modern day CR in the UK; the RAMIT trial, found no significant beneficial effects on mortality, cardiac or psychological morbidity, risk factors, HRQoL or activity level from CR [15]. Although methodological issues in this trial led to questions around the validity of the study findings [16], an important question around CR efficacy was raised. Since the RAMIT RCT the most recent 2016 Cochrane review on CR effectiveness identified no current RCTs which have been conducted with sufficient sample sizes to investigate efficacy [9]. Given the practical and ethical challenges, as CR is standard care, it seems improbable any such trial could occur. But the question remains with improvements in patient treatment, increasingly diverse programme components and changes to the profile of patients receiving CR today versus historic counterparts does modern day CR still benefit patients [17–20]. In an effort to overcome the aforementioned challenges, extend the external validity of trials and determine the benefit of current day CR in routine practice a recently published systematic review of RCTs and non-randomised studies investigated efficacy in the post–statin era in a mixed CR population [21]. The primary outcome; total mortality following CR, was confirmed although the secondary outcomes of cardiac mortality and re-hospitalisation were not evident contrary to the most recent Cochrane review of RCT evidence [9, 21]. Conversely another RCT review of CR in post-MI patients concluded a reduction in both all-cause and cardiac mortality as well as re-hospitalisation [22].

To further understanding of the effects of modern day CR in routine practice this systematic review will investigate a more specific homogenous CR population (AMI patients) and extend the outcomes considered by the CROS review. Specifically, recent observational studies investigating the effect of CR versus no rehab in AMI patients alone (with or without
revascularisation) considering HRQOL outcomes in addition to mortality, hospital re-admission, re-occurrence of AMI and re-vascularisation. CR programme format and the intervention components used will also be reviewed.

Methods

The study is reported and conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [23] and Guidelines for the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) [24]. The systematic review protocol was prospectively registered on the PROSPERO database of systematic reviews (registration number: CRD42015024021). A copy of the PRISMA checklist is included in the supplements (S1 Table).

Literature search

Medline, Embase, CINAHL, science citation index (web of science), CIRRIE and Open Grey were electronically searched for relevant articles. Combinations of medical subject headings and keywords around the following themes were used: cardiac population descriptors, CR intervention, CR use, patient outcomes. The search strategy was developed in conjunction with a trained information specialist and conducted in June 2015. An updated search was run in November 2016 to identify any further articles published since the initial search. The reference lists of included studies were also hand searched for further relevant studies. A copy of the Medline search strategy is included in the supplements (S2 Table).

Study selection

Titles and abstracts of identified citations were screened for inclusion by a single reviewer. Potentially eligible articles were then full text screened independently by two reviewers according to the inclusion criteria. Disagreements regarding eligibility were discussed and resolved by a third reviewer. In instances of unclear reporting authors were contacted to provide further information and clarity. The eligibility criteria are described as follows:

Participants: Male or female adults diagnosed with AMI; either ST-elevated (STEMI) or non-ST-elevated (nSTEMI) were included. Both medically managed (i.e. drug therapies) or revascularised (Coronary Artery Bypass Graft Surgery, or Percutaneous Coronary Intervention) AMI patients were included. The AMI population was chosen as the predominant cause of CHD related death and to minimise heterogeneity in the analyses population i.e. by factoring the impact of different care pathways.

Intervention: CR delivered as a structured, multi-component programme which included exercise and/or structured physical activity in addition to at least one of the following: information provision, education, health behaviour change, psychological support or intervention and social support. CR programmes using a mixture of supervised or unsupervised approaches conducted in any setting (inpatient, outpatient, community, home based) were included.

Control: Patients, as defined previously, who did not participate in CR. It was anticipated that patients in the control group were only medically supervised, usually by a general practitioner or equivalent, but may have also attended unstructured prevention programmes.

Study type: Observational studies (prospective or retrospective cohort, case-control data from routine practice) comparing CR attenders to non-attenders were included.

Primary outcome: All cause- and cardiac-related mortality. Secondary outcomes included all cause and cardiac-related hospital re-admission, re-occurrence of AMI, re-vascularisation and HRQOL.
Other criteria: As a review of CR practice in the current day the search strategy and population inclusion was date limited. In 2000 the National Service Framework for coronary heart disease was published in the UK, detailing modern standards of care, including CR services [25]. The American Heart Association published position statements on CR programmes and CR core components in 1994 [26] and 2000 [27], a position paper by the European Society of Cardiology in 2003 provided recommendations on the design and development of CR programmes [28] and in 2001 Cochrane published the first review to define exercise based CR [29]. In line with the establishment of international modern standards of care in CR the search strategy was restricted to publications from 2000 to present day. The populations within identified studies were then screened according to their recruitment date and excluded if pre-2000. Foreign language papers were included and translated where possible.

Data extraction

Data extraction was undertaken by one reviewer and independently checked for quality and accuracy by a second reviewer. Data items including study and population characteristics, intervention details, outcome measures and methods used to adjust for confounding were extracted. For each CR programme the components which formed the programme were identified and coded i.e. education, dietary advice etc. Adjusted effect outcomes were extracted for analyses where available. Data was extracted closest to one year follow-up. In instances where multiple adjusted outcome estimates were provided the following rules were used to decide which adjusted estimate was used in the meta-analyses: the estimate which adjusts for the maximum number of covariates, the estimate which is identified as the primary adjusted model, the estimate which includes the largest number of confounders considered important from the outset.

When multiple publications were identified for one study the primary study publication was extracted and the additional publications were searched for additional information. The extraction sheet was piloted on a sample of papers and refinements made prior to full data extraction.

Quality assessment

Individual observational studies were assessed for quality according to the checklist developed by Wells and colleagues [30]. In brief the checklist assesses study design, confounding, selective reporting and directness. The checklist was adapted for the purposes of this study. The quality assessment questions included were as follows: 1) Was there a relevant comparison group? 2) How were the groups formed? 3) Were the comparability of groups assessed by potential confounders? 4) Did the researchers describe how potential confounding domains were decided? 5) Did the researchers consider the following potential confounders: age, gender, ethnicity, SES, region, previous event, comorbidities? 6) Did the researchers control for confounding through matching at the enrolment stage or in the analysis (adjustment)? 7) Is there evidence that specified confounders did not cause confounding? 8) Did the analysis control for confounding with adequate care? 9) Is there evidence that the study cohort was selected from a larger cohort for which data was available? 10) Is there evidence of multiple adjusted analyses conducted but only one reported? 11) Were subgroups defined in unusual ways and statistically significant results reported? 12) Is there evidence of multiple methods being used for missing data and only one approach selectively chosen and reported? 13) Is there evidence of outcomes being converted to categorical data with unusual cut off points? Observational studies are more prone to bias than RCTs and as such it was critical that an exploration of planned adjustment for confounders was conducted [31]. Variables which studies may have
considered include: age, gender, ethnicity, socioeconomic status, region, previous cardiac event and presence of comorbidities [32–34].

Data synthesis
In order to pool data where the same outcome is reported in different formats a generic inverse variance method was used to generate an overall effect estimate for each outcome. A random effects model was used to account for study heterogeneity. Effect outcomes were reported as odds ratios (OR) with 95% confidence intervals (CI). Where meta-analysis was not possible a narrative synthesis was generated. Adjusted and unadjusted effect outcomes were presented in separate sub groups to account for the differing level of bias in each. It is well known that heterogeneity is often higher in systematic reviews of non-randomised studies [31]. Heterogeneity was evaluated through visual examination of the forest plots and the I² statistic. 'Low' heterogeneity was set at ≤25%, 'moderate' 50% and 'high' 75% [35].

Results
A total of 3,733 articles were identified from the initial search strategy, reducing to 2,382 after duplicates and date restrictions were applied. A further 13 articles were identified from author contacts and 261 articles from an updated literature run in November 2016. Full text screening was conducted on 196 articles, according to the eligibility criteria, which resulted in 8 included studies testing 10 CR interventions (Fig 1).

Quality assessment
Results of the quality assessment are presented in Fig 2. No study protocols were identified for the included studies, as such all questions relating to pre-publication of a protocol could not be considered and were removed. Most studies did not consider confounders i.e. analyses conducted without adjustment for socio-demographic background. However, for the majority of papers unusual cut-offs or subgroups and selective reporting of analyses or findings were not evident. All studies used appropriate comparison groups either formed through patient choice or physician decision. One study used a historic control which may have introduced bias [36].

Study characteristics
Characteristics of the included studies are presented in Table 1. The included studies comprised a total sample of 9,386 AMI patients typically followed up over 1 year. Patients were predominantly male in all studies and the age ranged from 49.9–70.0 years. Studies were conducted in a number of countries; Germany (n = 2), Spain (n = 2), United States of America (USA) (n = 1), Canada (n = 1), Korea (n = 1) and Denmark (n = 1). In terms of the CR intervention programmes most frequently paired exercise with an education component (n = 5) and typically included ≥3 intervention components (n = 8). European based studies tended to include a greater number of components in their CR programmes compared to the American and Canadian counterparts. Most used a health centre or clinic to deliver their interventions (n = 9) and included a group based approach (n = 7). Half of the interventions reported the involvement of a multi-disciplinary team the remaining studies did not report sufficiently to ascertain this point, although all programmes were described as multi-component.

Outcomes
All-cause mortality (Fig 3). Four studies assessed the impact of multi-component CR on all-cause mortality, two of which provided an adjusted outcome effect which could be
synthesised. CR was related to a decreased risk of death from AMI; unadjusted OR 0.25 (95% CI 0.16,0.40) $I^2 = 66\%$ and adjusted OR 0.47 (95% CI 0.38,0.59) $I^2 = 0\%$. One further study, which could not be synthesised with the adjusted ORs, reported an adjusted hazard ratio 0.08 (95% CI 0.01, 0.63) favouring CR [37].

**Cardiac-related mortality** (Fig 4). Two studies assessed the impact of multi-component CR on cardiac-related mortality, one of which provided an adjusted outcome effect. CR was related to a decreased risk of cardiac-related death from AMI; unadjusted OR 0.21 (95% CI 0.12, 0.37) $I^2 = 0\%$ and adjusted OR 0.43 (95% CI 0.23, 0.79).

**Hospital re-admission.** Data could not be pooled from the two identified studies assessing the impact of multi-component CR on re-admission due to method of finding reporting.
One study reported an adjusted effect, finding no significant effect from CR 0.96 (95% CI 0.81, 1.15).

Re-occurrence of MI (Fig. 5). Three studies assessed the impact of multi-component CR on recurrent MI, one of which provided an adjusted outcome effect. CR was related to a decreased risk of recurrent MI in unadjusted analysis only; OR 0.31 (95% CI 0.13, 0.74) $I^2 = 61\%$. Adjusted analysis found no significant effect OR 0.72 (95% CI 0.43, 1.21).

Re-vascularisation (Fig. 6). Two studies assessed the impact of multi-component CR on re-vascularisation following AMI, one of which provided an adjusted outcome effect. CR was not significantly related to a reduction in re-vascularisation in either unadjusted or adjusted effect measures; OR 1.07 (95% CI 0.86, 1.38) $I^2 = 0\%$ and OR 1.00 (95% CI 0.78, 1.28) respectively.

HRQOL. Data could not be pooled from the two identified studies reporting HRQOL outcomes due to the heterogeneity of the outcome measures [38, 39]. Both studies reported significant improvements in quality of life in at least one domain at 6 months [38] and 1 year [39]. Neither study adjusted for confounding.

Discussion

This study aimed to investigate routine CR in the context of modern cardiological practices. In addition it looked to extend the findings from the CROS review of observational CR data by exploring a homogenous patient sample (AMI only) and including HRQOL outcomes. A total of eight studies including 9836 AMI patients were eligible and were included in the analyses. Overall programmes reduced the risk of mortality, improved HRQOL but had no effect on re-vascularisation or re-hospitalisation. In an era where the existing RCT evidence base is aged, non-representative and the ethical challenges of conducting a new effectiveness trial when standard care is established as CR, this study has provided an important perspective on current day CR effectiveness in routine practice.
Table 1. Study characteristics.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Intervention Group N, Mean age (SD), Gender (% male)</th>
<th>Control Group N, Mean age (SD), Gender (% male)</th>
<th>Follow-up period</th>
<th>Inpatient/Outpatient &amp; Setting</th>
<th>Individual or group approach</th>
<th>Multi-disciplinary team involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldana S 03 &amp; O6, Ornish CR programme [38, 40]</td>
<td>USA</td>
<td>N = 28, 56.6 years (SD 9.4), 85% male</td>
<td>N = 28, 58.7 years (SD 12.5), 89% male</td>
<td>3 &amp; 6 months</td>
<td>Unclear, Healthcare centre</td>
<td>Both</td>
<td>Yes</td>
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<tr>
<td>Traditional CR</td>
<td>USA</td>
<td>N = 28, 59.9 years (SD 11.9), 71% male</td>
<td>As above</td>
<td>As above</td>
<td>Unclear, Healthcare centre</td>
<td>Both</td>
<td>Yes</td>
</tr>
<tr>
<td>Boulay P 04a, Short-term CR [46]</td>
<td>Canada</td>
<td>N = 37, 53.8 years (SD 9.9), 86.5% males</td>
<td>N = 54, 6.5 years (SD 9.7), 77.8% males</td>
<td>12 months</td>
<td>Inpatient &amp; Outpatient, Healthcare centre &amp; University clinic</td>
<td>Both</td>
<td>Unclear</td>
</tr>
<tr>
<td>Boulay P 04b, Long-term CR</td>
<td>Canada</td>
<td>N = 37, 54.3 years (SD 10.3), 78.4% males</td>
<td>As above</td>
<td>As above</td>
<td>Inpatient &amp; Outpatient, Healthcare centre &amp; University clinic</td>
<td>Both</td>
<td>Unclear</td>
</tr>
<tr>
<td>Caliani S 04 [39]</td>
<td>Spain</td>
<td>N = 113, 49.9 years (SD 8.4), Gender across groups 10 women</td>
<td>N = 40, 53.5 years (SD 8.5), Gender across groups 10 women</td>
<td>3 &amp; 12 months</td>
<td>Outpatient, Healthcare centre</td>
<td>Both</td>
<td>Yes</td>
</tr>
<tr>
<td>Coll-Fernandez R 14 [37]</td>
<td>Spain</td>
<td>N = 521, 56 years (SD 10), 90% male</td>
<td>N = 522, 87 years (SD 13), 71% male</td>
<td>18 months</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Junger C 10 [41]</td>
<td>Germany</td>
<td>STEMI patients: N = 1649, Median age 63.2 years, 73.6% male. NSTEMI patients: N = 1107, Median age 68.3 years, 71.5% male</td>
<td>STEMI patients: N = 783, Median age 70.0 years, 73% male. NSTEMI patients: N = 1008, Median age 71.2 years, 62.8% male</td>
<td>12 months</td>
<td>Inpatient, Specialist clinic</td>
<td>Group</td>
<td>Unclear</td>
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<tr>
<td>Kim C 11 [42]</td>
<td>Korea</td>
<td>N = 69, 61.93 years (±10.67), 71% male</td>
<td>N = 72, 64.49 (±9.31), 83% male</td>
<td>12 months</td>
<td>Unclear, Healthcare centre</td>
<td>Group</td>
<td>Unclear</td>
</tr>
<tr>
<td>Nielsen K 08 [43]</td>
<td>Denmark</td>
<td>N = 145, 59.8 years, Gender N/R</td>
<td>N = 55, 59.7 years, Gender N/R</td>
<td>12 &amp; 24 months</td>
<td>Outpatient, Specialist clinic</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Rauch B 14 [44]</td>
<td>Germany</td>
<td>N = 2513, 65 years (SD N/R), 76% male</td>
<td>N = 1047, 69 years (SD N/R), 71% male</td>
<td>3 and 12 months</td>
<td>Outpatient, Specialist clinic</td>
<td>Unclear</td>
<td>Yes</td>
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</table>

SD Standard deviation, N/R Not reported

https://doi.org/10.1371/journal.pone.0177658.t001
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Fig 3. All-cause mortality forest plot.

https://doi.org/10.1371/journal.pone.0177858.g003

In comparison to the two most recent reviews of RCT evidence [9, 22] the findings from this study and the CROS study (a review of observational data in mixed CR participants) [21] drew differing conclusions to trial data. Specifically, opposite effects in total mortality and re-hospitalisation were found between observational and trial data, with a reduction in total...

Fig 4. Cardiac-related mortality forest plot.

https://doi.org/10.1371/journal.pone.0177858.g004
The effectiveness of modern cardiac rehabilitation: A systematic review

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
<tr>
<td>2.3.1 Unadjusted outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boulay 2004b</td>
<td>-3.312</td>
<td>1.4862</td>
<td>7.5%</td>
<td>0.04</td>
<td>[0.00, 0.07]</td>
</tr>
<tr>
<td>Boulay P 2004a</td>
<td>-2.2083</td>
<td>1.1096</td>
<td>12.1%</td>
<td>0.11</td>
<td>[0.01, 0.097]</td>
</tr>
<tr>
<td>Coll-Fernandez R 2014</td>
<td>-1.2379</td>
<td>0.3655</td>
<td>37.2%</td>
<td>0.29</td>
<td>[0.14, 0.59]</td>
</tr>
<tr>
<td>Rauch B 2014</td>
<td>-0.4602</td>
<td>0.2486</td>
<td>43.1%</td>
<td>0.63</td>
<td>[0.39, 1.03]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
<td>[0.13, 0.74]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.39; Chi² = 7.76, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 2.65 (P = 0.01)

2.3.2 Adjusted outcome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
<tr>
<td>Rauch B 2014</td>
<td>-0.3285</td>
<td>0.293</td>
<td>100.0%</td>
<td>0.72</td>
<td>[0.43, 1.21]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
<td>[0.43, 1.21]</td>
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</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Chi² = 2.71, df = 1 (P = 0.10), I² = 63.0%

Fig 5. Re-occurrence of MI forest plot.
https://doi.org/10.1371/journal.pone.0177658.g005

mortality and no effect on re-hospitalisation found in observational studies. It may be argued that the observed differences may be due to the representativeness of trial evidence. Indeed the two recent trial based reviews of CR effectiveness [9, 22] include historical RCT trials which use exercise-only CR formats, include patients who had different care and treatment options historically versus modern day counter parts and the inherently different characteristics of RCT populations versus those receiving routine care. However, there were some similarities between trial and observational data; no reductions in recurrent MI were found and HRQOL

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
<tr>
<td>2.4.1 Unadjusted outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim C 2011</td>
<td>-0.5536</td>
<td>0.6509</td>
<td>3.2%</td>
<td>0.57</td>
<td>[0.16, 2.05]</td>
</tr>
<tr>
<td>Rauch B 2014</td>
<td>0.0829</td>
<td>0.1179</td>
<td>96.8%</td>
<td>1.10</td>
<td>[0.87, 1.36]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>1.07</td>
<td>[0.86, 1.35]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)

2.4.2 Adjusted outcome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>IV, Random</td>
<td>95% CI</td>
</tr>
<tr>
<td>Rauch B 2014</td>
<td>0.00</td>
<td>0.1268</td>
<td>100.0%</td>
<td>1.00</td>
<td>[0.78, 1.28]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>[0.78, 1.28]</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

Fig 6. Re-vascularisation forest plot.
https://doi.org/10.1371/journal.pone.0177658.g006
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improved. The positive effects on HRQOL found in AMI patient in this review are encouraging, however, as CROS did not consider HRQOL further work is needed to explore the effects in other CR populations.

With regard to the scope of evidence i.e. countries where evidence was available, only 8 studies conducted in 6 countries met the inclusion criteria. Observational data from other regions, particularly those with well-established CR programmes, would contribute substantially to a greater international perspective of current day CR performance, particularly in respect to alternative CR formats. Analysis of the programme characteristics did identify some differences between countries. Having a ‘multi-component’ CR programme formed part of the inclusion criteria for this review but a clear difference between American/Canadian interventions and European equivalents was evident. That is, European programmes appeared to include many more components into their programmes. This difference may be driven by European standards stipulating a menu based approach to suit the needs of individual patients [4, 5]. Regardless, the impact of these differences requires investigation to identify the best approach and format [4] and greater utilisation of registry data could be one feasible route. Additionally all except one study, which did not report clearly, used a healthcare or clinic setting. Given the thriving research base on the alternative approaches for CR setting, such as home-based strategies [45, 46], it was surprising that no alternative settings were identified. To understand the impact of format and the use of different programme components greater access to registry data, which captures such information, would be invaluable.

Limitations

No protocols were identified for the included studies, as such all quality assessment questions relating to pre-publication of a study protocol could not be assessed and were removed. There is a clear need for researchers of observational studies to pre-publish their study protocols. Many of the studies had small sample sizes and evidence of bias and thus the results from this review should be interpreted cautiously. In addition, only a few studies provided adjusted effect outcomes. Unadjusted outcomes are inherently bias, therefore adjusted and unadjusted outcomes were analysed separately and plotted alongside each other to permit comparison between studies where confounding had or had not been managed. Some heterogeneity was evident in the meta-analyses, but this did not exceed moderate levels and was thus appropriate to present graphically. Lastly due to insufficient data a sensitivity analysis on the impact of country of origin, study quality, and short versus long term follow-up was not possible as per the original review protocol. In addition, as we did not have access to individual patient level data we were unable to explore the impact of competing risk in our analyses.

Conclusion

Current observational evidence; from both this review of AMI patients and the mixed CR populations in the CROS review, appear to contradict the most recent trial based reviews with respect to total mortality and re-hospitalisation. Arguably these differences highlight that analysis of data which is closer to clinical practice yields different findings to those found in clinical trials, which are known to recruit less representativeness populations. The usefulness of historic trial data in the modern cardiological era should also be questioned. Encouragingly, however, the recent observational data shows CR reduces total mortality and improves HRQOL. Future work should seek to clarify which patient and service level factors determine the likelihood of achieving all-cause mortality, cardiac mortality or reduced re-admissions.
Supporting information
S1 Table. PRISMA checklist.
(DOCX)

S2 Table. Medline search strategy.
(DOCX)

Acknowledgments
The authors would like to acknowledge Melissa Harden at the University of York for her support developing the literature search strategy. These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions
Conceptualization: JS PD.
Data curation: JS PD AH.
Formal analysis: JS.
Funding acquisition: PD.
Investigation: JS AH.
Methodology: JS PD AH.
Project administration: JS.
Resources: PD.
Software: JS.
Supervision: JS PD.
Validation: JS.
Visualization: JS.
Writing – original draft: JS PD AH.
Writing – review & editing: JS PD AH.

References


Doi:10.1371/journal.pone.0177658

The candidate jointly conceived the idea for the paper, developed the study methodology, screened the identified literature and conducted the critical revisions to the paper following reviewer comments. The candidate developed and conducted the literature review, conducted the meta-analyses and prepared the first draft and subsequent revisions.

Jennifer Sumner
Alexander Harrison
Patrick Doherty
## Supplemental material

<table>
<thead>
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<th>Section/topic</th>
<th>#</th>
<th>Prisma Checklist item</th>
<th>Reported on page</th>
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<td><strong>TITLE</strong></td>
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<td><strong>Title</strong>&lt;br&gt;Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td><strong>Structured summary</strong>&lt;br&gt;Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>P2</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td><strong>Rationale</strong>&lt;br&gt;Describe the rationale for the review in the context of what is already known.</td>
<td>P3-5</td>
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<td><strong>Objectives</strong>&lt;br&gt;Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>P4-7</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td><strong>Protocol and registration</strong>&lt;br&gt;Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>P5</td>
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<td><strong>Eligibility criteria</strong>&lt;br&gt;Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<td><strong>Information sources</strong>&lt;br&gt;Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<td><strong>Search</strong>&lt;br&gt;Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<td><strong>Study selection</strong>&lt;br&gt;State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<td><strong>Data collection process</strong>&lt;br&gt;Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<td>Risk of bias in individual studies</td>
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<td>Summary measures</td>
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<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td>Synthesis of results</td>
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<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ for each meta-analysis).</td>
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16 rehabilitation/
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18 rehabilitat$.ti,ab.
19 secondary prevention/
20 exercise therapy/

21 physical exertion/

22 (physical$. adj (fit or fitness or train$ or thera$p$ or activit$ or exercis$)).ti,ab.

23 ((exercis$ or fitness) adj (treatment or intervent$ or program$ or therapy)).ti,ab.

24 Patient Education as Topic/

25 ((patient$ or health) adj (education or promot$)).ti,ab.

26 health education/

27 health promotion/

28 ((lifestyle or life-style) adj (treatment or intervent$ or program$ or therapy)).ti,ab.

29 self care/
| 30 | (self adj (manage$5 or care or motivate$)).ti,ab. |
| 31 | counseling/ |
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| 39 | attend$.ti,ab. |
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| 41 | uptake.ti,ab. |
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Paper 3: Does The Timing Of Cardiac Rehabilitation Impact Fitness Outcomes? An Observational Analysis
Does the timing of cardiac rehabilitation impact fitness outcomes? An observational analysis

Jennifer Fell, Veronica Dale, Patrick Doherty

ABSTRACT
Objectives: To ascertain the characteristics associated with delayed cardiac rehabilitation (CR) and determine if an association between CR timing and fitness outcomes exists in patients receiving routine care.

Methods: The study used data from the UK National Audit of Cardiac Rehabilitation, a data set which captures information on routine CR practice and patient outcomes. Data from 1 January 2012 to 8 September 2015 were included. Logistic regression models were used to explore the relationship between timing of CR and fitness-related outcomes as measured by patient-reported exercise level (150 min/week: yes/no), Dartmouth quality of life physical fitness scale and the incremental shuttle-walk test.

Results: Based on UK data current CR practice shows that programmes do not always adhere to recommendations on the start of prompt CR, that is, start CR within 28 days of referral (42 days for coronary artery bypass graft (CABG)). Wait time exceeded recommendations in post myocardial infarction (post-MI), elective percutaneous coronary intervention (PCI), MI-PCI and post-CABG surgery patients. This was particularly pronounced in the medically managed post-MI group, median wait time 40 days. Furthermore, statistical analysis revealed that delayed CR significantly impacts fitness outcomes. For every 1-day increase in CR wait time, patients were 1% less likely to improve across all fitness-related measures (p<0.05).

Conclusions: With the potential for suboptimal patient outcome if starting CR is delayed, efforts should be made to identify and overcome barriers to timely CR provision.

KEY QUESTIONS
What is already known about this subject?
- Current guidelines state patients should be seen early, by the outpatient cardiac rehabilitation (CR) team, and start CR within 4 weeks of referral. Despite this, delays occur, but the impact of this is unknown.

What does this study add?
- This multicentre analysis identified the characteristics of patients associated with delayed CR, notably, post-MI patients experience the longest delays. Analyses found that an association between timing of CR and patient response exists.

How might this impact on clinical practice?
- Given the importance of "exercise-based" CR reducing mortality, it is important that programmes identify barriers and prioritise timely pathways of care to prevent avoidable delays to the start of CR.

INTRODUCTION
Cardiovascular diseases are common and burdensome, responsible for an estimated 30% (17.5 million) of all deaths globally in 2012 and costing an estimated £18.9 billion in the UK during 2014. Based on national and international guidelines, cardiac rehabilitation (CR) is offered as an effective secondary prevention intervention, proven to reduce premature cardiovascular and all-cause mortality and improve health-related quality of life (QoL). CR is also a cost-effective therapy with an estimated cost per life year gained of less than £2000.

The National Audit of Cardiac Rehabilitation (NACR), funded by the British Heart Foundation, is a database which facilitates the monitoring of CR services in the UK in terms of service delivery and patient outcome. In 2014, 311 programmes were identified as delivering a core CR programme and 257 provided data to the NACR. Despite clinical minimum standards published in the UK and Europe, variation in practice can be observed, including the timing of CR. Deviation from evidence-based standards may be accounted for by increasing demands on programmes and decreasing resources. There is, however, a perception that such delays may not only reduce the chances of enrolment but also the impact of CR, and emerging evidence appears to demonstrate this may be the case.
Current guidance states patients should be seen early, by the outpatient CR team, and start CR within 4 weeks of referral.\textsuperscript{3} 5 8 9 13 Timing deviations occur in practice, but to date, it is unclear what the impact of such digressions from clinical guidelines could be. This study will ascertain the characteristics associated with delayed CR and the association between CR timing and patient outcome, namely physical activity status and fitness outcomes. Physical activity-related outcomes are especially critical given the emphasis of exercise-based CR reducing mortality.\textsuperscript{4} Findings from this project will establish if prioritisation of wait time reductions should take precedence.

METHODS
This observational study is reported following the guidelines: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).\textsuperscript{14} In the UK, CR is delivered in accordance with national standards, running for a minimum of 8 weeks or 56 days (median duration of CR 51–56 days\textsuperscript{7}) and comprising of a multi-disciplinary team based either in the community or an outpatient hospital setting.\textsuperscript{8} 13 The aim of CR is to facilitate health behaviour change through supervised exercise, educational classes on risk factors, physical activity, diet and smoking cessation and psychosocial support.

As part of routine practice, programmes undertake baseline and post-CR assessments, shortly after CR completion, to monitor progress in patients. Centres across England, Wales and Northern Ireland enter data into NACR, varying in size and case mix providing a representative sample. Data are collected and hosted by the Health and Social Care Information Centre. Through annual data sharing agreements, approval is granted to use these data to monitor and report on the quality of CR. Analyses were conducted using all available data from centres across the UK, to minimise selection bias, which entered data into NACR from 1 January 2012 to 8 September 2015.

Participants
Figure 1 details the flow of patients in this study. Adult (≥18 years) patients with acute coronary syndrome (ACS) starting CR from one of four patient groups were included: medically managed postmyocardial infarction (post-MI), elective percutaneous coronary intervention (PCI), MI-PCI and postcoronary artery bypass graft (CABG) surgery. Patients were defined as completing CR if the duration of CR exceeded 7 days and a completion date was entered. Only patients starting CR, attending a pre-CR and post-CR assessment with at least one completed physical activity outcome measure were included.

Timing categories
CR timing (ie, time between referral and start of core CR) was included in the analyses as a continuous variable to determine the impact on outcome for every day increase in CR wait time. A separate analysis investigated the impact of CR timing according to the definition of ‘early’ or ‘late’ CR as per current recommendations, that is, start within 4 weeks of referral. For this, a categorical CR timing variable was generated as follows:
- CR ‘on time’ (0–28 days),
- Delayed CR (29–365 days).

Timing was adjusted for CABG patients, where recovery from surgery (eg, sternotomy) is an important step before rehabilitation can start. Timing groups for CABG patients were as follows: on time (0–42 days) and delayed CR (49–365 days).

Outcome measures
Patient-reported physical activity level (150 min/week: yes/no), Dartmouth Quality of Life in relation to physical fitness (healthy status score 1–3/non-healthy status score 4–5)\textsuperscript{10} and a direct measure of fitness the incremental shuttle-walk test (ISWT), which assesses how far and fast a patient can walk without stopping while walking speed is gradually increased,\textsuperscript{16} were included. These outcomes capture both a patient-reported perspective and a clinician-assessed measure of fitness. Change in distance (metres) before CR and after completion of CR was calculated for the ISWT and categorised into <70 m improvement in distance or ≥70 m distance improvement. This cut-off is based on a recent study which proposes a 70 m improvement in distance as the minimum considered meaningful to a patient.\textsuperscript{16}

Statistical analysis
All analyses were conducted using STATA V.13.1. Descriptive statistics were generated for early and late CR groups and compared for statistical significant differences using $\chi^2$ test, student t test or Wilcoxon rank-sum test as appropriate. Logistic regression was performed to investigate the relationship between CR timing and patient outcome after CR completion. Analyses accounted for known confounders of fitness: age, gender, number of comorbidities, duration of CR (days), baseline body mass index (BMI), systolic and diastolic blood pressure (mm Hg), smoking status (smoker/non-smoker), ethnicity (British, non-British), treatment (revascularised or medically managed) and baseline

![Figure 1](patient_flow_diagram.png)
physical activity level. To take account of the nested nature of the data, that is, patients treated within centres, the Huber-White-sandwich estimator robust SEs method was used.

RESULTS
Patient characteristics are presented in table 1. As typical in the UK, CR was accessed primarily by older British males with at least one comorbidity. Physical activity level was generally low at baseline with only 33% of patients reporting at least 150 min of physical activity per week. The median duration of CR received was 57 days, which meets the minimum standard of 8 weeks (56 days). Patients starting CR late were statistically significantly more likely to be older, female, non-British, lower BMI, at least one comorbidity, higher systolic blood pressure, lower diastolic blood pressure, currently smoke, lower physical activity level (<150 min/week) and shorter baseline ISWT distance (all p<0.05). Participants in both early and late CR groups were predominantly patients with MI-PCI. In terms of patient improvement following CR, the extent of benefit was smaller for late CR attenders across the three fitness-related outcomes. In early CR attenders, the proportion achieving healthy physical activity levels and normal fitness-related QoL improved by 31% and 36%, respectively. Median improvement in ISWT was 120 m. For late CR, attenders values were 27%, 29% and 90 m, respectively.

The median wait time between CR referral and CR start exceeded recommendations at 39 days, with 63% of the population classified as late starters of CR. The proportion of delayed patients was 69% for MI, 64% MI-PCI, 56% for PCI and 63% for CABG patients. Figure 2 presents the median wait time (days) by patient group against recommended wait times (28 or 42 days for CABG). In each patient group, median wait time exceeded the recommended maximum waiting time, the delay was particularly extended in the post-MI population, which exceeded the maximum recommended wait time by 12 days.

Outcomes
The findings from the logistic regression analyses are presented in table 2. After multivariate adjustment, late CR timing was found to be a significant independent predictor of decreased fitness level compared with early CR. Similarly, CR timing when included as a continuous measure was also a significant predictor.

DISCUSSION
Current guidelines and papers in cardiac care recommend the early start of CR where appropriate. However, evidence shows in some cases, there is disconnect between recommended practice and the ‘real-life’ conduct of CR. Overall, 65% of our study population were classified as late CR attenders and median wait times in each patient group exceeded maximum recommendations on wait time. One explanation for the higher proportion of late attenders may be comorbidity burden. A total of 73% of late CR attenders had at least one comorbidity compared with 69% in early attenders. Case complexity could certainly delay the start of rehabilitation. Inconsistency in delay time across groups is also concerning. Out of all the patient groups, post-MI patients notably exceeded the maximum recommended wait time by the largest number of days (12 days). This may seem contrary to expectations, as post-MI patients undergo no invasive revascularisation procedures, which can delay CR start due to recovery period.

| Table 1 | Patient characteristics at baseline (pre-CR) overall and by early and late CR groups |
|-------------------------|---------------------------------|------------------------|------------------------|
| **Baseline characteristic** | **Overall (n=32 899)** | **Early CR (n=12 254)** | **Late CR (n=20 645)** |
| Mean age, years (SD) | 64.91 (10.73) | 63.86 (10.76) | 65.54 (10.67)* |
| Gender, n males (%) | 25 012 (77) | 9467 (79) | 15 545 (76)** |
| Ethnicity, n British (%) | 23 191 (66) | 8792 (87) | 14 399 (85)** |
| Post-MI (%) | 4280 (13) | 1313 (11) | 2967 (14)** |
| MI-PCI (%) | 13 331 (40) | 4774 (39) | 8557 (41)** |
| PCI (%) | 7505 (23) | 3320 (27) | 4185 (20)** |
| CABG (%) | 7783 (24) | 2847 (23) | 4936 (25) |
| Mean body mass index (SD) | 27.99 (4.73) | 28.09 (4.73) | 27.93 (4.74) |
| One or more comorbidities, n (%) | 23 927 (72) | 8469 (69) | 15 058 (73)** |
| Mean systolic blood pressure (SD) | 129.34 (20.07) | 128.60 (19.58) | 129.78 (20.34)** |
| Mean diastolic blood pressure (SD) | 74.31 (11.37) | 74.53 (11.15) | 74.19 (11.59)* |
| Non smoker, n (%) | 18 010 (69) | 7354 (90) | 10 650 (68)** |
| Physical activity ≥150 min/week, n (%) | 9876 (33) | 3976 (35) | 6000 (33)** |
| Healthy fitness status on QoL, n (%) | 11 373 (44) | 4237 (42) | 7136 (45)** |
| Median shuttle-walk distance | 305 m | 305 m | 340 m** |

*p<0.005 versus early CR. **p<0.001 versus early CR.
CABG, coronary artery bypass graft; CR, cardiac rehabilitation; MI, myocardial infarction; PCI, percutaneous coronary intervention; QoL, quality of life.
Regardless of CR timing, improvements in fitness-related outcomes were observed pre-CR to post-CR. However, the extent of improvement was reduced in late CR attenders. To explore the impact of CR timing on outcome in detail, two analytical approaches were used; timing as a continuous measure to explore the relationship between increasing wait time and outcome and timing as a categorical measure (early/late) to explore the relationship in the context of current guidelines. In each approach, it was observed that CR timing was a significant predictor of patient outcome in terms of fitness level. Based on these analyses, the likelihood of reporting a positive physical activity level and fitness outcome was reduced when CR is delayed. This was consistent regardless of whether the measure was patient reported or clinician assessed. This seems to fit with a recent study of 1241 CR patients which concluded delayed enrolment is directly related to patient outcome (metabolic equivalent of tasks (METs) and weight improvement). Additional evidence has also suggested that lifestyle changes peak in the first 6 months for patients with ACS patients undergoing exercise and lifestyle interventions, thus timing of CR is critical to optimise response.

Furthermore, a number of studies have shown several outcomes can be positively influenced by starting CR early, including mortality and cardiovascular events reductions, functional improvements, cardiorespiratory measures, 6 min walk test, Qol, and QoL with each outcome showing a greater improvement from early CR practice. The safety of early enrolment has also recently been assessed in open heart patients finding no difference in major event rates between early and late enrollees to CR. Clearly the case for early CR is strong, perhaps even to the point that a reduction in the recommended wait times may be warranted. Aside from clinical outcomes, additional evidence suggests that CR timing may even impact initial enrolment to CR. One randomised controlled trial found an early CR orientation session increased

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<th>Table 2</th>
<th>Results from logistic regression—relationship between CR timing and patient outcome post-CR</th>
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<td>CR timing (days)</td>
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<tr>
<td>Physical fitness</td>
<td>0.996</td>
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<td>QoL</td>
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<td>Shuttle-walk test</td>
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Analyses adjusted for age, gender, number of comorbidities, duration of CR (days), BMI, systolic and diastolic blood pressure, smoking status, ethnicity, treatment, baseline fitness status, OR, p value and 95% confidence intervals (CI). BMI, body mass index; CR, cardiac rehabilitation; QoL, quality of life.

Cardiac risk factors and prevention

Ethics approval The audit data used in this project came from the National Audit of Cardiac Rehabilitation (NACR). Data for this audit are collected and hosted by the Health and Social Care Information Centre. Through annual data sharing agreements, approval is granted for use of these data to monitor and report on the quality of CR and is covered under the 251 exemption.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Further requests for data or information in relation to this article should be made to the corresponding author.

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Contributors JF, PD and VD all contributed to the study design, analysis and writing of this manuscript.

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Competing interests None declared.

attendance by 18%. A further investigation into wait time and enrolment, using routine patient records, also reported an association; for every 1-day increase in wait time patients were 1% less likely to enroll.14 12

Given the potential implications for CR attendance and the importance of delivering a successful CR ‘exercise component’, any factors which negatively influence the extent of success of fitness-related outcomes, such as a delayed CR start, should be avoided if possible.

Limitations
To our knowledge, this is the first large-scale, multicentre analysis (n=32 899 eligible patients) which has investigated the effects of delayed CR timing on patient outcomes using routinely collected UK patient data. Although CR programmes are encouraged to provide complete patients records, it was expected that a proportion of patient data would be missing due to non-completion of patient records. The demographics of those included in the analyses were, however, typical of the UK population accessing CR.7 In addition, analyses were adjusted for a number of confounding measures which may influence physical activity status and fitness outcomes. Disease severity was not included, as this is not captured in the NACR database; however, comorbidities and other baseline characteristics will have partially accounted for this.

CONCLUSION
The observed association of CR timing and patient outcome in these analyses provides evidence to support the continued need for timely CR as directed by current guidance. The annual NACR report shows many programmes are not delivering timely CR and in these instances barriers need to be identified and overcome to ensure a consistent and effective service. Notably post-MI patients appear to experience the greatest delays and this should be investigated further. The clear association between exercise-based CR and reduced mortality means it is especially important that any potential causes of suboptimal improvement in fitness are avoided.4 Although it is acknowledged that timing of CR should also be based on a case-by-case basis, care should be taken to prevent avoidable delays, that is, long waiting lists. Future research should also consider the effects of mode of CR delivery on patient outcomes.


The candidate was jointly responsible for the study conception, methodology development and critical revisions to the paper following reviewer comments. The candidate conducted the analyses and prepared the first draft and subsequent revisions.

Jennifer Sumner
(nee Fell)

V.M. Dale

Patrick Doherty
Paper 4: Does Service Timing Matter For Psychological Outcomes In Cardiac Rehabilitation? Insights From The National Audit Of Cardiac Rehabilitation
Does service timing matter for psychological outcomes in cardiac rehabilitation? Insights from the National Audit of Cardiac Rehabilitation

Jennifer Sumner1,2, Jan R Böhnke1,3 and Patrick Doherty1

Abstract
Background: The presence of mental health conditions in cardiac rehabilitation (CR) patients such as anxiety and depression can lead to reduced programme adherence, increased mortality and increased re-occurrence of cardiovascular events undermining the aims and benefit of CR. Earlier research has identified a relationship between delayed commencement of CR and poorer physical activity outcomes. This study wished to explore whether a similar relationship between CR wait time and mental health outcomes can be found and to what degree participation in CR varies by mental health status.

Methods: Data from the UK National Audit of Cardiac Rehabilitation, a dataset that captures information on routine CR practice and patient outcomes, was extracted between 2012 and 2016. Logistic and multinomial regression models were used to explore the relationship between timing of CR and mental health outcomes measured on the hospital anxiety and depression scale.

Results: The results of this study showed participation in CR varied by mental health status, particularly in relation to completion of CR, with a higher proportion of non-completers with symptoms of anxiety (5% higher) and symptoms of depression (8% higher). Regression analyses also revealed that delays to CR commencement significantly impact mental health outcomes post-CR.

Conclusion: In these analyses CR wait time has been shown to predict the outcome of anxiety and depression status to the extent that delays in starting CR are detrimental. Programmes falling outside the 4-week window for commencement of CR following referral must strive to reduce wait times to avoid negative impacts to patient outcome.

Keywords
Anxiety, depression, cardiac rehabilitation, audit

Received 19 June 2017; accepted 16 October 2017

Introduction
An estimated 85 million people in Europe live with cardiovascular disease.1 As survival rates improve, following acute cardiac events, this number is only set to rise.2 Although improvements in life expectancy are positive, with increasing age multimorbidity i.e. living with more than one chronic condition becomes more common.3 For example frequently those with chronic conditions experience mental health problems such as depression and anxiety.4 A systematic review of depression prevalence in acute myocardial infarction survivors reported major depression was present in 19.8% of the population and the proportion with significant symptoms varied between 15% and 31% depending on the type of screening instrument used.5 Comorbid depression and anxiety are especially concerning: impacting quality of life, persisting for long periods of time, are associated with increased

1Department of Health Sciences, University of York, UK
2Saw Swee Hock School of Public Health, National University of Singapore, Singapore
3School of Nursing and Health Sciences (SNHS), University of Dundee, UK

Corresponding author:
Jennifer Sumner, Department of Health Sciences, University of York, UK.
Email: jenry.sumner@york.ac.uk
healthcare costs and elevated mortality. A higher lifetime risk of depressive or anxiety disorders has also been observed in those with a history of cardiovascular disease.

In light of increasingly multimorbid populations, cardiac rehabilitation (CR) has long since shifted from its origins as a pure exercise regime. In 2000 the national service framework for coronary heart disease was published in the UK, detailing modern standards of care, including CR services. This was followed in 2003 by a position statement by the European Society of Cardiology, which provided recommendations on the design and development of CR programmes. CR in Europe is now expected to be multi-component and multidisciplinary typically including education and psychological support. As part of modern practice, baseline assessments including the hospital anxiety and depression scale (HADS) are conducted upon enrolment to CR in the UK. The HADS has been shown to be appropriate for screening and as a patient-reported outcome in cardiac populations. Its use means participants' care can be tailored to the needs of the individual patient such as providing psychological support.

For successful CR appropriate management of mental health conditions is critical. The presence of anxiety or depression may exacerbate the underlying cardiac condition through reduced programme adherence, lower use of medical care and the pursuit of unhealthy behaviours such as smoking. The presence of anxiety and depression has also been linked to increased mortality and re-occurrence of cardiovascular events. Thus, ineffective identification and treatment of comorbid depression and anxiety undermines the goals of CR.

In order to deliver successful CR it is important to identify factors which impact mental health. Previous research on CR services has found associations between CR wait time and physical activity outcomes, showing that longer wait times significantly reduce the likelihood of improvement in fitness-related measures. In this study we explore whether programme delivery, in particular timing, may also impact mental health outcome and how participation in CR may differ between symptomatic and non-symptomatic patients. In particular, this study investigates the participation of patients eligible for CR with and without symptoms of anxiety and depression and whether delays in initiating care predict mental health outcome following CR, measured using HADS.

Methods
This study is reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) checklist. In the UK CR is delivered in accordance with national standards and for most patients includes centre-based CR (80%) with an emerging trend for home-based self-management approaches. Ideally, programmes should run for 12 weeks twice weekly and consist of multiple components: physical activity, education, dietary modification and psychological support. Data on service delivery, utilisation, patient characteristics and their respective outcomes are entered onto the National Audit of Cardiac Rehabilitation (NACR) by practitioners involved in CR delivery, according to a data dictionary (http://www.cardiacrehabilitation.org.uk/nacr/downloads.htm). Participation in NACR is high: in 2016 an average of 72% of all CR programmes entered data onto the NACR database. Typically, CR-induced patients are approached by the CR team and referred to the service while the patient is still in hospital after the acute treatment phase or shortly after discharge. For those that enroll a pre-assessment takes place, during which patient sociodemographic and clinical characteristics are recorded. Following completion of the CR programme the clinical assessment is repeated.

Participants
Data from the NACR was extracted from 1 January 2012 to 31 August 2016. Adult patients (≥18 years) with acute coronary syndrome were included. During the study period 137,178 patients started core CR and 93,870 completed core CR. Patients who started CR and had a completed baseline HADS assessment were included in the investigation of CR participation (N = 56,233). A total of 39,588 patients started and completed CR and had both a baseline and post-CR HADS assessment. These patients formed the main analysis sample. For analyses of the association between CR wait time and mental health outcome missing data were imputed for those who started and completed CR in centres with data for least 10 patients, generating a sample of 92,086 for a sensitivity analysis.

Measures
Current guidance states that patients should be seen early by the outpatient CR team and start CR within 4 weeks of referral, and ideally run for 12 weeks twice weekly. Three variables were defined to capture participation in CR: (a) wait time, i.e. time between referral to CR and start of CR; (b) duration of CR (days), i.e. between start and end date of CR exceeding 7 days; and (c) non-completion of CR defined as those with a CR start date entry but no completion date. For the regression analyses CR wait time (i.e. time between referral and CR start) was included as a continuous variable (days) to determine the impact on HADS outcome.
for each single day increase in CR wait time, and separately as a categorical variable to assess the impact of CR wait time according to current recommendations (on time 0–28 days, delayed 29–365 days). Some CR patients undergo more invasive surgical procedures as part of treatment such as bypass surgery, i.e. coronary artery bypass graft (CABG). For these patients timing categories were adjusted as recovery from surgery (e.g. sternotomy) takes longer and is an important step before rehabilitation can commence. For CABG patients timing groups were defined as ‘on time’ 0–42 days and ‘delayed’ 43–365 days.

The HADS14 is a screening tool for symptoms of anxiety and depression. It is typically self-completed by patients under the guidance of a trained medical professional. The HADS consists of 14 statements of which seven describe symptoms connected to depression (e.g. ‘I feel as if I am slowed down’) and seven are anxiety related (e.g. ‘I feel tense or wound up’). Patients respond on four categorical anchors (coded from 0 to 3). No individual item data were available to evaluate the reliability of HADS scores in the audit sample, but it has previously been found to be acceptable.34 The correlation between baseline and post-CR assessments was 0.73 (95% confidence interval (CI) 0.72–0.73).

In our main analysis anxiety and depression scores were analysed categorically (no symptoms/symptoms present) according to established clinical cut-offs with scores less than 8 representing low or no symptoms of anxiety or depression.14,15 Changes in HADS category between pre and post-CR were also derived and categorised as: (a) ‘symptomatic to non-symptomatic’; (b) ‘no change in symptomatic patients’; (c) ‘non-symptomatic to symptomatic’; (d) ‘no change in non-symptomatic patients’.

Statistics
All analyses were conducted using STATA version 14.2. Summary statistics are presented as mean with standard deviation (SD), medians with interquartile ranges or percentages as appropriate. The median time until start of CR and duration of CR were calculated overall and by anxiety and depression classifications. Chi-squared or rank sum tests were used to investigate the statistical difference between symptomatic and non-symptomatic participants and a t-test was used to compare pre and post-CR HADS scores. Logistic regression analyses were performed to investigate the relationship between CR wait time and post-CR outcome (HADS category), and multinomial logistic regression models with ‘non-symptomatic to symptomatic’ as a reference category were used for change in anxiety and depression between pre and post-CR. Both analyses were adjusted for age, gender, number of comorbidities (0–5+) calculated from 19 prospecified comorbidity options as detailed in the NACR data dictionary (http://www.cardiacrehabilitation.org.uk/nacr/downloads.htm), CR duration, ethnicity (white British/other), relationship status (partnered/single), employment status (unemployed/employed/retired), history of previous cardiac event (present/absent), treatment received (revascularised/non-revascularisation), year of initiating event and baseline anxiety and depression score (for the CR wait time and post-CR outcome analyses only). As the data were clustered within CR centres we used cluster-robust standard errors to evaluate the significance of predictors. For the logistic and multinomial regressions missing data were also imputed via multiple imputation chained questions.35 The following variables were included in the imputation: age, gender, ethnicity, number of comorbidities, employment status, relationship status, CR duration, history of previous cardiac event, treatment received, year of event, and baseline and post-CR HADS scores. Twenty iterations were run and the quantity and pattern of missing data was assessed prior to imputation (detail presented in Table 1). To explore the relationship between wait time and HADS, marginal probabilities were calculated and explored visually. The amount of variance due to data clustering by centre was also explored using intraclass correlations for HADS scores, wait time and CR duration. Post-estimation checks were performed to investigate how well the statistical models fit to the data. Pearson chi-squared goodness-of-fit tests were performed to test whether there is a statistical difference between observed and expected values (for multinomial logistic regressions this was done using logistic regressions for all comparisons). In addition, for the logistic model specification tests were run36 to test whether non-modelled non-linear relationships were present.

Ethics
The NACR is hosted by NHS Digital, through which designated researchers are approved to access anonymised patient-level data related to CR delivery processes and patient outcome pre and post-rehabilitation. These agreements are assessed annually as part of data governance approval between the NACR and NHS Digital. The aforementioned agreements and anonymity of the dataset meant that a separate ethical application was not required as part of this study.

Results
Cohort characteristics
Patient characteristics are presented in Table 1. A total of 39,588 patients completed CR and had a pre and
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Post-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>65.1 (SD 10.60)</td>
<td></td>
</tr>
<tr>
<td>Gender, n men (%)</td>
<td>30,121 (78%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n British (%)</td>
<td>28,697 (87%)</td>
<td></td>
</tr>
<tr>
<td>One or more comorbidities, n (%)</td>
<td>29,326 (74%)</td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
<td>33,894</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>10,083 (30%)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>5,184 (15%)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>18,627 (55%)</td>
<td></td>
</tr>
<tr>
<td>Marital status: partnered, n (%)</td>
<td>30,823</td>
<td></td>
</tr>
<tr>
<td>Previous cardiac event, n (%)</td>
<td>24,769 (80%)</td>
<td></td>
</tr>
<tr>
<td>Undergone previous revascularisation, n (%)</td>
<td>34,410 (87%)</td>
<td></td>
</tr>
<tr>
<td>Median wait time to start CR from referral (days)</td>
<td>36 days (IQR 22.77)</td>
<td></td>
</tr>
<tr>
<td>Mean wait time to start CR from referral (days)</td>
<td>45 days (SD 38.26)</td>
<td></td>
</tr>
<tr>
<td>Median CR programme duration (days)</td>
<td>59 days (IQR 47.81)</td>
<td></td>
</tr>
<tr>
<td>Mean CR programme duration (days)</td>
<td>67 days (SD 35.78)</td>
<td></td>
</tr>
<tr>
<td>Symptoms of anxiety present, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean anxiety score (SD)</td>
<td>11.015 (28%)</td>
<td>8394 (21%)*</td>
</tr>
<tr>
<td>Symptoms of depression present, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean depression score (SD)</td>
<td>5.43 (4.04)</td>
<td>4.69 (3.77)*</td>
</tr>
<tr>
<td>Mean depression score (SD)</td>
<td>67.34 (17%)</td>
<td>4637 (12%)*</td>
</tr>
<tr>
<td>Mean depression score (SD)</td>
<td>4.20 (3.50)</td>
<td>3.36 (3.22)*</td>
</tr>
</tbody>
</table>

SD: standard deviation; IQR: interquartile range; CR: cardiac rehabilitation.
*N = 39,588 unless otherwise stated.
N = 25,045 had data on all these variables.
*X2 and *t-test all P < 0.001.

Post-CR HADS assessment. Participants were primarily men, were British, with a mean age of 65 years. The majority had at least one comorbidity, were in a relationship, were retired, had undergone previous revascularisation surgery and a third of participants had experienced a previous cardiac event. At baseline, 28% of patients had some symptoms of anxiety and a further 17% had symptoms of depression. Between the pre and post-CR period the proportion of symptomatic patients significantly decreased as well as the mean HADS scores.

In terms of data completion of the 56,233 patients who started and completed CR and had a completed baseline HADS assessment, 70% (n = 39,588) had a post CR HADS assessment entered onto the NACR dataset. Demographic characteristics between those who had a missing post-CR HADS assessment (n = 16,557) and those with a completed baseline and post-CR HADS assessment were similar; mean age 65.1 versus 64.2 years and the proportions for remaining demographics did not differ by more than 5% (data not shown).

We assessed the size of the clustering effect due to centres on our core variables in this analysis by determining intraclass correlations (ICC), which describe the amount of variance in these variables due to differences between the rehabilitation centres. The ICC for HADS depression scores at baseline was 0.02 (95% CI 0.01–0.02) and post-CR was 0.02 (95% CI 0.01–0.02), and the ICCs for HADS anxiety were 0.01 (95% CI 0.01–0.02) and 0.01 (95% CI 0.01–0.02) baseline and post-CR, respectively. The ICCs for wait time to start CR from referral (days) and CR programme duration (days) were 0.14 (95% CI 0.10–0.17) and 0.23 (95% CI 0.18–0.28), respectively. ICCs were small for HADS, indicating similar symptom distributions across rehabilitation centres, but ICCs were high for wait time and duration, which indicates by centre variation for wait time and duration. Since it has long been established that even small cluster effects can have detrimental impacts on statistical models, we proceeded with our strategy to use cluster-robust standard errors.

Participation in CR

The median wait time for starting CR ranged between 36 and 37 days in those with or without symptoms of anxiety or depression. The duration of CR was 1 day longer in those with symptoms of anxiety (58 days) versus those without, and 4 days longer in those with
Table 2. Median wait time and duration of CR by change in HADS anxiety and depression category.

<table>
<thead>
<tr>
<th>Change in anxiety and depression category from baseline to post-CR</th>
<th>Change in anxiety category</th>
<th>Change in depression category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Median wait time (days)</td>
</tr>
<tr>
<td>Symptomatic to non-symptomatic</td>
<td>4,880 (12%)</td>
<td>35</td>
</tr>
<tr>
<td>No change in symptomatic patients</td>
<td>6,135 (16%)</td>
<td>36</td>
</tr>
<tr>
<td>Non-symptomatic to symptomatic</td>
<td>2,259 (6%)</td>
<td>36</td>
</tr>
<tr>
<td>Remains non-symptomatic patient</td>
<td>26,314 (66%)</td>
<td>37</td>
</tr>
</tbody>
</table>

CR: cardiac rehabilitation; HADS: hospital anxiety and depression scale.

Table 3. Results from logistic regression: CR wait time (late CR or CR wait time in days) and likelihood of being symptomatic following CR.

<table>
<thead>
<tr>
<th>Observed data</th>
<th>Imputed data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety symptoms OR (95% CI)</td>
<td>Depressive symptoms OR (95% CI)</td>
</tr>
<tr>
<td>OR 1.13 P = 0.002 (1.04, 1.23)</td>
<td>OR 1.24 P &lt; 0.001 (1.12, 1.38)</td>
</tr>
<tr>
<td>OR 1.001 P = 0.001 (1.0008, 1.003)</td>
<td>OR 1.002 P &lt; 0.001 (1.001, 1.003)</td>
</tr>
<tr>
<td>OR 1.04 P = 0.07 (0.99, 1.10)</td>
<td>OR 1.09 P = 0.01 (1.01, 1.001)</td>
</tr>
<tr>
<td>OR 1.0008 P = 0.02 (1.0001, 1.001)</td>
<td>OR 1.001 P = 0.001 (1.0004, 1.001)</td>
</tr>
</tbody>
</table>

CR: cardiac rehabilitation; OR: odds ratio; CI: confidence interval.

Symptoms of depression (61 days) versus those without (P < 0.001). The median wait time and CR duration are presented by a change in HADS category from pre to post-CR in Table 2. Wait time varied by no more than 2 and 4 days for change in HADS category for anxiety and depression, respectively. Duration of CR varied by 3 and 5 days for change in HADS anxiety and depression category, respectively. The proportion of non-completers was higher in those with symptoms of anxiety 28% versus 23% and higher in those with symptoms of depression 31% versus 23% in non-symptomatic patients (both P < 0.001).

CR wait time and outcome

Tables 3 and 4 present the results of the logistic and multinomial regression analyses. Statistically significant associations between HADS category (post-CR) and CR wait time were observed, i.e. increasing CR wait time increases the likelihood of symptomatic HADS anxiety or depression scores (≥8) post-CR. At a wait time of 28 days, the longest period starting CR would still be seen as on time, the predicted probability of being non-symptomatic for anxiety and depression was 79% and 89% decreasing to 76% and 86% by 168 days (6 months from referral), respectively (Figure 1). Testing model fit, Pearson chi-squared goodness-of-fit tests were non-significant (P = 0.92 and P = 0.90, respectively) and the specification tests revealed if at all only minor specification error.

For change in the anxiety category the findings were to the effect that delayed or increasing CR wait time is detrimental to mental health change from pre to post-CR. Statistically significant associations were observed for those who changed from the symptomatic to non-symptomatic category and those who remained non-symptomatic and CR wait time. For change in depression from pre to post-CR statistically significant associations were observed for those who changed from symptomatic to non-symptomatic, those who remained symptomatic and those who remained non-symptomatic and CR wait time. Testing model fit, 14 of the 16 Pearson chi-squared goodness-of-fit tests were non-significant (P > 0.39) indicating acceptable fit, but
Table 4. Results from multinomial logistic regression: CR wait time (late CR or CR wait time in days) and change in anxiety and depression category.

<table>
<thead>
<tr>
<th>Change in HADS category</th>
<th>Observed data</th>
<th>Imputed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in anxiety category RRR (95% CI)</td>
<td>Change in depression category RRR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Late CR</td>
<td>CR wait time</td>
</tr>
<tr>
<td>Non-symptomatic to symptomatic reference group</td>
<td>0.85 P = 0.04 (0.74, 0.99)</td>
<td>0.99 P = 0.06 (0.994, 0.9991)</td>
</tr>
<tr>
<td>Symptomatic to non-symptomatic</td>
<td>1.04 P = 0.58 (0.89, 1.21)</td>
<td>0.99 P = 0.85 (0.997, 1.001)</td>
</tr>
<tr>
<td>No change: symptomatic</td>
<td>0.93 P = 0.26 (0.82, 1.05)</td>
<td>0.99 P = 0.03 (0.996, 0.9998)</td>
</tr>
</tbody>
</table>

RRR: relative risk ratio; CI: confidence interval; CR: cardiac rehabilitation.
Analyses adjusted for age, gender, comorbidity, CR duration, ethnicity, relationship status, employment, history of previous cardiac event, treatment received and year of initiating event.
Data were clustered with CR centres using cluster-robust standard errors.

Discussion

Current CR guidelines recommend early commencement of CR, when appropriate, as part of the initial care for CHD patients, provided that no contraindications are present. However, studies show that there are significant variations in the health regions and between patient groups, with the time interval between CR and the intervention difficult to quantify.

In this study, we explored the relationship between patient characteristics and the likelihood of being recommended for CR in the 4-week waiting list. The results of this study showed that participants with a wait time of 188 days were more likely to be recommended for CR than those with a wait time of 168 days and 188 days (post-CR, respectively). The post-168 days group had a significantly lower wait time in the post-168 days group.

For anxiety and depression change categories, the model showed a significant association between the likelihood of being recommended for CR and anxiety and depression category. The post-168 days group had a significantly lower wait time in the post-168 days group.

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role to shed light on such delays or uncover new best practice examples.

When comparing the participation in CR services by HADS category at baseline and by change in HADS category the variation in median wait time was limited. However, wait time was still in excess of guidelines, which recommend CR commencement within 4 weeks of referral. As the data from these analyses has shown and in a previous analysis of CR wait time and physical activity outcomes, delays in starting CR can be detrimental to patient outcome so it is important to avoid delays which are not driven by clinical necessity. However, trials-based meta-analytical evidence has suggested that later psychological treatment initiation (≥2 months post event) is more beneficial to mortality outcomes than early initiation. This shows that further research on the relationship between time to start of CR (psychological treatment initiation specifically) and a whole breadth of CR outcomes is needed.

In terms of the duration of CR some variation was observed in those who were symptomatic at baseline (1 day extra if anxious, 4 days extra if depressed) and by change in HADS category, e.g. those who remained non-symptomatic undertook shorter CR programmes than those who remained or developed mental health symptoms. It is unknown whether this substantially impacted patient care and outcome; however, the median programme duration for the population with HADS data (59 days) was below the recommended duration of CR, i.e. 12 weeks (84 days) and below the 2016 national UK average of 63 days. Although CR duration was longer in those who were symptomatic, the proportion of non-completers was also higher in those who had symptoms of anxiety (5% higher drop out) and in those with symptoms of depression (8% higher drop out). This seems to fit with previous research, which has reported drop out from CR is greater in those with higher anxiety and depression scores.

With regard to associations between CR wait time and HADS outcome a relationship was observed in these analyses to the effect that the likelihood of having symptoms of anxiety or depression post-CR (HADS score ≥8) increases with every extra day between referral and start of CR. Similar effects were also observed when investigating CR wait time in accordance with guidelines defining ‘early CR’ (defined as 0–28 days) with a 13–24% increase in the likelihood of observing anxiety and depression symptoms following ‘delayed’ CR. The significant associations between CR wait time and HADS outcome remained, albeit the effects were smaller, when using imputed data, except when using timing as a categorical variable for anxiety, which did not reach significance. The impact of timing on outcome was also reflected in the predicted probability of being non-symptomatic, which decreased over time. Analyses by change in HADS category found significant associations for those changing from symptomatic and non-symptomatic for anxiety with both CR timing variables and for depression with the categorical timing variable only. As with the first analysis increasing or delayed CR wait time appears to impact change.
in outcome negatively. The results from the observed data indicate that programmes which fall outside wait time recommendations may inadvertently impact outcome with respect to HADS. However, analyses of change in HADS category using imputed data found only a negative trend for those changing from symptomatic and non-symptomatic for anxiety and depression with increasing or delayed CR wait time, and the results did not reach significance.

Although overall anxiety and depression scores were shown to reduce from pre to post-CR, not all programmes enter post-CR assessments onto NACR. In this study of those who had a baseline HADS score and had completed CR, 30% did not have a post-CR HADS score entered. A total of 21% of the population remain anxious or develop symptoms of anxiety post-CR (12% for depression), and this is associated with a heightened risk of mortality and re-occurrence of cardiovascular disease. Varying treatment approaches, i.e. dose and duration, could be explored to determine their impact on this subpopulation.

This study also highlights the need for improved clinical data capture, one aim of the British Association for Cardiovascular Prevention and Rehabilitation (BACPR)/NACR certification programme. Pre and post assessments using measures such as the HADS can be seen, by some, as posing a substantial time burden on patients and services; however, a tailored intervention with guided long-term management is the cornerstone of effective CR. Newer technologies using computerised adaptive testing systems that have been used successfully in similarly challenging areas such as cancer/palliative care are also under development for CR and provide future ways to less burdensome but accurate approaches to assess patients' mental health. Incentive-based approaches to improve data capture could also be considered, but may not be the most powerful motivator as noted in a recent report by the Healthcare Quality Improvement Partnership (HQIP) on engaging clinicians in quality improvement through audit.

Limitations

This UK-based analysis represents a large and current investigation into the impact of CR wait time on anxiety and depression outcomes in routine practice, a clear strength of this study. Known relevant confounding variables and data clustering were managed effectively, although it is acknowledged that a measure of disease severity was not included in this analysis as this is not collected in NACR. The main limitation of this analysis is the lack of consistent assessment and documentation of mental health outcomes even for audit purposes. Some of the missing data is due to participants not completing their CR programme, thereby missing follow-up assessment, while some is due to services collecting outcomes with other measures (including the PHQ-9 would have increased the sample size by 983 and by 978 for GAD7 but the majority of the loss is due to services documentation practices. As outlined in the introduction, mental health outcomes merit attention, because they are predictive of mid and long-term cardiac events including evidence that depression and anxiety are differentially predictive of these. For many patients post-CR data were not available, which is troubling because our results show that a sizable share of patients potentially deteriorate in their mental health status (Table 2). Overall, this points to the importance of ensuring high data quality in audits for all clinically important variables. Finally, the results of these analyses have only been determined with one specific instrument, the HADS. In 2000 the National Framework for Coronary Heart Disease was published by the Department of Health, setting standards for modern practice including the use of HADS. Since then HADS has been the preferred clinical screening tool. Nevertheless, evidence is increasingly questioning whether the HADS is the most optimal choice for screening; therefore, results need to be replicated with other instruments.

Conclusions

Audit of CR services shows variation in service delivery and in some cases practice, which falls outside of recommended guidelines. In these analyses, CR wait time has been shown to predict the outcome of anxiety and depression status to the extent that delays in starting CR are detrimental. Programmes falling outside the 4-week window for commencement of CR following referral must strive to reduce wait times to avoid negative impacts to patient outcome.

Author contribution

JS and PD contributed to the conception or design of the work. JS, PD and JRB contributed to the acquisition, analysis, or interpretation of data for the work. JS, PD and JRB drafted the manuscript. JS, PD and JRB critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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References


The candidate conceived the idea for the paper, conducted the analyses and prepared the first draft and subsequent revisions. The candidate jointly developed the study methodology and critical revisions to the paper following reviewer comments.

Jennifer Sumner

Jan R Böhnke

Patrick Doherty
Paper 5: Relationship Between Employment And Mental Health Outcomes Following Cardiac Rehabilitation: An Observational Analysis From The National Audit Of Cardiac Rehabilitation
Relationship between employment and mental health outcomes following Cardiac Rehabilitation: an observational analysis from the National Audit of Cardiac Rehabilitation

Alex S. Harrison *, Jennifer Sumner, Dean McMillan, Patrick Doherty
University of York, Department of Health Sciences, York, UK

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ABSTRACT

Background: Employment status has been shown to impact mental health state and intervention outcomes, yet to be studied in a Cardiac Rehabilitation (CR) population. This observational study investigated the relationship between employment status and mental health outcomes following Cardiac Rehabilitation (CR).

Methods: All patients with an eligible cardiovascular incident entered into the National Audit of Cardiac Rehabilitation (NACR) 1 January 2013–31st December 2015. Logistic regression comparing the association between employment status and normal mental health categories.

Results: A total of 24242 CR patients with completed post CR assessments were included and had representative age and gender distribution (mean 55 years, 73.26 male). At baseline the unemployed status had a lower proportion of patients in normal healthy categories than other groups (7-test and chi-squared p = < 0.05). The regression analyses revealed no significant association between retired and employed groups and outcome. There was significant association between unemployed patients and all mental health outcomes except anxiety; all p values < 0.05 and odds ratios between 0.525 and 0.772 showing less likelihood of achieving the normal healthy category.

Conclusions: This is the first UK study, using routinely collected data, to investigate in coronary heart disease patients the impact of employment status on outcomes. The findings were that when weighted for baseline differences, unemployed patients mostly had poorer outcomes. Teams involved in CR delivery should take particular care when interpreting mental health baseline measures when setting CR goals, especially in relation to unemployment patients, and efforts should be made in providing more patient tailored interventions.

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1. Introduction

Cardiac Rehabilitation (CR) is a highly evidenced based intervention for a variety of cardiac conditions, (1) significantly reducing cardiovascular mortality (RR 0.74, 95% CI 0.64–0.86) and hospital re-admission post CR (RR 0.82, 95% CI 0.70–0.96). [1,2] The modern United Kingdom (UK) CR population includes patients with conditions such as myocardial infarction, heart failure and angina, along with treatments such as percutaneous coronary interventions, coronary artery bypasses graft and valve surgery. [1] The benefits of CR are derived from modifications to lifestyle risk factors and the management of psychosocial factors associated with well-being. The approach is globally recognised as multi-disciplinary and comprehensive including structured education sessions, exercise based interventions and psychosocial support with agreed core components and minimum standards [3–5] yet less than 25% of programmes have access to psychosocial services. [6]

Current evidence in a post Percutaneous Coronary Intervention (PCI) population showed a link between employment, specifically unemployment, and lowered quality of life at baseline and 12 months post treatment [7]. This link between employment and health has scarcely been studied in CR, often only in uptake and participation [7–12]. The work by Strens et al. showed employment status at baseline was associated with reduced participation in CR post PCI (OR 0.54 CI 95% 0.44–0.68) or surgical intervention (OR 0.51 CI 95% 0.36–0.73) [8]. A study of patients following myocardial infarction found that unemployment was significantly associated with reduced intention to attend CR (p = 0.007) and increased drop out (p = 0.044) [9]. In a US study of underserved populations, patients were found to be less likely to attend CR if they were unemployed; however, conflict with work has also been identified as a common reason to not complete. [11] Although there is evidence of employment status affecting uptake and completion of CR, there is a dearth of evidence as to whether CR, as an intervention, is as
effective in different employment statuses in terms of patient outcome. As such the aim of this study was to ascertain the general patient characteristics by employment status and investigate the association between employment status (employed, unemployed and retired) and patient outcome following CR; specifically mental health and quality of life (QoL).

2. Methods

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13]

2.1. Data

The analyses were performed using routinely collected patient-level data from the UK NACR database from 1st January 2013 to 31st December 2015. According to the 2015 NACR report a total of 164 CR programmes across the UK enter into the NACR audit.[6] Information on patients’ initiating event, treatment, individual risk factors, medication use, characteristics and outcomes of CR users is captured. Data is collected under 201 approvals which are reviewed annually by the Health and Social Care Information Centre (HSCIC).

The analysis included all CR programmes in England, with valid patient data at both pre- and post-CR assessment including depression score as measured by the Index of Multiple Deprivation (IMD). Patients who had Myocardial Infarction with or without revascularisation were included to account for type of diagnosis/treatment. All patients with valid diagnosis/treatment entered were included, minimising selection bias.

2.2. Cardiac Rehabilitation

CR is conducted according to the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) core components.[8] Typically programmes run for 8–12 weeks, twice weekly with structured education and exercise components.

2.3. Employment status

Employment status was categorised as employed, unemployed or retired. Being employed was classified as either full or part-time employment, self-employed or as part of a government training scheme. Unemployed was defined as; unemployed, looking after family/home, permanently sick/disabled, temporarily sick or injured, student or other reasons for not working.

Employment status is defined in a variety of ways, most commonly employed/unemployed comparisons are made sometimes including a third group; such as retired.[14] In the UK CR population the mean age of males is 65 years and females is 70 years, with approximately two thirds of population reported as being retired.[6] As such this study will include three employment groups; employed, unemployed and retired.

2.4. Outcome measures

Anxiety and depression symptoms were separately measured on the Hospital Anxiety and Depression Scale (HADS), licensed to NACR (score range 0–21) with higher scores representing worse symptoms, patients were grouped as healthy normal category (score ≤8) and unhealthy score (score >8).[15] Quality of life in relation to feelings and general quality of life were assessed on the Dartmouth COOP (score per item 1–5), responses were dichotomised (healthy normal score 1–3, unhealthy score 4–5).[16]

2.5. Statistical Analysis

The analyses were conducted in STATA 13.1. Baseline characteristics were compared across groups using Chi² or F-test as appropriate. Standardised differences were calculated for continuous variables, with |0.1| classified as meaningful. Unemployed and retired groups were compared to the baseline employed group.[16] Regression models were run comparing the unemployment and retired populations to the reference category employed. Relevant important covariates were included in the analysis. Age (years), gender (male/female) and number of comorbidities have both been shown to influence the outcomes following a variety of different interventions, including CR.[17,18] The duration of CR (length of core rehabilitation) was accounted for in analysis. The type of event/treatment prior to CR is likely to affect the patients’ outcomes, to account for this variation patients were coded as medically managed or revascularised as shown in the NACR statistics report.[6] The IMD was calculated and ranked, from the most deprived to the least deprived regions, at for all 209 clinical commissioning groups and was included in this analysis.[19] Individual patients were assigned an IMD score according to where their General Practitioner (GP) was located within England. IMD was split into 10 equal sized groups ‘deciles’, with 1 being the most deprived group.

Logistic regressions were used to investigate the association between employment status, as an independent variable, and health outcomes as the dependent variable. Significance was set at the p < 0.05 level. Data model checking was performed to ensure that the models were a good fit through assumptions associated with the regressions.

3. Results

3.1. Study population

The study sample is summarised in Fig. 1 and the population characteristics are summarised in Table 1. A total of 24,242 patients were included in the analyses. The population is representative of patients accessing CR,[8] with an average age of 65 years (SD 11.5) and majority male participants (73.2%). The average duration of CR for this study falls within the NICE guidelines of 8–12 weeks, with this population averaging 9 weeks. The distribution of the employment statuses is similar to the national level, which has stayed static at 58% retired for the past 6 years.[6] The patients were evenly distributed across the IMD deciles with the highest proportion in the 8th decile.

In terms of baseline scores by employment group, mean HADS were 2 points higher on average in the unemployed group (mean anxiety 7.7, depression 6.4) compared to the other two groups. Overall unemployed patients had the smallest proportion classified as normal on the HADS. The unemployed group also had the smallest proportions of patients reporting normal QoL readings in relation to feelings and general QoL, around 10% lower in comparison. The number of comorbidities was lowest in the employed group and duration of CR was greater, by 4 days, in the unemployed group. Naturally, the age was significantly different in the retired population with a 14 years greater average.

Table 1 also shows the proportion change from baseline to post rehabilitation into the normal group (HADS < 8 and Dartmouth ≤ 3) for the 4 mental health outcomes split by employment status. The results show that all groups had improvements across the four outcome measures, but the largest improvements were observed in the unemployed group.

3.2. Outcomes

The results from the regression analyses are presented in Table 2. The results consistently, apart from anxiety, showed that unemployed patients are significantly associated with worse mental health post rehabilitation.

![Fig. 1. Flow diagram showing patients' numbers from assessment 1 with a valid employment status field, starting core rehabilitation and then a valid assessment 2 post rehabilitation. Of the number with assessment 1 49% go on to have an assessment 2.](image-url)
rehabilitation (all p < 0.05). The depression results showed unemployed patients were 26% less likely to be in the normal category (p < 0.034), and patients were 23–45% less likely to be in the normal category for Dartmouth feelings and QoL (p < 0.001). No significant associations were found between the retired population and mental health outcomes.

4. Discussion

The overriding result of this study is that although all employment groups show improvements in all post CR mental health outcomes, when compared to the employed group, unemployed patients were less likely to be in the normal category, post CR, for depression and Dartmouth feelings and QoL. Anxiety was inputted in a model as well, however, no significant association was found despite unemployed patients having a lower percentage in the baseline normal group. Interestingly, work by Meyer et al. showed the complexity surrounding anxiety and outcome when they found that some level of anxiety, even as high as ≥10 on the HADS score, is associated with a beneficial reduction in cardiovascular events in a subset of cardiac patients undergoing PCI (p = 0.014) [20].

When compared at baseline, unemployed patients’ mental health is consistently worse than the employed or retired population. Although the unemployed group make the greatest improvements pre to post CR this is likely due to worse pre CR starting point and some level of the other groups experiencing ceiling effects.

The unemployed patients’ at follow-up were significantly (15–26%) less likely to be in the normal category for the HADS Depression and Dartmouth questions; this result was not significantly represented in the anxiety measure.

This seems consistent with the literature, in that unemployment has an association at baseline with poorer mental health [7,10,21]. The work by Waddell concluded a similar effect of employment status on mental health outcomes, in that unemployed status can be detrimental to mental health [21]. Additionally Brown and Jin’s work also showed higher odds of poorer mental health in unemployed patients [12,22].

To date the literature investigating the effect of employment on CR, has only compared how patients differ at uptake and dropout [8–11]. This research has extended knowledge on the characteristics of those accessing CR from different employment groups and has identified an association between employment and outcome. In addition, to existing research this current study has identified that from initiating event through to completion of CR there is a need for service tailoring to make sure all employment groups benefit from this intervention.

Overall this study enforces the importance of employment status on the CR population. Unemployed patients are less likely to attend CR and when they do attend they are less likely to be in three of the normal mental health outcome groups. This study’s results, along with work on attendance and drop out suggest that commissioners may need to look at aligning the recruitment to and the delivery of CR by employment status [8–12].

4.1. Limitations

One limitation of this study is the level of missing data. Although sufficiently prevalent for the purposes of this analysis, the inclusion of England only patients and ~31% missing data at the post rehab assessment may have limited the generalisability of the findings, although the population did appear to be representative of patients accessing CR in the UK [13].

5. Conclusion

This study identified a strong association between employment status and mental health outcomes. The extent of benefit to patients is significantly influenced by employment status in that being unemployed led to reduced benefit in depression and QoL compared to patients who were employed or retired. Existing evidence has already established a link between employment and mental health at baseline; however, this is the first study to show this impact on patient outcomes. As recommended by national associations, CR teams need to assess patients,
based on the core components of CR, and consider employment status when tailoring care for individual patients. Future research should consider the staffing profile and types of tailored interventions that would enable unemployment patients to derive the same benefit.

Conflict of Interest

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

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References


The candidate jointly developed the idea for the paper, the study methodology and contributed substantially to the preparation of the manuscript and critical revisions to the paper following reviewer comments.

Alexander Harrison

Jennifer Sumner

Dean McMillan

Patrick Doherty
## Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<td>BACPR</td>
<td>British Association for Cardiovascular Prevention and Rehabilitation</td>
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<td>BDI</td>
<td>Becks Depression Inventory</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<td>CABG</td>
<td>Coronary Artery Bypass Surgery</td>
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<td>CCG</td>
<td>Clinical Commissioning Group</td>
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<td>CHD</td>
<td>Coronary Heart Disease</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CR</td>
<td>Cardiac Rehabilitation</td>
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<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<td>HADS</td>
<td>Hospital Anxiety Depression Scale</td>
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<td>HF</td>
<td>Heart Failure</td>
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<td>Health Related Quality of Life</td>
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<td>ICC</td>
<td>Intra Class Correlations</td>
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<td>IMD</td>
<td>Index of Multiple Deprivation</td>
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<td>ISWT</td>
<td>Incremental Shuttle Walk Test</td>
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<td>METS</td>
<td>Metabolic Equivalents</td>
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<tr>
<td>MICE</td>
<td>Multiple Imputation Chained Equations</td>
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<tr>
<td>MOOSE</td>
<td>Meta-analyses and Systematic Review of Observational Studies</td>
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<tr>
<td>NACR</td>
<td>National Audit of Cardiac Rehabilitation</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>ONS</td>
<td>Office of National Statistics</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
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<td>PHQ</td>
<td>Patient Health Questionnaire</td>
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<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic reviews and Meta-Analysis</td>
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<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>STEMI</td>
<td>ST-Segment Elevation Myocardial Infarction</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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References


