Determinants of cardiac rehabilitation engagement, uptake and adherence in the percutaneous coronary intervention patients

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Abstract

Purpose: Despite the proven benefits of cardiac rehabilitation (CR) it remains underutilised in the percutaneous coronary intervention (PCI) cohort in many healthcare systems. The objective of this thesis is to contribute to the growing area of CR research by systematically reviewing CR utilisation determinants in the literature then validate those determinants against routinely collected clinical data.

Methods: A systematic review was conducted to identify CR utilisation determinants in the literature. Data from the UK National Audit of Cardiac Rehabilitation (NACR) for patients who underwent PCI in 2013 to 2016 was retrieved. Three hierarchical logistic regression models were constructed, using multiple imputation as appropriate, to assess the impact of the identified determinants on CR engagement, uptake and adherence. To account for mode of CR delivery on adherence rates, an online survey was administered to 296 CR programmes across the UK.

Results: During the study period, a total of 149,597 cardiac events were recorded in the NACR dataset. Out of this cohort 70,303 (47%) patients underwent a PCI procedure and a total of 59,807 PCI patients were eligible to receive CR. From the CR eligible cohort, 38,246 (63.9%) patients engaged in CR then 28,263 (73.9%) started and finally 22,173 (78.5%) patients completed the programme. The constructed logistic regression models revealed 19 determinants of CR engagement, 23 determinants of CR uptake and 13 determinants of CR adherence. A total of 167 programmes (56.4%) responded to the survey and the results showed that 104 (62.3%) programmes are delivering CR in group- and home based settings while 61 programmes deliver CR in group-based setting only. The Pearson Chi-square test revealed no significant association between mode of CR delivery and adherence rate ($p = 0.53$, OR: 0.93, 95% CI: 0.87 to 1.01).

Conclusion: This thesis revealed that current CR programmes are not attractive to those who are most deprived, diabetic and smokers. The research has also shown that CR utilisation is not a single patient decision but is also related to service level factors, over which healthcare systems have more direct control.

Table of Contents

List of Tables

List of Figures

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Author's Declaration

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

- **Publications arising from this thesis**

1. Al Quait, A. et al., 2017. In the modern era of percutaneous coronary intervention: Is cardiac rehabilitation engagement purely a patient or a service level decision? European Journal of Preventive Cardiology, p.204748731771706. Available at: http://journals.sagepub.com/doi/10.1177/2047487317717064.
2. Al Quait, A. & Doherty, P., 2017. 5972 Impact of age and gender on cardiac rehabilitation uptake in percutaneous coronary intervention patients. European Heart Journal, 38(suppl_1). Available at: http://academic.oup.com/eurheartj/article/doi/10.1093/eurheartj/ehx493.5972/4086392/5972Impact-of-age-and-gender-on-cardiac.
3. Al Quait, A. & Doherty, P., 2017. Overview of cardiac rehabilitation evidence, benefits and utilisation. Global Journal of Health Sciences, 9(12), p.38. Available at: http://www.ccsenet.org/journal/index.php/gjhs/article/view/72537.
4. Abdulrahman Al Quait, Jassas Alotaibi, Patrick Doherty. Determinants of cardiac rehabilitation engagement, uptake and adherence. PROSPERO 2017 CRD42017075214 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017075214

1 Introduction

1.1 Background

Percutaneous coronary intervention (PCI) has developed significantly since its introduction in 1977 and nowadays represents the first choice of treatment for acute coronary syndrome (ACS). Underpinning the success of PCI procedures is an improved rate of survival and more attention is being paid towards reducing the risk of recurrent events and improving patients' quality of life. Extensive research has shown that a comprehensive cardiac rehabilitation (CR) programmes reduce mortality, hospital readmission and improve quality of life (Anderson et al. 2016). Accordingly, enrolment into CR programmes following a cardiovascular event is a Class 1 level A recommendation of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology (Ruano-Ravina et al. 2016).

Despite the proven benefits of CR it remains underutilised in many healthcare systems, however, with major inequities in access for certain patient groups such as the elderly and female patients (Sumner et al. 2016). Furthermore, it has previously been observed that utilisation rates are lower than expected in patients undergoing percutaneous coronary interventions (PCI) in most European countries (< 30%) (Humphrey et al. 2014). In the literature, the term 'CR utilisation' tends to refer to the measure of the eligible CR patients' use of rehabilitation services available to them. Throughout this thesis, the term 'CR utilisation' is deployed to refer to the use of core CR services (Figure 1.4) available to eligible patients from the first point of contact at baseline assessment (CR engagement) to starting (CR uptake) through to completion of this phase by conducting final CR assessment (CR adherence).

The aim of this PhD thesis is to review the existing literature critically and thus to identify the factors that determine optimal CR utilisation in the eligible PCI population. The thesis will also assess the extent to which these factors identified in the literature are applicable to the CR population in England by conducting a retrospective secondary analysis of the British Heart Foundation (BHF) National Audit of Cardiac Rehabilitation (NACR) dataset. Understanding these factors and validating them against routinely collected clinical data

should make an important contribution to our understanding of the relatively low CR utilisation rates in this cohort despite its known benefits.

Specifically, the research seeks to investigate the factors that are associated with patients attending an initial CR baseline assessment (CR engagement), starting CR by at least attending one outpatient session and then successfully completing the outpatient CR programme. The primary question of the thesis is therefore: 'what are the factors that determine CR engagement, uptake and adherence in the PCI population?' where engagement is defined here as attending the initial CR baseline assessment session.

The overall structure of this thesis takes the form of eight chapters. The second chapter of the thesis is concerned with an overall systematic literature review of CR utilisation while the third chapter will give a clear and detailed explanation of the methodology used in this thesis. Next, three themed chapters will evaluate and discuss CR engagement, uptake and adherence separately. These three chapters will be followed by a synthesis chapter which will try to promote a more unified understanding of the low CR utilisation rates. The final chapter will conclude the findings of the research, focusing on the implications of those findings and how they might be explored further in future studies.

The rest of this introductory chapter will provide a framework for the thesis by giving an overview of the key topics discussed in the thesis such as coronary artery disease, its prevalence and how it is treated. The evidence for and history of CR, how it is conducted in the UK, and the guidelines that apply to its use will also be discussed. The aim, therefore, is that, by the end of this chapter, the reader will appreciate why the PCI population was specifically selected and how improving the utilisation of CR will lead towards better patient care, improved cost effectiveness and enhanced patient satisfaction in this growing PCI population.

1.2 Coronary artery disease (CAD)

Cardiovascular diseases (CVD) are the leading cause of premature death in the world. In 2012, an estimated 17.5 million people died from cardiovascular diseases, representing 31% of all global deaths. Out of these, 7.4 million were due to Coronary Artery Disease (CAD)

(WHO 2015). While CVD is an overarching term that includes all diseases of the human body arteries, CAD is a condition specifically affecting the coronary arteries that supply the heart with blood and oxygen. The primary cause of CAD is a progressive aggregation of plaque in the coronary arteries, a process called atherosclerosis (Goff et al. 2014).

Coronary Heart Disease (CHD) is a common term for the build-up of plaque in the coronary arteries, which could eventually lead to a heart attack. Often, CHD and CAD are used interchangeably in medicine; however, CHD is actually a result of CAD. Another term sometimes confused with CAD is Acute Coronary Syndrome (ACS). Strictly speaking, ACS is a sub-category of CAD. CAD can be either symptomatic or asymptomatic, but ACS is almost always represented by a symptom, such as chest pain (Sanchis-Gomar et al. 2016).

1.3 Myocardial infarction (MI)

Myocardial Infarction (MI) or Acute Myocardial Infarction (AMI), commonly known as a heart attack, is one of the most dramatic presentations of CAD (NICE 2013). When a progressive aggregation of plaque in the coronary arteries results in a decreased delivery of oxygen and nutrients to the myocardium of the heart, accompanied by (or sometimes without) increased myocardial metabolic demand, damage to the heart muscle occurs (ischemia) (Bolooki & Askari 2010).

The first working group to define MI was convened by the World Health Organisation (WHO) in 1959 in order to study disease prevalence (Thygesen & Searle 2013). The first WHO definition was based on electrocardiogram (ECG) findings and patient symptoms. Later definitions published by WHO defined MI as a combination of two of three characteristics: chest pain, a rise in cardiac enzymes - such as the protein troponin - and a typical ECG pattern involving the prominence of Q waves. The diagnosis of MI was therefore still mainly ECG based (Ago & Realized 1979).

Recent developments in medical technology have heightened the need for a more precise definition of MI. The Joint Working Group of the European Society of Cardiology (ESC) and the American College of Cardiology Foundation (ACCF) published its first consensus document for the redefinition of MI in the year 2000. This placed more emphasis on a

diagnostic combination of a biochemical approach relying on cardiac biomarkers and a prospective approach considering ST changes in the ECG rather than Q waves. With this definition the phrase ST Elevation MI (STEMI) was born (Alpert et al. 2000).

The ESC and ACCF working group was joined by the American Heart Association (AHA) and the World Health Federation (WHF) to form a global task force to describe MI (Thygesen & Searle 2013). The updated universal definition of MI was presented in the ESC conference in Munich 2012 and simultaneously published in five medical journals. The major changes in this updated version include the differentiation between myocardial ischemia and myocardial injury. Another important change was the revised criteria for the diagnosis of acute myocardial ischemia related to PCI and coronary arterial bypass grafting (CABG) (Thygesen et al. 2012).

1.4 Prevalence of CAD

Although the huge increase in the number of people accessing cardiology services can be looked at as a demonstration of success of modern cardiology services, equally it can be also looked at as a sign of failing at prevention. In 2014, there were nearly seven times as many CVD prescriptions dispensed in England as there were in 1981. In the UK, it is estimated that nearly 2.29 million people are currently living with CAD, around 9.25 million with hypertension, 493,000 with heart failure and 1.06 million with atrial fibrillation (Bhatnagar et al. 2015). Around 146,000 heart attacks occur each year. This translates to someone in the UK having a heart attack roughly every three minutes (Townsend et al. 2015).

In Europe, CVD is the most common cause of death, making up 45% of all deaths, equating to more than 4 million deaths per year in total. Of these, the largest proportion of deaths are attributed to CAD: 19% of deaths in men and 20% of deaths in women (Nichols et al. 2014). In the United States, CAD is also the most common type of heart disease, and is associated with the deaths of over 370,000 people annually. Every year about 735,000 Americans have a heart attack. Of these, 525,000 suffer a first heart attack and 210,000 occur in people who have already had a heart attack (Mozaffarian et al. 2015). The image worldwide is no brighter, the World Health Organisation (WHO) estimates that 7.4 million people died from

CAD in 2012 with over three quarters of those deaths taking place in low- and middle-income countries (WHO 2015).

1.5 Challenges in modern cardiology

The growth of demand for cardiology services and the rapid advances in modern cardiology have resulted in two main challenges: coping with the escalating costs of treatment and the associated increased pressure on hospital resources, which leads to limitations in bed capacity.

1.5.1 Cost

Cardiovascular diseases are the most costly contributor to national healthcare expenditure. The Centre for Economics and Business Research (CEBR) launched research in August 2014 looking at the costs of CVD in six major European markets (France, Germany, Spain, Italy, Sweden and the United Kingdom). These markets account for 74% of the European Union's Gross domestic product (GDP) and 64% of its population. Across these six countries, the total financial impact of CVD, including direct and indirect costs, is estimated to be €102.1 billion in 2014. By the end of the decade this is set to rise to €122.6 billion (Figure 1.1) (CEBR 2014).

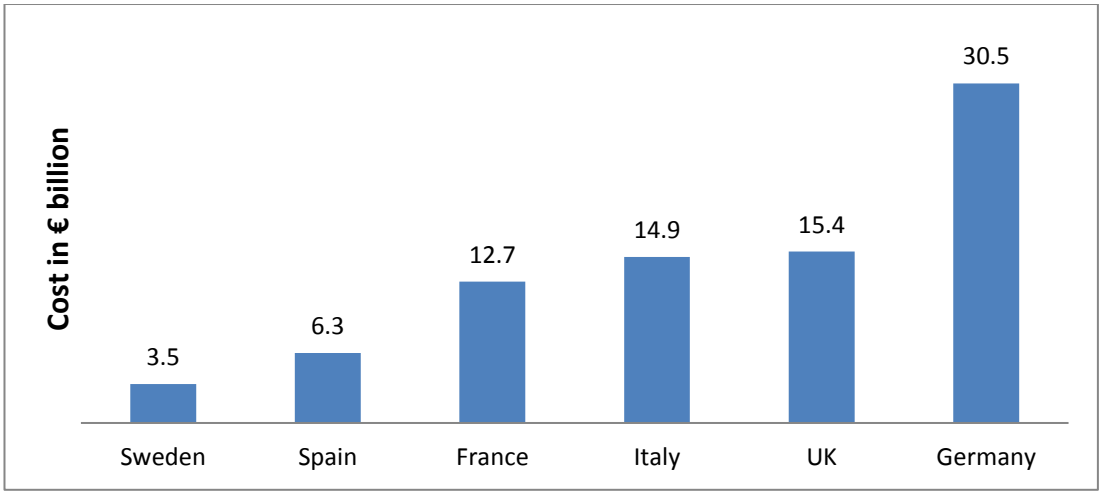


Figure 1.1 Estimated total cost from CVD in 2014[1].

[1] Chart courtesy of the Centre for Economics and Business Research (CEBR) 2015.

In 2014, the UK faced a total cost of €15.4 billion from CVD (Figure 1.1), equivalent to 1.4% of GDP. The largest component of this (€11.4 billion) was the direct cost of healthcare provision. Indirect costs also contribute substantially to the overall economic burden, however: €3.9 billion from productivity lost as a result of premature mortality and €0.1 billion from productivity lost as a result of morbidity. In 2020 the total cost of CVD is expected to increase by another €3.7 billion to reach €19.1 billion (CEBR 2014). The situation in the United States is similar: the overall spending on cardiovascular diseases has grown at a compound annual growth rate of 5.7% since 1996 (Miller et al. 2011).

This increase in cost can be associated with major breakthroughs in the way CVD is treated with more people than ever surviving heart attacks. Moreover, the life expectancy of other patient groups, such as those with heart failure and babies with congenital heart conditions, has also increased, and since these patient groups require medical attention throughout their lives their treatment has significant cost implications (Piepoli et al. 2015).

1.5.2 Capacity

Matching capacity and demand has always been a challenge in cardiology. The main challenge is to have a hospital bed available when a patient needs it. Although this challenge is applicable in all healthcare specialities, it is more vital in cardiology as early administration of medical interventions improves the patient's chances of survival. Timing plays a vital role in situations where primary PCI is required since this form of revascularisation therapy should be done as soon as possible. This is because heart muscle starts to infarct once the coronary artery is blocked and the sooner it is revascularised the better the outcome for the patient. Primary PCI offers significantly better clinical outcomes for patients in that mortality is reduced by one-third, re-infarction by half, and stroke by two-thirds compared to in-hospital thrombolysis (Hartwell et al. 2005).

A demonstration of the success of PCI procedures is the huge increase in the number of patients accessing the service. In 1991, about 10,000 PCI procedures were performed in the UK, whereas by 2014 this had increased to 96,143 procedures, of which 25,276 (26.3%) were primary PCIs. On the other hand, the number of CABG procedures remained almost stable with 16,700 surgeries performed in 1991 and 17,513 surgeries in 2014 (Figure 1.2) (BCIS 2014). As medical technology improves, the duration of a PCI procedure is also

becoming shorter which enables an increased number of patients to access the service every day. This, however, increases the demand on hospital beds in departments such as cardiac wards, intensive care units and the emergency department.

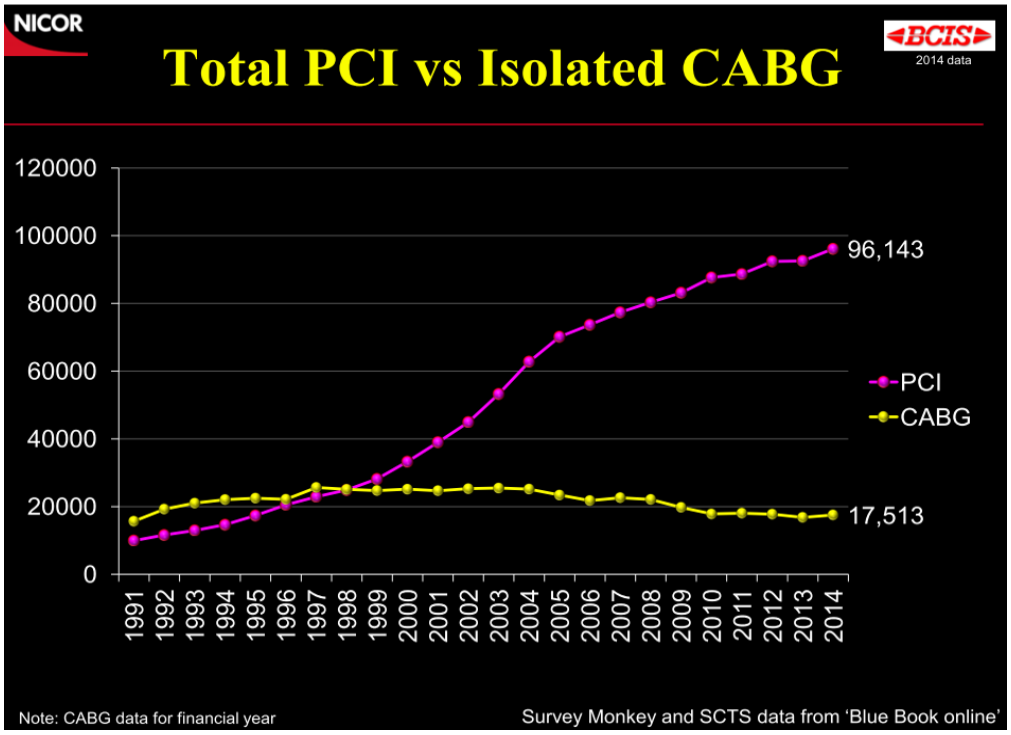


Figure 1.2 Total PCI vs Isolated CABG procedures as presented by BCIS[2].

1.6 Treatment of CAD

Although CAD cannot be completely cured, treatment can help to manage the symptoms and reduce the risk of further complications. CAD can be managed effectively through a combination of lifestyle changes, medication and (in some cases) a coronary revascularisation procedure. With the right treatment, the symptoms of CAD can be significantly reduced and the heart muscle function improved (Windecker et al. 2014).

1.6.1 Medical treatment

Many different medicines are used to treat CAD and these can be classified according to what they treat. According to the National Institute for Health and Care Excellence (NICE) guidelines, all patients who have had MI should be offered four types of drug: antiplatelet

[2] Chart courtesy of British Cardiovascular Intervention Society (BCIS) 2014.

agents, statins, beta-blockers and Angiotensin-Converting Enzyme (ACE) inhibitors (NICE 2015).

Antiplatelet agents are used to reduce the risk of blood clot formation, since blood clots would likely result in a heart attack. Antiplatelet medicines are usually given in the form of dual therapy (aspirin plus a second antiplatelet agent), but if the patient has high levels of cholesterol a cholesterol-lowering medicine called a statin may also be prescribed (NICE 2013).

Beta-blockers are among the most important drugs used by cardiologists nowadays. They work mainly by blocking the action of hormones like adrenaline, which in turn reduces the heart activity. They are used after a heart attack to treat ongoing conditions including angina, heart failure and some heart rhythm disorders (Timmis 2015).

ACE inhibitors are commonly used to treat high blood pressure and function by blocking the activity of a hormone called angiotensin II, which causes the blood vessels to narrow (Whitehurst et al. 2006).

1.6.2 Revascularisation procedures

Revascularisation is the restoration of blood flow to an organ. In medicine, revascularisation is defined as "the restoration of perfusion to a body part or organ that has suffered ischemia" (Oxford Dictionary 2014). The two main methods of revascularisation are Coronary Artery Bypass Grafts (CABG) and Percutaneous Coronary Intervention (PCI).

CABG is a surgical procedure that may take between three and six hours under general anaesthesia. The surgeon starts by removing a healthy vein(s) and/or an artery from another part of the patient's body (usually the leg). Traditionally, the surgeon will cut the patient's chest in half through the breastbone (sternum) then retract the rib cage in order to expose the heart. When the heart is exposed, the blood is diverted around narrowed or clogged parts of the coronary artery by connecting (or grafting) the healthy artery or vein to bypass the blocked portion. During surgery, the heart beat is stopped so the surgeon can perform the bypass procedure on a "still" heart. A machine called a "cardiopulmonary bypass pump" takes over for the heart and lungs during the procedure. Surgeons usually bypass multiple

coronary arteries during one surgery. Recently, a novel CABG procedure aiming to decrease the invasiveness of traditional CABG while preserving equivalent outcomes has been developed (Javaid et al. 2007). Minimally invasive CABG (MICS CABG) is a surgical procedure that allows the surgeon to perform revascularisation off-pump, without a sternotomy and through small incisions, equivalent to that of a regular CABG (Lapierre et al. 2006).

PCI, or coronary angioplasty, is a non-surgical, less invasive procedure, where a long, flexible hollow plastic tube called a catheter is inserted into a blood vessel through a tiny incision in the patient's arm or groin. A micro balloon attached to the catheter is then inflated to widen the artery and a small mesh tube called a stent is often used to help keep the artery open. A PCI procedure is usually less than one hour long and it requires much less recovery time for the patient compared to CABG. PCI may not be recommended, however, if multiple coronary arteries have become blocked or narrowed.

The first CABG procedure was performed in 1964, and the first PCI thirteen years later by a German radiologist, Andreas Gruentzig, in Switzerland (Windecker et al. 2014). Since then, the field of cardiology has made great strides in improving both the longevity and the quality of life of patients. There has been substantial progress in the understanding of cardiovascular pathophysiology, as well as in the application of these advances to clinical cardiology. Concurrent improvements in medical technology have led to exciting developments in the field of invasive and non-invasive cardiology.

PCI has developed significantly since its introduction in 1977, and has now overtaken CABG as the dominant revascularization treatment for CAD (Astin et al. 2008). PCI is the first choice for coronary reperfusion during acute MI, with thrombus aspiration and stenting of the culprit lesion, and is also widely regarded as the treatment of choice for coronary revascularisation in cases of acute coronary syndrome and stable angina, or silent ischemia (Varenne & Hemery 2008).

The growth in popularity of PCI is due to the speed of the procedure, patient preference over CABG and increasing patient populations, including patients with multi-vessel coronary artery disease, acute MI or cardiogenic shock, and elderly patients. Success rates and

complications for PCI have remained stable or even improved, despite the expanding indications and the persistent problem of restenosis (i.e. renewed narrowing of an already treated artery (Windecker et al. 2014).

1.6.3 Prevention

There is a general consensus in the medical literature that many incidents of cardiovascular disease can be avoided or at least delayed. Prevention and control in cardiovascular care can be classified into two main types depending on the targeted population:

1. Primary prevention (general public).
2. Secondary prevention (CVD patients).

Primary prevention aims to delay or prevent the onset of CVD. The potential advantages of primary prevention strategies in cardiovascular care have been tested in large prospective cohort studies. For example, Stampfer and colleagues assessed the combination of lifestyle practices on the risk of CHD by following 84,129 women (age 30 – 55 years) for 14 years. The primary objective of their study was to estimate the proportion of coronary events that could potentially be prevented by adherence to a set of dietary and behavioural guidelines. All women were free of diagnosed CVD, cancer and diabetes at baseline. The population was then defined into low risk and high risk subjects. The low risk subjects were those women who maintained a healthy weight and diet, exercised routinely and did not smoke tobacco for the follow-up period. The low risk population experienced an 83% decrease in the incidents of coronary events compared to the high risk group indicating that primary prevention is very effective (Stampfer et al. 2000).

The evidence that most cardiovascular disease is preventable continues to grow, driving major cardiac bodies and associations, such as the American Heart Association (AHA) and the European Society of Cardiology (ESC), to publish periodical guidelines for primary prevention. WHO estimates that the risk of CAD increases two- to threefold for an individual who smokes tobacco. In contrast, the number of cardiac events reduce by 50% in people who stop smoking, and the risk of CAD, including MI, also decreases significantly

over the first two years after quitting smoking (WHO 2011). Collectively, many cardiovascular diseases can be reduced by making simple lifestyle changes.

With respect to secondary prevention, many evidence-based studies and randomised control trials have shown that the majority of known risk factors contributing towards cardiovascular disease progression are modifiable by preventive measures including therapeutic lifestyle changes and adjunctive drug therapies of proven benefit (Windecker et al. 2014). In the AHA guidelines it was stated that:

"Indeed, the growing body of evidence confirms that in patients with atherosclerotic vascular disease, comprehensive risk factor management reduces risk as assessed by a variety of outcomes, including improved survival, reduced recurrent events, the need for revascularization procedures and improved quality of life" (Goff et al. 2014).

Other lifestyle changes that will reduce the risk of CAD progression include healthy eating, being more physically active, lowering blood pressure and cholesterol levels, controlling diabetes, reducing alcohol consumption and maintaining a healthy weight. The sum of all these activities is commonly known in cardiovascular care as "cardiac rehabilitation".

1.7 Cardiac rehabilitation (CR)

In medicine, while saving a patient's life is clearly vital, it is also important to attempt to help patients recover a good quality of life. Experiencing a heart attack or a hospital admission following a cardiac event can be very stressful and patients who suffer such a dramatic event will definitely need support to live with their developing heart condition. In particular, they will benefit from lifestyle change interventions to stay as healthy as possible and therefore reduce the risk of suffering another event. Knowing that CAD is a long term and progressive condition, the concept of rehabilitation in cardiac care is that the recipients gain the knowledge, skills and support necessary to live as normal a life as possible alongside their cardiac condition.

CR has been defined by various organisations and national entities and can be encompassed by:

"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).

Traditionally, exercise training is known as the core component of CR. Current practices guidelines, however, push towards "comprehensive rehabilitation" and thus CR's regulating bodies drive programmes to add other components to optimise the reduction of risk factors and improve adherence to healthy behaviours among recipients. Those additional components include health education, advice on the reduction of cardiac risk factors and stress management.

1.7.1 Historical background to CR

For centuries, bed rest was considered essential in the treatment of a disease, and mobility restrictions were imposed on most patients, and particularly patients with heart disease. This practice was not challenged until 1802 when Heberden reported the observation of an angina patient who improved after sawing wood for half an hour a day (Didier et al. 2010). Despite some evidence of the benefits of physical activity for heart patients, the misguided focus on bed rest persisted until chair therapy was introduced in the 1940s. A few years later, daily short walks of 3 to 5 minutes were allowed four weeks after the coronary event (Mampuya 2012). Since then advances in clinical research have led to better ways of understanding heart disease management.

The early evidence of the benefits of physical activity started in 1953 when a study conducted by Morris and Heady showed that CHD was at least one third higher in light occupation workers (bus drivers) compared to heavy occupation workers, in this case bus conductors (Morris & Heady 1953). Albeit being a very important study, the decrease in CHD incidents was erroneously attributed to the extra physical activity performed by heavy occupation workers. Subsequent analysis of anthropometric data, from the London Bus

Company tailors, revealed that many of the bus conductors where lighter in body weight compared to bus drivers on commencing their jobs with the company. In 1966, Saltin and co-workers conducted a study on five men, each 20 years of age, to compare the effects of three weeks of bed rest and eight weeks of intense physical exercise on the subjects' physical condition. Regardless of its small sample size, this study, which was known as the 'Dallas Bed Rest and Training Study', enriched the early discussions and analyses of the positive impact of exercise and the detrimental effects of bed rest on subjects' physical condition (McGavock et al. 2009).

In the late 1970s, the concept of prescribing exercise therapy for post-MI patients began to gain momentum as it became increasingly clear that immobilisation and reduced activity results in poor long-term prognosis and survival (Lear & Ignaszewski 2001). The establishment of the benefits of exercise therapy on patients' prognosis led to a surge of interest in the effects of exercise therapy on morbidity and mortality rates which then revealed undeniable improvements. Since that time a large and growing body of literature has emerged to establish the physiologic basis of the benefits of exercise and this has led to the development of CR programmes.

Nowadays, CR is a complex intervention that has eventually evolved from the emphasis on exercise therapy to become a comprehensive secondary prevention programme that provides patients with supervised exercise and education sessions to help them to recover and get back to as full a life as possible (Dalal et al. 2015). CR has been proven to be as much a part of CAD treatment as medicines are. Unfortunately, the proven benefits of CR are not matched by a strong endorsement of CR in the cardiology community. A possible reason behind this reticence can be the development of powerful drugs and new therapeutic technologies that have made it difficult for CR to compete in its own right. Particularly if a cardiologist is attracted to the immediate and short-term results of the conventional direct medical interventions (Mampuya 2012). Recent years, however, have seen increasingly rapid advances in the field of cardiology. These recent developments have led to a better understanding of heart disease management which is in turn reflected in a renewed interest in CR.

1.7.2 Modern CR

Historically, the main objective of CR as an exercise-based programme was to improve patients' regular physical activity after a cardiac event (Mampuya 2012). Since CR has evolved into a comprehensive secondary prevention programme, the objectives of CR, and indications and contraindications for its use have also developed in sophistication. Current CR programmes are designed to stabilise or even reverse the progression of heart disease by controlling all modifiable risk factors (Dalal et al. 2015). They are also concerned with improving patients' quality of life by restoring their wellbeing. All this should be achieved with the maximum safety levels to patients.

1.7.2.1 Objectives of CR

The main objective of CR continues to be helping recipients to regain their autonomy by improving regular physical activity after a cardiac event. Controlling the modifiable risk factors and therefore reducing the negative effects of CAD is another objective of CR. The term risk factor is defined by WHO as:

"*any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury"* (WHO 2014).

Obviously, the more risk factors a patient has for a specific disease, the greater the chance they have of acquiring that disease. In cardiology, there are modifiable risk factors (those that can be controlled) and unmodifiable risk factors (which cannot be changed). Unmodifiable risk factors for CAD include age, gender, ethnicity and family history. Although unmodifiable risk factors cannot be changed, making changes to patients' lifestyles can significantly reduce the risk of acquiring CAD prematurely. Other characteristics that may lead to an increased chance of acquiring CAD include social, economic and cultural change (e.g. urbanisation). Stress and poverty are also other determinants of an increased chance of getting CAD (WHO 2014). These characteristics and determinants are not direct causes of CAD but can be looked at as "the causes of the causes". Modifiable risk factors that may have an adverse impact on the prognosis of CAD include: hypertension, hypercholesterolemia, diabetes, sedentary lifestyle, obesity and smoking (Montalescot et al. 2013). Curing or at least controlling these factors can significantly reduce the progression of CAD disease.

A comprehensive CR programme should also educate recipients about their conditions so as to allow them to become responsible for their medical treatment and lifestyle changes and therefore achieve optimal outcomes (Dalal et al. 2015). These education sessions should be delivered in a structured workshop-based teaching programme and by a skilled and experienced multidisciplinary team such as dietitians, psychologists, exercise specialists, etc. (BACPR 2017). Anxiety and depression, for example, have been reported to be associated with lower exercise capacity, fatigue and sense of wellbeing. The use of a skilled and experienced psychiatrist to educate recipients about stress management and self-control tools can help recipients to have a better control of other risk factors (Sign 150 2017).

Lastly, CR programmes should aim to limit the physiological and psychological effects of heart disease by controlling disease symptoms and the side effects of medications. This should have a favourable impact on patients' quality of life, making the benefits of CR more tangible to recipients and therefore encouraging them to complete the programme, foster healthy behaviours and thus achieve optimal outcomes (Dalal et al. 2015).

1.7.2.2 Indications of CR

The literature on CR has highlighted several patient groups that should benefit from joining a CR programme. Generally accepted indications for CR include: MI, CABG, PCI, valve repair or replacement and angina. The recent trends in CR which encourage programme commissioners to tailor special programmes for special patient groups have widened the scope of CR to include patients with heart failure and heart transplants. Different countries allocate different resources into CR, however, and therefore the indications for CR may vary between countries. In the UK, the National Institute for Health and Care Excellence (NICE), Department of Health, British Association for Cardiovascular Prevention and Rehabilitation (BACPR), and wider European guidelines agree that the patient groups listed in (Table 1.1) will benefit from a CR programme (Dalal et al. 2015).

Table 1.1 Patient groups who benefit from CR.[3]

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

1.7.2.3 Contraindications & safety

Contraindications for the use of CR are only concerned with the exercise aspect of the programme while all other parts of CR are considered relatively safe. Since the exercise in a CR programme is medically prescribed and supervised, the risks of CR are considered to be low, and most patients referred to CR are eligible to participate in the programme. Furthermore, the capacity of CR providers to tailor their programme to suite the medical needs of individual patients has reduced the contraindicated patient groups even further. Nonetheless, medically unstable or life threatening conditions are examples of patients who are not eligible to enrol in a CR programme (Thomas et al. 2010).

The literature on CR has highlighted a number of studies that have documented the safety of exercise in a CR programme. In 2007, the AHA issued a statement to discuss the potential complications of exercise in a CR programme. This statement has estimated the incidence of exercise-related cardiovascular complications in CHD patients as one cardiac arrest per 116,906 patient-hours of supervised exercise, one MI per 219,970 patient-hours of

[3] Modified from (Dalal et al. 2015).

supervised exercise, one death per 752,365 patient-hours of supervised exercise and one major complication per 81,670 patient-hours of supervised exercise (Thompson et al. 2007).

Another observational study from a French registry with a population of 25,000 patients has reported one cardiac incident per 50,000 hours of supervised exercise. This is equivalent to 1.3 cardiac arrests per million patient-hours (Pavy et al. 2006). A qualitative Japanese study surveyed 136 hospitals operating core phase CR amounting to 383,096 patient-hours of supervised exercise. The incident rate of all adverse events was 12 per 383,096 patient-hours while life-threatening events (death, cardiac arrest, AMI and cardiac rupture) occurred at the rate of one per 383,096 patient-hours of supervised exercise. This is equivalent to 3.13 and 0.26 events per 100,000 patient-hours of supervised exercise respectively (Saito et al. 2014).

Taken together, these results suggest that supervised exercise in a CR programme is generally safe. These findings can only be extended to CR programmes that are equipped to handle major emergency events such as cardiac arrest. In addition, it should be noted that subjects in the above studies are medically evaluated before enrolling in the programme which could decrease the number of incident rates. In general, all these considerations support safety in supervised exercise programmes but they should not be extrapolated to home based programmes.

1.7.3 CR Benefits

The benefits of CR for the indicated patient groups have been reviewed comprehensively in several systematic reviews and meta-analyses including seven Cochrane reviews. These benefits are the result of all components of a comprehensive multi-disciplinary CR programme. In this section, the benefits of a comprehensive CR programme will be assessed with brief supporting evidence from the literature.

1.7.3.1 Mortality

A 2016 Cochrane review and meta-analysis of 63 randomised control trials (RCT) with 14,486 participants with a median follow-up of 12 months showed that CR has a varied effect on mortality. In this review 47 trials with a total sample size of 12,455 subjects reported all-cause mortality. Reduction in all-cause mortality between control and intervention groups was not statistically significant in these studies (relative risk (RR): 0.96;

95% confidence interval (CI): 0.88 to 1.04). On the other hand, 27 trials (n = 7,469) reported cardiovascular mortality and showed a statistically significant reduction of cardiovascular mortality (RR: 0.74; 95% CI: 0.64 to 0.86). Twenty studies in this review reported both types of mortality and results in this sub-group were consistent with the overall meta-analysis results (all-cause mortality RR: 0.91, 95% CI: 0.82 to 1.01; cardiovascular mortality RR: 0.78, 95% CI: 0.67 to 0.90) (Anderson et al. 2016).

Another systematic review and meta-analysis of 34 RCT's with a total pooled population of 6,111 subjects has revealed a reduction in all-cause mortality for CR patients compared to control groups by 26% (odds ratio (OR): 0.74, 95% CI: 0.58 to 0.95). It also showed a reduction in cardiovascular mortality by 36% (OR: 0.64, 95% CI: 0.46-0.88) (Lawler et al. 2011). Conversely, a UK based trial titled 'Rehabilitation after myocardial infarction trial (RAMIT)' reported no significant difference in mortality between patients referred to rehabilitation and controls at two years follow up period (RR: 0.98, 95% CI: 0.74 to 1.30) or after 7–9 years (RR: 0.99, 95% CI: 0.85 to 1.15) (West et al. 2012). The negative findings of this trial can be attributed to the biased study design and failure to recruit a large enough sample size for the trial (< 1000 patient in each arm of trial). In fact, RAMIT was designed to measure the effectiveness of CR as provided in 'real life' rather than if CR 'works' (Doherty & Lewin 2012).

This section has attempted to provide a brief summary of the literature relating to the impact of CR on all-cause mortality and cardiovascular mortality. In general, it seems that enrolling in a CR programme can impact rates of mortality favourably. The inconsistency in the literature may be due to several reasons related to the included studies such as study periods, duration of CR, and intensity of CR or whether CR was delivered effectively.

1.7.3.2 Hospital admissions

To date, the latest Cochrane systematic review has shown that the risk of hospital admission was reduced by 18% when comparing exercised-based CR with usual care (RR: 0.82; 95% CI: 0.70 to 0.96) (Anderson et al. 2016). This data is based on 15 RCTs with a population size of 3,030 patients. Another systematic review aiming to update a previously published Cochrane systematic review of exercise-based CR for heart failure patients, measured hospital admission as a CR outcome. This study systematically reviewed 33 trials with six or

more months of follow-up and included only patients with reduced ejection fraction (<40%) and New York Heart Association class II and III (n= 4,740). The findings revealed a reduced risk of overall hospital admission (RR: 0.75; 95% CI: 0.62 to 0.92) and heart failure-specific admission (RR: 0.61; 95% CI: 0.46 to 0.80) in patients who received comprehensive CR compared with no exercise controls (Sagar et al. 2015). A drawback of this study, however, was the inclusion of trials with relatively small sample sizes and short-term follow-up. This reflected on the number of hospital admissions reported by the majority of the included trials.

It has been previously discussed in this chapter (section 1.5) that the main two challenges in modern cardiology are cost and capacity. It can therefore be assumed that CR, by reducing the number of hospital admissions, is a significant tool in facing the challenges in modern cardiology. It can thus also be said that the outcomes of CR go beyond the benefits to individuals and encompass improvements to the whole cardiac care system.

1.7.3.3 Quality of life and psychological wellbeing

Two of the main objectives of a comprehensive CR programme are to improve the quality of life and the psychological state of the patient. Improvements in quality of life can be achieved through improvement in exercise performance (fitness) and through alleviation of symptoms, i.e. reducing chest pain, dyspnoea and fatigue (Mampuya 2012). A Cochrane review of exercise-based CR for CHD patients reported 20 trials, with a total population of 5,060 subjects, assessing Health Related Quality of Life (HRQL) using a variety of validated generic or disease-specific outcome measures. Fourteen of the 20 trials (65%) documented an increase in HRQL in one or more domains in patients subsequent to a CR programme compared to controls. Within these 14 trials, five reported a higher level of HRQL in at least one-half of the subscales (Anderson et al. 2016). The authors of the Cochrane review, however, expressed the HRQL scores as mean differences and were unable to quantify the effect of the 14 trials together due to the heterogeneity among the included studies.

This view is supported by another Cochrane systematic review that was conducted on heart failure patients. Sagar et al. (2015) reviewed a total of 18 trials which reported a validated HRQL measure. Thirteen of those 18 trials (72%) reported higher HRQL scores in patients following exercised-based CR programmes compared with control subjects (Sagar et al.

2015). This finding provides a valuable insight into the subject as all 13 trials used the same validated HRQL scoring measure, the disease-specific Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Another benefit of CR is to improve the psychological state of the patient by stress reduction and the enhancement of the overall sense of psychosocial wellbeing. A meta-analysis of 23 RCTs with a total population size of 3,180 CAD patients was conducted to evaluate the impact of including a psychosocial component within a standard exercise-based CR programme. Patients who received psychosocial intervention showed greater reductions in psychological distress (with effect size differences of 0.34) (Linden et al. 1996). An American observational study tried to assess improvements in depression in patients who developed heart failure due to CHD after receiving a comprehensive CR programme. Depressive symptoms were assessed at baseline and after CR by standard questionnaire (Kellner Symptom Questionnaire). In patients who completed CR (n= 151) depressive symptoms decreased by 40% post CR, from 22% to 13% ($p < 0.0001$). In addition, Depressed patients who completed CR had a 59% lower mortality (44% vs 18%, $p < 0.05$) compared to depressed dropout subjects (n= 38) (Milani et al. 2011). This study, however, suffers from the limited sample size, especially in the dropout subjects and also from using a questionnaire that is not well established for measuring depressive symptoms in clinical trials of depression.

Furthermore, two observational studies, one British (n= 465,825) and one American (n= 635), reported improvements in anxiety and depression after CR (Al Quait & Doherty 2016; Lavie & Milani 2006). Although the main objective of both studies was to compare levels of improvement in a range of outcomes between young and old patients, varied improvements in anxiety and depression were evident post CR in both groups with younger patients achieving better outcomes.

1.7.3.4 Cardiovascular risk profile

Modern CR programmes are designed to provide a reduction in the modifiable cardiovascular risk factors (see section 1.7.2.1). A systematic review and meta-analysis of 34 RCT's (n= 6,111) examined the effect of CR on modifiable risk factors. Overall, trials found a more favourable effect on the prevalence of risk factors among subjects who were

randomised to CR compared with controls. The risk factors in which improvements were observed in the intervention groups in these trials were smoking cessation, blood pressure and total cholesterol, whereas changes in body weight were minimal in both groups (Lawler et al. 2011).

Another systematic review and meta-analysis of 23 trials and a total population size of 3,180 (2,024 intervention subjects and 1,156 controls) CAD patients reported the impact of CR on selected modifiable risk factors. The findings revealed that patients who received CR showed a greater reduction in systolic blood pressure, heart rate and cholesterol level (with effect size differences of -0.24, -0.38, and -1.54, respectively) (Linden et al. 1996). These results must be interpreted with caution, however, since the effect of medical drugs such as statins and beta-blockers could not be excluded.

In a large cohort retrospective observational study (n= 465,825) Al Quait & Doherty conducted an evaluation of nine patient outcomes pre and post CR. The outcomes reported in this analysis were Body Mass Index (BMI), waist size, total cholesterol, blood pressure, smoking, walking fitness, physical activity, anxiety and depression. Although the primary objective of the study was to determine if CR outcomes were influenced by age in CHD patients, undeniable improvements were documented in modifiable risk factors in both groups. This analysis revealed that elderly patients achieved better outcomes in body shape risk factors while younger patients achieved much better outcomes across a wider range of risk factors, in particular with regards to smoking cessation (Al Quait & Doherty 2016).

1.8 CR in the UK

The availability of CR and how it is organised varies across countries. This is mainly to do with differences in health policies and politics since different countries allocate different resources into the healthcare system. Resource allocation is largely dependent on the income of each country, with high income countries generally investing more in healthcare services, and therefore CR, than low income countries (Grace et al. 2016). Worldwide, the availability of CR is low compared to the benefits it offers, as only 38% of countries globally have CR programmes. More specifically, 68% of those programmes are allocated in high income countries, 28.2% in middle income countries and only 8.3% in low income countries (Turk-

Adawi et al. 2013a). The provision, pathway and guidelines of CR can therefore be different across countries.

1.8.1 History of CR in the UK

The earliest attempt to promote CR in the UK goes back to the year 1970 when Groden and co-authors circulated a questionnaire to all active adult cardiologists of the British Cardiac Society to assess their attitude towards CR. With a 75% response rate, the survey revealed that 74.3% of cardiologists were in favour of developing special services for the rehabilitation of cardiac patients whereas 25.7% felt that such special services were not indicated (Groden et al. 1971). The same study, however, found just nine cardiologists were in a position to offer CR to their patients in a special CR centre. In 1989 the number of CR centres had risen to 99 and by the year 1992 the BHF could identify 151 centres (Bethell et al. 2000). This figure continues to rise and in the first NACR report in 2007, 360 UK programmes have been identified (NACR 2007).

Until the introduction of the first guidelines and audit standards in 1996, there had been no protocol for the provision of CR in the UK and there was no information on what most programmes did, nor who their subjects were (Bethell et al. 2000). Two years prior to the introduction of the first national guidelines, specifically in January 1994, Thompson and colleagues posted a survey to the senior nurse of 244 centres in England and Wales to determine the level of CR provision. With a 100% response rate the results showed that most programmes were based in hospitals (92%) and had been in operation for between three months and 17 years. Content-wise, 100% of the programmes were delivering education and supervised exercise sessions, 96% were delivering stress management sessions and 40% counselling (Thompson et al. 1996). In 1997, the BACPR, which was then known as BACR and had been established in 1993, embarked on a three stage questionnaire survey designed to evaluate the quality of CR provision in the UK, promote record keeping and to measure CR outcomes (Bethell et al. 2000). Since then, research into CR in the UK has evolved and significant funding has been attracted from sources including the BHF, the Department of Health and the Medical Research Council (Thompson 1998). This has resulted in placing the UK into the top countries in Europe in CR utilisation (NACR 2016).

In 2000, a target was set for England that, by 2002, 85% of MI, PCI and CABG patients should be invited to attend CR (NACR 2007). To ensure that this target is met and that all established guidelines are adhered to, the National Audit of Cardiac Rehabilitation (NACR) was formally established in 2005, led by Prof Bob Lewin, and the first national audit report was published in 2007. In 2013 the NACR, under Prof Doherty's leadership and supported by the BHF, took a significant step in transforming the audit into a service improvement and quality assurance system where the ultimate beneficiaries are CVD patients. Nowadays, the overall mean uptake to CR in the UK has achieved a significant milestone by reaching 50%. This improvement brings the UK into the top 2% of countries in Europe (NACR 2016).

1.8.2 Structure

Traditionally, CR in the UK has been delivered by clinicians in supervised groups of patients in outpatient hospital clinics or community centres (Dalal et al. 2015). NICE clinical guidelines advise the National Health Service (NHS) on caring for people with specific conditions, such as heart disease, and the treatment they should receive, while the BACPR is an association that represents CR professionals in the UK and is responsible for setting the standards by which clinicians work. The NACR, funded by BHF and hosted by the University of York, collects comprehensive audit data to support the improvement and monitoring of CR services in terms of their uptake, quality and clinical outcomes. The BACPR works in conjunction with the NACR to develop a certification system which ensures that CR programmes in the UK are meeting minimum standards. The structure of NACR in the UK is illustrated in Figure 1.3.

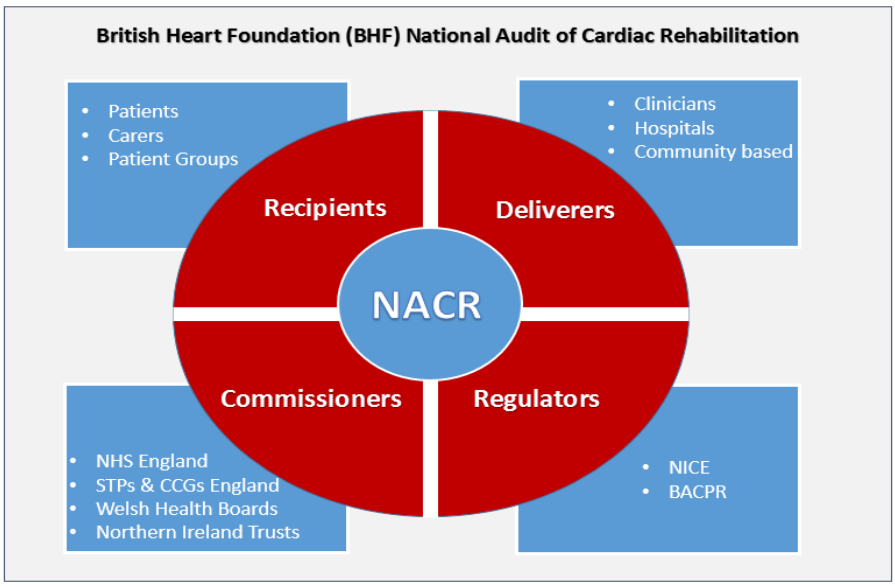


Figure 1.3 Structure of NACR in the UK.[4]

1.8.3 Pathway

Recent guidance from the UK Department of Health commissioning guide for CR refers to a six stage pathway of care that begins with patient presentation (diagnosis of a cardiac event) and is followed by identification for eligibility, referral and recruitment, baseline assessment and the development of a care plan, delivery of a comprehensive CR programme, the completion of a final CR assessment and then discharge and transition to long term management (Figure 1.4).

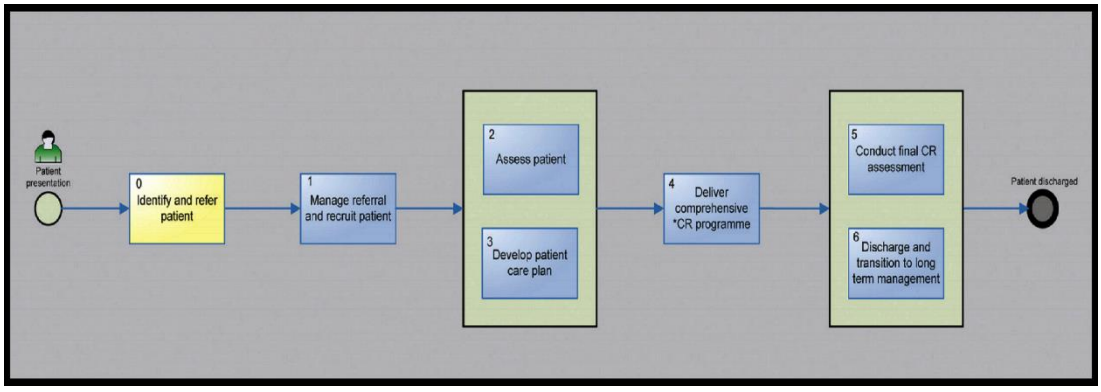


Figure 1.4 Department of Health Commissioning Guide Six-Stage CR Patient Pathway of Care.[5]

[4] Adapted version from the NACR website.
[5] Courtesy of BACPR 2017.

Each stage in this pathway is vital for CR uptake, adherence and outcomes and, overall, it should have an effect on long-term behavioural change leading to the desired health outcomes (BACPR 2017).

1.8.4 Standards

Formal CR programmes vary between countries in terms of their delivery, intensity and duration. All programmes, however, are seeking the presentation of evidence-based best practice to provide effective prevention and rehabilitation services to their recipients. As the association in charge of setting the standards by which CR clinicians work, BACPR continuously revises and updates CR standards in the UK.

In the updated third edition of the BACPR Standards and Core Components (2017), these standards and core components have been reduced from seven to six with the aim of this reduction being to increase the emphasis on measurable clinical outcomes, audit and certification (BACPR 2017). The six standards for cardiovascular prevention and rehabilitation as issued by BACPR are:

Standard One *The delivery of six core components by a qualified and competent multidisciplinary team, led by a clinical coordinator.*

Standard Two *Prompt identification, referral and recruitment of eligible patient populations.*

Standard Three *Early initial assessment of individual patient needs which informs the agreed personalised goals that are reviewed regularly.*

Standard Four *Early provision of a structured cardiovascular prevention and rehabilitation programme (CPRP), with a defined pathway of care, which meets the individual's goals and is aligned with patient preference and choice.*

Standard Five *Upon programme completion, a final assessment of individual patient needs and demonstration of sustainable health outcomes.*

Standard Six *Registration and submission of data to the National Audit for Cardiac Rehabilitation (NACR) and participation in the National Certification Programme (NCP_CR).* (BACPR 2017).

These revised standards and core components place health behaviour change and education at the very centre of CR programmes whilst placing equal emphasis on risk factor management and psychosocial health. Standard six, for instance, has been designed in order to ensure that CR programmes in the UK are meeting, or at least working towards, the minimum standards.

1.8.5 Utilisation

Existing research recognises the critical role played by CR in heart disease prevention. Despite the robust evidence of the clinical benefits and cost effectiveness of CR, utilisation rates vary widely worldwide, ranging from 20% to 50% (Dalal et al. 2015). Different healthcare policies and CR delivery systems among countries may explain, at least partially, this variability (Grace et al. 2016).

In the year 2000 England set a target that, by 2002, 85% of MI, PCI and CABG patients should be invited to attend CR. The first NACR report in 2007, however, revealed that this target was far from being met on the ground: of the 152,417 new eligible cardiac patients in the year April 2005 to March 2006, only 65,012 received CR, around 40% (NACR 2007). A few years later, the NHS England CVD strategy for 2015/16 set a target to increase CR uptake to 65% for patients admitted with CAD (NHS England Guideline 2014). The 2016 NACR report showed that the overall uptake of eligible patients in CR programs is only 50%, a 3% increase from 2015 and 5% increase from 2014 (NACR 2016). Although current CR utilisation rates in the UK fall below national recommendations, however, they still far exceed those seen in other European countries, with an overall mean of 30% (Humphrey et al. 2014). In fact, with a 51% average CR uptake in 2016, CR programmes in the UK are among the highest uptake figures globally (NACR 2017).

To date, however, little research has been conducted in regards to CR utilisation in the growing PCI population (see Figure 1.2) and it is not clear what factors influence this. Figure 1.5 illustrates CR utilisation rates in PCI patients for the past six years in the UK.

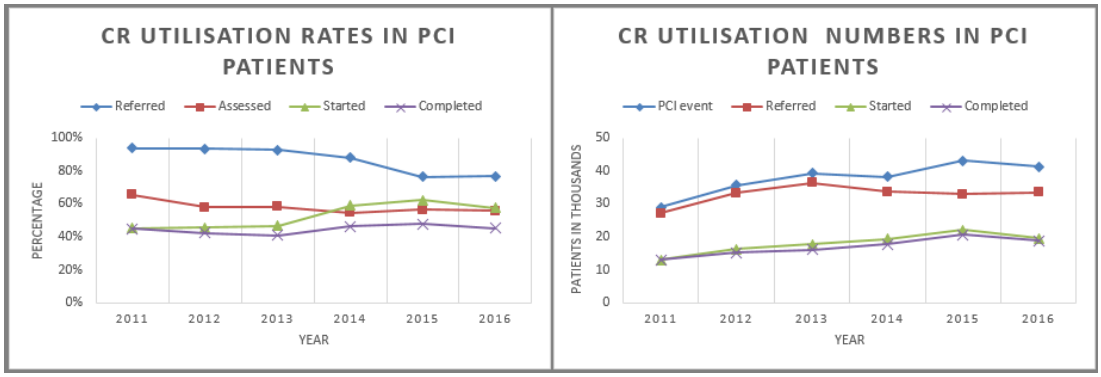


Figure 1.5 CR utilisation rates in PCI patients as measured by NACR.

The graph shows that there has been a gradual increase in the number of patients starting CR over the years although the number of referred patients dropped starting from the year 2013. Figure 1.5 also reveals that the number of PCI procedures has increased from around 28,000 in 2011 to more than 41,000 patients in 2016 (46%). It also shows that the gap between those starting and those completing the CR programme is getting wider, however, this might be attributed in part to the fact that the quality of data entry in the NACR portal has improved in recent years.

When CR utilisation rates are analysed in respect to the type of treatment received, more gaps can be seen. The NACR 2016 report has shown low uptake rates in patients following MI (39%) and elective PCI (45%) compared to the world-leading uptake rate in the CABG population (60%). This is of major concern when we realise that there were 92,445 PCI procedures carried out in the UK in 2012 compared to 16,791 CABG procedures (Townsend et al. 2015). In other words, around 50,000 eligible CR patients were not offered CR to prevent further MI and the progression of CAD (NACR 2014). Although NHS England's CVD strategy for 2015/16 has an ambition to increase the uptake of CR to 65% for patients admitted with CAD, only a 2% increase in uptake has been recorded from the previous year (NACR 2015; England & Guideline 2014; NACR 2016). Looking deep into the differences and into those factors that may contribute to low uptake rates might help inform future strategies to increase CR uptake (Karmali et al. 2014).

1.9 Thesis aim, question and structure

There are two primary aims of this PhD thesis: first, to review the existing literature critically and thus to identify the determinants of optimal CR utilisation in the eligible PCI population. Second, this thesis will assess the extent to which those determinants identified in the literature are applicable to the CR population in England by conducting a retrospective secondary analysis of the NACR dataset. In general, this thesis aims to contribute to the growing area of CR research by exploring those determinants in the PCI population and validating them against routinely collected clinical data. It is hoped that the findings of this research will make an important contribution to our understanding of the relatively low CR utilisation rates in this cohort despite the known benefits of CR.

The first study in this thesis seeks to investigate the factors that are associated with patients attending an initial CR baseline assessment (CR engagement). The second study will examine the factors associated with starting CR by at least attending one outpatient session. In the third study, the determinants that lead patients to complete the outpatient CR programme will be evaluated. The fourth and final study in this thesis will be a synthesis of the three previous studies in an attempt to find the common factors that affect the patient journey in CR from engagement to completion. The primary question of this thesis is therefore: 'what are the factors that determine CR engagement, uptake and adherence in the PCI population?'

The overall structure of this thesis takes the form of eight chapters, including three themed chapters that will discuss CR engagement, uptake and adherence separately. These three chapters will be followed by a synthesis chapter which will try to promote a more unified understanding of the low CR utilisation rates. The second chapter of the thesis is a systematic review of CR utilisation determinants while the third chapter will give a clear and detailed explanation of the methodology used in this thesis. The final chapter will conclude the findings of the research, focusing on the implications of its findings and how they might be explored further in future studies.

2 Systematic review of CR utilisation

2.1 Background

This PhD thesis is constructed to identify and evaluate the determinants of Cardiac Rehabilitation (CR) engagement, uptake and adherence in percutaneous coronary intervention (PCI) patients since CR utilisation rates worldwide are still below desirable. Furthermore, it has previously been observed that utilisation rates are lower than expected in patients undergoing PCI in most European countries (Humphrey et al. 2014). This is of a concern particularly with PCI being nowadays the first method of choice for coronary revascularisation in cases of acute coronary syndrome (ACS) and stable angina, or silent ischemia (Varenne & Hemery 2008).

A considerable amount of literature has been published on CR. These studies are different in design, targeted population and era. As this might be a significant source of heterogeneity when conducting the analysis and synthesis of literature, this chapter has evaluated trials and cohort studies separately taking into account population type and the date of each study. However, search strategy, search terms, sources searched and inclusion/exclusion criteria are identical despite the study design.

Although this study is specifically targeting patients undergoing interventional cardiology often referred to as a PCI patient cohort, there is a tendency in the CR literature to include mixed population in the analysis. This is of a concern especially if we believe that there may be some intrinsic patient related clinical factors in the PCI cohort like age, number of comorbidities and hospital length of stay that is different from other CR indication groups such as heart failure patients.

This study attempts to systematically review the existing literature around the determinants of CR utilisation. This goal will be achieved through the adaption of a validated systematic search strategy, analysis and synthesis of the available literature. However and due to the anticipated clinical heterogeneity in the included studies, the results will be synthesised under each identified determinant in the included studies. A key strength of the present review is that the searched articles were screened by two reviewers. This approach decreases

the risk of missing relevant evidence as reviews conducted without the aid of a second reviewer are more vulnerable to study selection bias. Furthermore, using search strategy and inclusion criteria established in advance reduces the risk of study selection based on individual's preferences, practice or products (Centre for Reviews and Dissemination 2009). This approach also maintains transparency and reproducibility of systematic review method.

2.2 Methods

Adopting the systematic review techniques in reviewing the literature should allow for a transparent and concise way of identifying and evaluating studies that investigated the determinants of CR utilisation (Tashakkori 2010). This systematic review applied a robust approach to searching and evaluating literature and used validated search strategies, data analysis and quality assessment tools. Three previously published systematic reviews investigating CR were consulted to develop the methods of this review (Sumner et al. 2017; Rauch et al. 2016; Dressler et al. 2012). Although these reviews were concerned with CR outcomes not determinants, relevant methods like sections of search strategy were adopted (see section 2.2.3). The detailed methods of this review has been registered and published in the PROSPERO database (CRD42017075214).

2.2.1 Inclusion criteria

The first step was to set up criteria of the literature that best serve the review's focus, goals and coverage. This was achieved by explicitly specifying a comprehensive inclusion and exclusion criteria for eligible studies to be included in the review Table (2.1). These criteria were chosen first as they are fundamental to identify other parts of the review such as search strategy and quality assessment tools (Randolph 2009).

Table 2.1 Review inclusion criteria.

	Inclusion criteria
Study design	Randomised and non-randomised study designs. Quantitative or mixed methods studies.
Population	
➢ **Age**	> 18 years.
➢ **Diagnosis**	CAD
➢ **Treatment**	Revascularisation (PCI or CABG)
Objective	Investigating CR engagement, uptake or adherence determinants.
Comparative groups ➢ **Exposed**	Patients participating in an outpatient multidisciplinary CR in supervised settings within 12 months from referral.
➢ **Comparators**	Patients offered CR but didn't engage or start or complete the programme within 12 months from referral.
Primary outcome	Engaging, starting or completing a multidisciplinary CR programme.
Publication	Fully published articles.
Language	Published in English.

2.2.2 Databases searched

All relevant key databases for health sciences that are provided by the University of York library at the time of literature search have been addressed. The review has searched the following seven databases: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8, 2017), EBSCOhost Research Databases CINAHL Plus (August week 3 2017), MEDLINE (Ovid, 1946 to August week 3 2017), EMBASE (Ovid, 1980 to August week 03 2017), AMED (Allied and Complementary Medicine) (1985 to July 2017), PsycINFO (1806 to July Week 5 2017) and Scopus (Elsevier B.V August week 03 2017).

2.2.3 Search strategy

The Cardiac Rehabilitation Outcome Study (CROS) review developed a sensitive search strategy that was developed by a graduate information scientist for seven databases in order to identify two types of study designs: trials and observational studies (Rauch et al. 2016).This section of their search strategy that captures all study designs around CR will be utilised.

Sumner et al review (2017) which was investigating non-randomised studies developed a search strategy in conjunction with a trained information specialist (Sumner et al. 2017). Part of this strategy was a combinations of medical subject headings and keywords around cardiac population descriptors. This part will be used in this review. Permission was gained from one of the main authors of each of the above studies to use the relevant aspects of their approach.

Dressler et al (2012) conducted a review to assess interventions to increase CR uptake. The search strategy for this review was developed by experts in the field of CR in the UK and included not only terms related to cardiac disease and CR but also an extensive selection of terms of potentially underrepresented population groups in CR programmes (Dressler et al. 2012). These terms were suggested by the literature and included older women, ethnic minorities and patients with lower socioeconomic status. This part of their search will be used to identify studies that was concerned with investigating barriers against CR utilisation.

A combination of the selected sections from each review will be constructed to form five main search terms that best fits the objectives of this thesis review. The five main search terms used to identify relevant literature are illustrated in (Appendix 1.1). These terms are: CR indications, rehabilitation terms, utilisation terms, CR determinants terms and study design terms.

Utilising a search strategy based on these terms is believed to be more accurate in capturing relevant literature since it was developed by specialists and experts in the field. However, this review has been conducted without date restrictions and only published studies in English have been retrieved. An example of a search strategy used for MEDLINE database is shown in (Appendix 1.2).

2.2.4 Selection of studies

Results were retrieved, assessed and irrelevant titles were excluded from the review by the author (AQ). The remaining abstracts were evaluated independently against the previously determined inclusion and exclusion criteria by two researchers (AQ & JA). In case of disagreement, joint discussions were held to resolve the issue. If any disagreement persists, the third author (PD) was consulted. Excluded studies were listed along with the reason for exclusion in (section 2.3.2).

2.2.5 Data extraction

A data extraction sheet has been developed to capture information on each study design, country of origin, date, aim, measures outcomes, sample size, population mean age and gender distribution. Where ambiguity incomplete data were found in any study regarding the above data extraction fields, N/A mark was placed in that field as it was difficult to contact the authors for further information (Appendix 9-3).

2.2.6 Quality assessment tools

As systematic reviews aim to identify all available literature relating to a particular subject, it also aim to assess the quality of identified studies to achieve unbiased results (Schulz et al. 1995). The objective of study quality assessment is to quantify in a scientific way how much 'truth' its findings has and whether these findings are relevant to the settings or targeted population (Centre for Reviews and Dissemination 2009). It is therefore fundamental for systematic reviews to assess individual studies against key parameters such as risk of bias and lack of applicability (Whiting et al. 2003). With the aim to standardise research quality, considerable efforts were deployed to develop appropriate research quality assessment tools. Most available quality assessment tools are proposed to assess the methodological quality of studies. This is normally achieved by evaluating the study internal validity, external validity and statistical analysis (Verhagen et al. 2001). In principal, three types of assessment tools are available: scales, simple checklists and checklists with summary scales (Stang 2010). The outcome of these tools can be used in different ways such as weighting studies or addressing gaps in the methodology of included studies (Deeks et al. 2003).

As illustrated in Table 3.1, different study designs can be arranged in a hierarchy based on their susceptibility to bias. However, this categorisation does not take into account quality variations among studies in the same design (Centre for Reviews and Dissemination 2009). As a result, quality assessment tools tends to be specific to particular study designs, and if reviews cover different study designs, separate assessment tools will be used. For this review, trials have been assessed using the Cochrane risk of bias table (Higgins et al. 2011) while nonrandomised studies have been assessed using the checklist developed by Wells and colleagues (Wells et al. 2013).

The Cochrane risk of bias table was developed by 16 statisticians, epidemiologists, and review authors to cover six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Within each domain, one or more items are assessed. For each item, bias risk assessment is in two parts; the judgment (high, low or unclear risk of bias) and a free text description to summarise how this judgment was reached (Higgins & Green 2011). Although this tool is valuable in assessing the internal validity of trials, it lacks the ability to assess the external validity or the applicability of the outcomes. These issues can be assessed by evaluating different parameters such as how narrow is the inclusion criteria and clinical relevance of the primary assessed outcome.

The checklists of methodological issues on nonrandomised studies developed by Wells group covers five methodological domains: study design, confounding, selective of analysis reporting, selective of outcome reporting and directness of evidence. Each domain is framed by several questions that the reviewer can response to using the quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS-2) tool (i.e. ‘yes’, ‘probably yes’, ‘probably no ’, and ‘no’) (Wells et al. 2013). Sumner et al (2107) used an adapted version of Wells checklist for the purpose of assessing the quality of observational studies included in their CR outcomes systematic review. The same adapted version will be utilised in this review (Sumner et al. 2017).

Nonrandomised studies are more susceptible to bias than trials as treatment selection in this type of design is often influenced by subject characteristics (Austin 2011). Therefore, the absence of confounding cannot be assumed between exposed and unexposed subjects. As a

result, exploration of planned adjustment for confounding factors should be conducted and the use of a validated quality assessment tool is favourable.

2.2.7 Data synthesis and analysis

Selected abstracts were imported into Mendeley desktop reference manager (version 1.17.9) and all duplicates were removed. If more than one publication was found to the same study, the most relevant paper to the review objectives was included. As the main objective of this review is to systematically review existing literature around CR utilisation determinants and due to the anticipated clinical heterogeneity in the included studies, the results were synthesised under each identified determinant.

2.3 Results

This section focuses on literature search results and the final study selection process. It will also cover an overview of the studies included in the final review with their bias assessment results.

2.3.1 Literature search results

The electronic databases search revealed a total of 604 studies. The results per database searched are shown in Table 2.4 below. This search was conducted on the third week of August 2017.

Table 2.2 Literature search results by database.

Database	Initial search results	After title screening
MEDLINE (Ovid)	91	70
CINHAL Plus (EBSCO)	112	72
Cochrane library (CENTRAL)	8	7
AMED (Ovid)	13	8
EMBASE (Ovid)	304	123

PsycINFO (Ovid)	1	1
Scopus	75	50
Total	604	331
Duplicates	-	46
Total (-) duplicates	-	285

Of the 604 titles found, 273 were excluded due to obvious irrelevance after title screening. Results were then uploaded to the referencing manager and a further 46 titles were removed due to duplication. The remaining 285 studies qualified to abstract screening phase. After abstract screening 228 titles were excluded and 79 studies progressed to full text analysis. Upon further appraisal, 32 studies failed to meet the inclusion criteria and a final of 46 articles have been included in the review. Figure 2.1 illustrates the selection process and the reasons for exclusion.

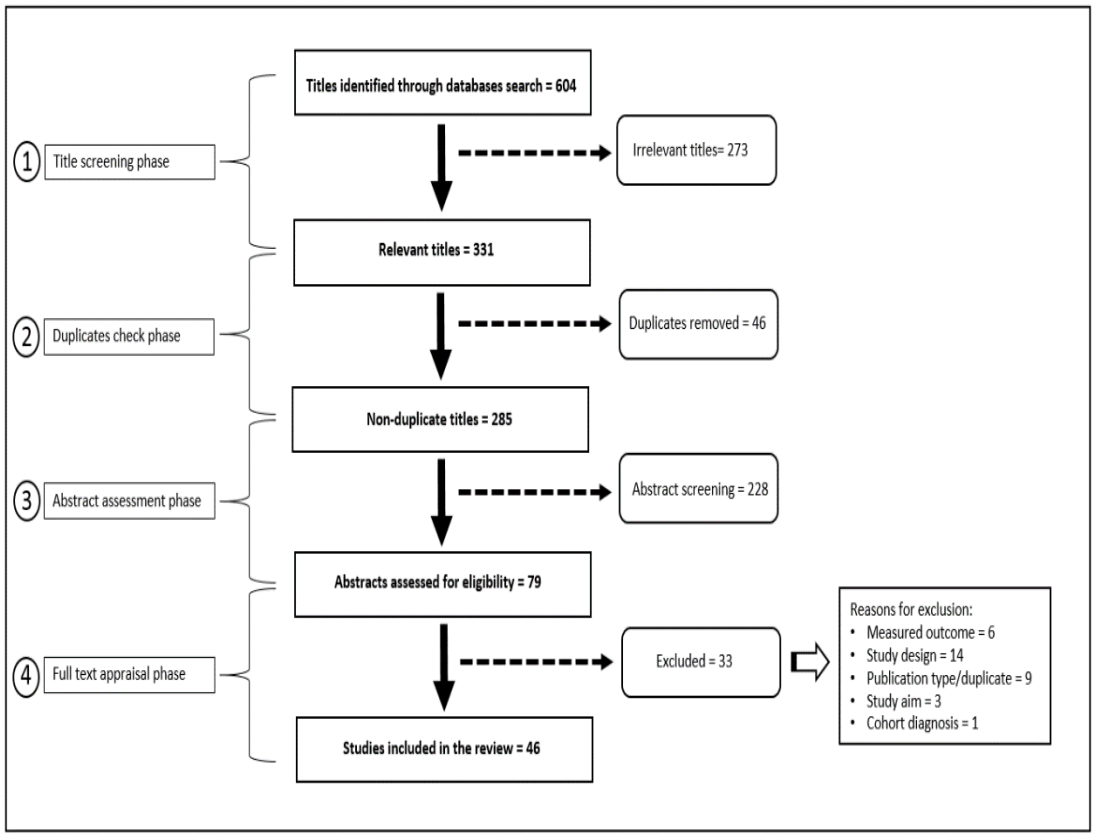


Figure 2.1 Study selection process.

2.3.2 Excluded studies

Table 2.3 lists excluded studies from the review with the reason for elimination. Studies have been excluded if they don't meet one or more of the inclusion criteria.

Table 2.3 Excluded studies with justification.

#	Study	Exclusion justification
1	Johnson & Heller (1998)	Unrelated measured outcome
2	Wyer et al (2001)	Study design – literature review
3	King et al (2001)	Publication – double publication
4	Daly et al (2002)	Study design – literature review
5	Beswick et al (2004)	Study design – systematic review
6	Jolly et al (2004)	Study design – qualitative study
7	Jolly et al (2005)	Unrelated study aim
8	Jones et al (2007)	Study design – qualitative study
9	Cooper et al (2007)	Study design – qualitative study
10	Beckie et al (2008)	Unrelated measured outcome
11	Sharp & Freeman (2009)	Study design – qualitative study
12	Martin et al (2011)	Publication – conference abstract only
13	Taylor et al (2011)	Study design – systematic review
14	Valencia et al (2011)	Study design – literature review
15	Gravely (2011)	Population diagnosis – heart failure patients
16	De Vos et al (2012)	Study design – qualitative study
17	Barboza et al (2012)	Publication – conference abstract only
18	Ghisi et al (2012)	Unrelated measured outcome
19	Mellville et al (2012)	Unrelated measured outcome

20	Reges et al (2012)	Publication – double publication
21	Martin & Woods (2012)	Unrelated measured outcome
22	Prior et al (2013)	Publication – conference abstract only
23	Shanmugasegaram et al (2013)	Unrelated measured outcome
24	Nielsen et al (2013)	Unrelated study aim
25	Samayoa et al (2014)	Publication – conference abstract only
26	Mikkelsen et al (2014)	Study design – No comparator group
27	Colella et al (2015)	Study design – systematic review
28	Doll et al (2015)	Study design – Descriptive analysis only
29	Grace et al (2015)	Study design – No comparator group
30	Pack et al (2015)	Unrelated study aim
31	Pola et al (2016)	Publication – conference abstract only
32	Kuijpers et al (2017)	Publication – conference abstract only
33	Pedersen et al (2017)	Publication – conference abstract only

2.3.3 Included studies analysis

All forty-six studies included in the review were conducted in the modern era of cardiology between the years 1995 and 2016 and only four studies conducted before 2001 (< 10%) (Rauch et al. 2016; Sumner et al. 2017). Collectively, these studies should reflect the current CR practice knowing that in the year 2000 the National Service Framework for CHD was published in the UK establishing modern standards of care including CR services. Moreover, in the year 1994 the American Heart Association published position statement on CR programmes and CR core components which was again updated in 2000. In 2003, the European Society of Cardiology released recommendations on the design and development of CR programmes (Sumner et al. 2017). The reviewed studies were conducted in 8 different countries: 9 in Canada, 8 in US, 5 in UK, 2 in Australia, 1 in Israel, 1 in Denmark, 1 in Switzerland and 1 in Iran.

The studies included a total of 398,667 participants (ranging from 131 to 267,427) with eight studies having relatively small sample size (< 200) and five studies having relatively large sample size (> 10,000). The mean age of participants across all studies is 63.4 years (ranging from 55 to 73.5 years) with female representation of 30.32% of the total sample (ranging from 15.5% to 78.5%) whereas 8 studies were investigating CR utilisation determinants in female gender only (Missik 1999; Gallagher et al. 2003; Allen et al. 2004; Mochari et al. 2006; Sanderson et al. 2010; Beckie & Beckstead 2010; Beckie et al. 2015; S. L. Grace et al. 2016).

In this review, 3 studies investigated CR engagement as the only outcome (N = 4,564), 29 studies investigated the determinant of CR uptake as the only outcome (N = 341,989), 10 investigated CR adherence as the only outcome (N = 28,633), 3 investigated both CR uptake and adherence determinants (N = 19,945) and 1 study investigated both CR engagement and uptake determinants (N = 3536).

The population diagnosis reported in all studies was Myocardial Infarction (MI) in 18 studies, ACS in 7 studies, CAD in 6 studies, CHD in 3 studies, and mixed diagnosis in 12 studies. The revascularisation method across studies was PCI, CABG or medical treatment in 23 studies, PCI or/and CBAG in 11 studies, CABG only in 5 studies, PCI only in 1 study and 6 studies failed to report on this item.

With regards to study design, the review consists of 2 RCT's (Beckie & Beckstead 2010; S. L. Grace et al. 2016) and 44 observational studies. Among the observational studies 25 utilised the prospective approach while 19 used retrospective approach. Out of the 44 observational studies included in this review 18 conducted secondary analyses of other datasets to investigate the study outcome. The extraction sheet containing all the data will be in (Appendix 9-3).

2.3.4 Quality assessment

The way individual studies' are executed and designed can threaten the validity of their findings. Therefore strong systematic reviews utilise explicit and systematic quality assessment methods in order to minimise bias in the collated evidence. In this review and as discussed in section (2.2.6), trials were assessed using the Cochrane risk of bias table

(Higgins et al. 2011) while nonrandomised studies have been assessed using the checklist developed by Wells and colleagues (G. Wells et al. 2013; Rauch et al. 2016). Results of the quality assessment of randomised trials are presented in (Table 2.4). Both trials were conducted with the aim to measure the effect of CR programme type (women-only, mixed sex or home based) on female participants' adherence to CR. Since this is the case, it was impossible to blind study participants from knowledge of which CR programme they were randomised into.

Table 2.4 Cochrane risk of bias table for included RCT's.

⊕ Low risk of bias ⊖ Risk of bias ? Unclear		*Grace et al (2016)*	*Beckie & Beckstead (2010)*
Domain	*Sub-domain*		
Selection bias	Random sequence generation	⊕	⊕
	Allocation concealment	⊕	⊕
Reporting bias	Selective reporting	⊕	⊕
Other bias	Other sources of bias	⊕	?
Performance bias	Blinding (participants & personnel)	⊖	⊖
Detection bias	Blinding (outcome assessment)	⊕	⊕
Attrition bias	Incomplete outcome data	⊕	⊕

Results of nonrandomised studies are presented in (Figure 2.2). In randomised trials confounding may arise from flaws in the randomisation process whereas confounding in nonrandomised studies may arise from different potential confounding variables. The researcher in nonrandomised studies has to carefully decide what variables to include in the analysis and what statistical methods to utilise to control confounding (G. A. Wells et al. 2013). In the majority of studies it was difficult to judge if there was no effect of confounding as these studies failed to justify the selection of the included variables. Another keynote about the investigated studies was the insufficient reporting about how missing

values were treated. However, all studies created appropriate comparison groups and no unusual categorical cut-offs or unusual subgroups were evident.

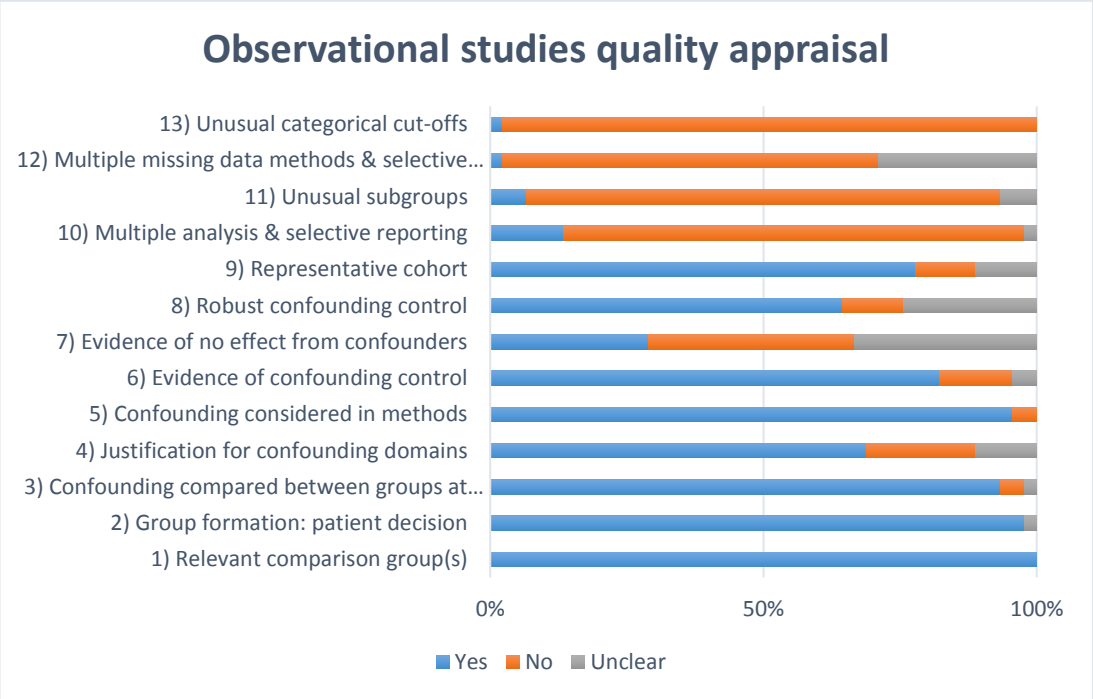


Figure 2.2 Nonrandomised studies quality assessment results.

2.4 Cardiac rehabilitation utilisation determinants

A total of 604 studies were found using the pre-specified selection criteria, and 46 were included in the final review. This is 17 studies more than a recent systematic review conducted to analyse factors affecting CR utilisation (Ruano-Ravina et al. 2016). Below is a data synthesis of all reported determinant in the included studies. For clarity, those determinants were grouped under four main categories; patient's socio-demographics, cardiac risk factors, lifestyle & health status and service level factors (Table 2.5). This synthesis will start by outlining the determinants of CR engagement, CR uptake and finally CR adherence.

Table 2.5 Reported CR utilisation determinants in the included studies.

	Patient's socio-demographics	Cardiac risk factors	Lifestyle & health status	Service level factors
1	Age	Hypertension	Wellbeing	Referral profession
2	Gender	Diabetes	Angina	Referral Source
3	Ethnicity	Hyperlipidaemia	Previous event	Hospital length of stay
4	Marital status	Family history	Smoking	CR type
5	Education	Being overweight	Alcohol intake	Confirmed joining date
6	Employment	Physical inactivity	Transportation	Treatment type
7	Social deprivation	Anxiety	Settlement location	Previous CR
8	Social support	Depression	Religion	Language

2.4.1 Engagement determinants

The adopted search strategy has identified 3 studies (N = 4,564) that investigated CR engagement (Grace et al. 2008; Grace et al. 2010; Grace et al. 2011) while 1 study (N = 3,536) investigated both CR engagement and uptake (Smith et al. 2006). A note of caution is due here since the main purpose of two out of the four included studies was to investigate the impact of referral strategy on CR engagement (Grace et al. 2010; Grace et al. 2011). However, Grace et al (2010) reported other determinants beside the main measured determinant (referral strategy) while the other study Grace et al (2011) only reported the

impact of referral strategy on CR engagement. The main features of the included four studies are outlined in Table (2.6).

Table 2.6 Main features of included engagement studies.

	Smith et al (2006)	Grace et al (2008)	Grace et al (2010)	Grace et al (2011)	Average
Sample size	3,535	1,268	661	2,637	2,025
Mean age	64	66	61.2	65	64.1
Female %	20.9	28.0	23.8	26.8	24.9
Country	Canada	Canada	Canada	Canada	-
Study design	Retrospective secondary	Prospective primary	Prospective primary	Prospective primary	-
Diagnosis	CAD	CAD	ACS	ACS	-
Treatment	CABG	Mixed	Mixed	PCI/CABG	-

The results of quality assessment for the four included studies in CR engagement is presented in Figure (2.3). These studies were assessed for quality according to the adapted checklist explained in (section 2.2.6). According to the displayed results in Figure (2.3) the included studies are ranked as high quality observational studies.

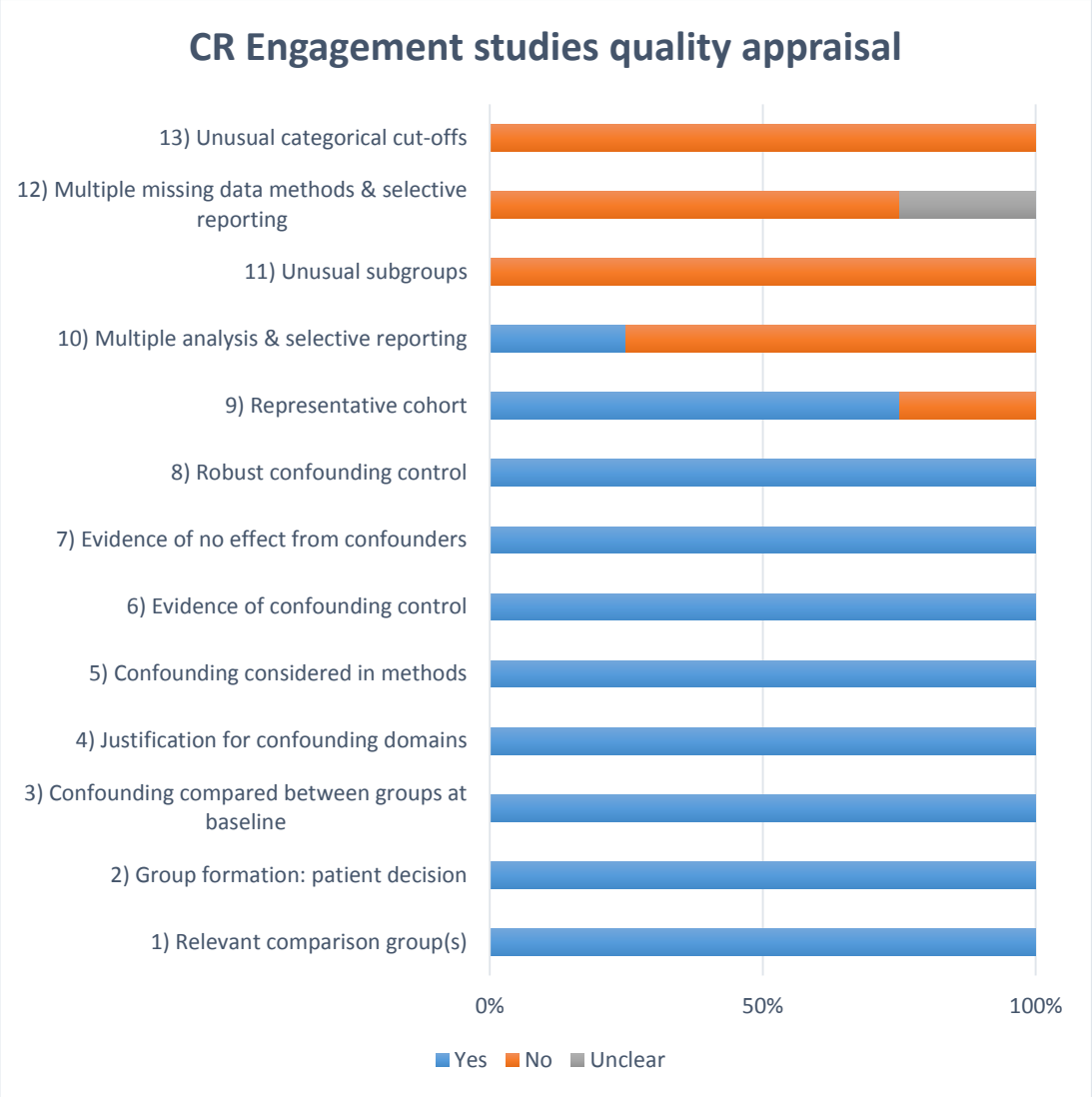


Figure 2.3 Quality assessment results for CR engagement studies.

A summary of the CR engagement determinants as reported in the investigated studies is displayed in (Figure 2.4). The figure bars are colour coded according to the role of the determinant in CR engagement while the labels in the centre of each bar reflect the total number of studies that investigated that determinant.

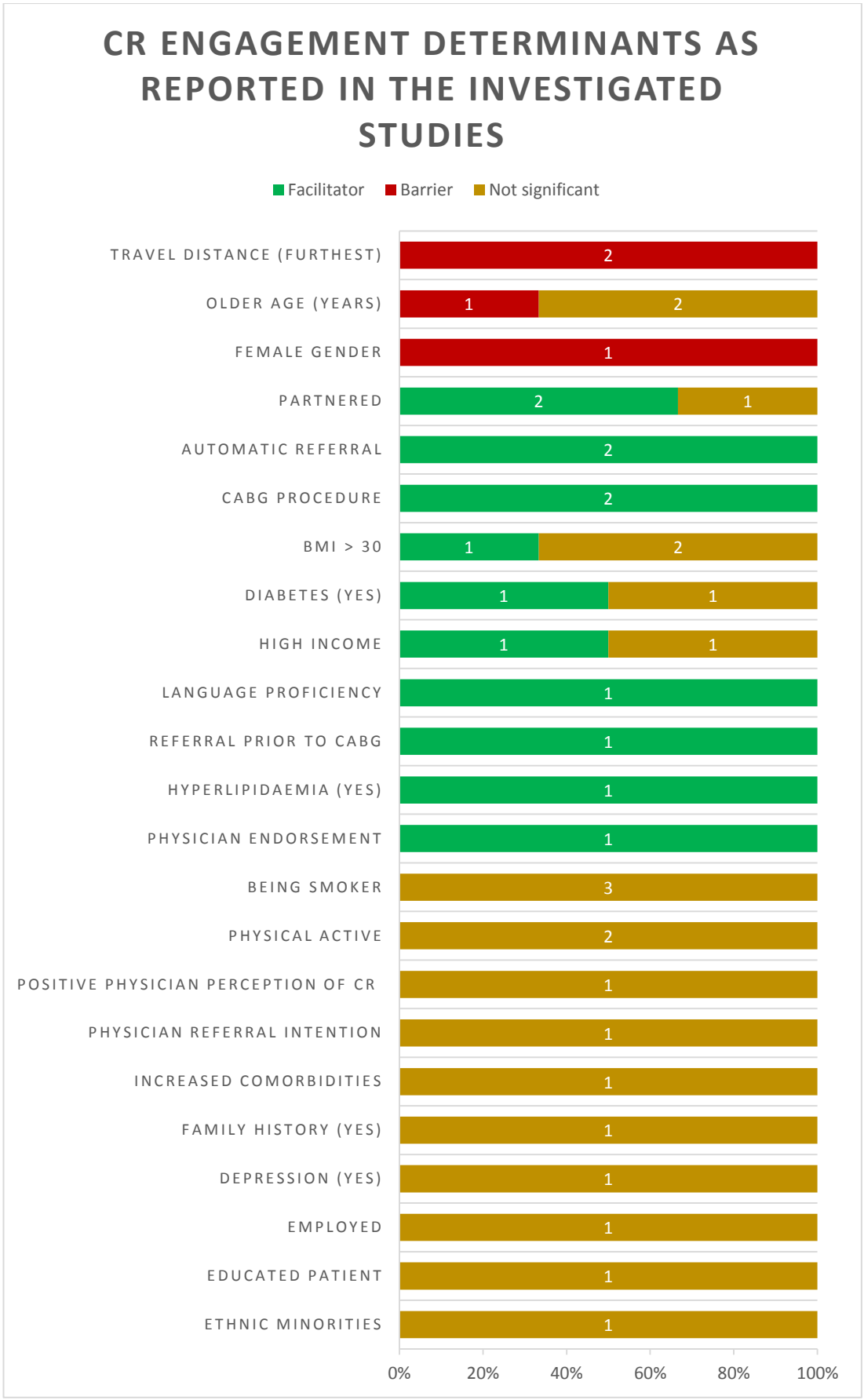


Figure 2.4 Determinants of CR engagement as reported in the investigated studies.

2.4.1.1 Patient's socio-demographics

Only one study has found that younger age is a significant determinant of engaging in CR in a multivariate analysis (OR: 1.3, 95% CI: 1.1 to 1.5, p = 0.001) (Smith et al. 2006). Grace et al (2008) has found that the mean age of engaged patients (65.7 years) at the baseline level is significantly less than the mean age of the non-engaged group (68.2 years) ($p < 0.001$). However, this association was not significant in the final logistic regression model (p = 0.61) (Grace et al. 2008). The same non-significant association between age and CR engagement was reported by Grace et al (2010) (OR: 1.02, 95% CI: 0.99 to 1.04, p =0.16). Gender was also significant determinant of CR engagement in only one study Smith et al (2006) as male patients were 1.6 times more likely to engage in CR compared to their female counterparts (OR: 1.59, 95% CI: 1.34 to 1.89, $p < 0.001$).

The effect of patient's ethnic group was reported only in one study Grace et al (2010) and found not to be statistically significant (OR: 0.58, 95% CI: 0.30 to 1.10, p = 0.10). Patient's marital status was found to be significant in two studies (Smith et al. 2006; Grace et al. 2008) and non-significant in one study (Grace et al. 2010). Patients living with a spouse were found to be 1.4 more likely to engage in CR (OR: 1.39, 95% CI: 1.16 to 1.68, $p < 0.001$) (Smith et al. 2006). Grace et al (2008) found in an adjusted analysis that marital status has significant correlation with CR engagement (p = 0.01). The same study also proved that employment status, family income and education level have no significant correlation with CR engagement (p = 0.42, p = 0.93 and p = 0.88 respectively) (Grace et al. 2008). This in contrast to the finding of Grace et al (2010) which found that family income is a strong predictor of CR engagement (OR: 1.66, 95% CI: 1.03 to 2.67, p = 0.04) (Grace et al. 2010).

2.4.1.2 Cardiac risk factors

Smith et al (2006) reported in three modifiable cardiac risk factors; diabetes, obesity and hyperlipidaemia. The study concluded that diabetic patients are 22% more likely to engage in CR (OR: 1.22, 95% CI: 1.04 to 1.44, p = 0.017). Patients with a body mass index (BMI) > 30 were 24% more likely to engage in CR (OR: 1.24, 95% CI: 1.04 to 1.47, p = 0.015). Hyperlipidaemia patients were also more likely to engage in CR by 45% compared with

patients not diagnosed with hyperlipidaemia (OR: 1.45, 95% CI: 1.24 to 1.69, $p < 0.001$) (Smith et al. 2006).

The bivariate analysis conducted by Grace et al (2008) revealed that diabetes, depressive symptoms, family history, exercise behaviour and BMI are not significantly associated with CR engagement ($p > 0.05$) (Grace et al. 2008). The logistic regression model run by Grace et al (2010) has also concluded that activity status and BMI are not associated with CR engagement (OR: 1.01, 95% CI: 1.00 to 1.02, $p = 0.15$) (OR: 0.97, 95% CI: 0.92 to 1.02, $p = 0.19$) respectively (Grace et al. 2010). All included studies failed to report on hypertension and anxiety levels.

2.4.1.3 Lifestyle & health status

The strongest independent predictor of engaging in CR that was found by Smith et al (2006) is the geographical proximity to the CR centre (OR: 3.09, 95% CI: 2.52 to 3.78, $p < 0.001$). This single predictor was accounted for approximately 80% of the overall explained variance for engaging in CR (Smith et al. 2006). This finding is supported by the findings of the mixed logistic regression analysis conducted by Grace et al (2008) which concluded that shorter distance to CR centre is statistically significant predictor of CR engagement ($p = 0.001$) (Sherry L. Grace et al. 2008).

Smith et al (2006) also found that patients with a previous CABG are 89% more likely to engage in CR than their counterparts (OR: 1.89, 95% CI: 1.36 to 2.63, $p < 0.001$) (Smith et al. 2006). Smoking status of patient at the time of the cardiac event was investigated in three of the included studies. Surprisingly all three studies agreed that the smoking status is not associated with the CR engagement. Other medical conditions that might prevent exercise as reported by patients were found not statistically significant with CR engagement (Sherry L. Grace et al. 2008). All other listed determinants under this category have not been addressed in the included studies.

2.4.1.4 Service level factors

This set of determinants mainly revolve around how the service has been introduced/delivered to the patient and what type of treatment the patient received. To

investigate the type of referral on CR engagement Grace et al (2010) compared automatic versus usual referral to CR services. Patients automatically referred to CR were 2.1 times more likely to engage in CR (OR: 2.10, 95% CI: 1.35 to 3.28, $p < 0.01$) (Grace et al. 2010). One year later Grace et al (2011) have dedicated their study to investigate the impact of referral strategy on CR engagement. Basically they compared the engagement rate of four different referral strategies. They concluded that automatic referral combined with a patient discussion can achieve the highest engagement rates (OR: 8.41, 95% CI: 3.57 to 19.85) (Grace et al. 2011). Also, the ability to speak the first language of the country is a major determinant of CR engagement as found in one study (OR: 2.73, 95% CI: 1.67 to 4.47, $p < 0.001$) (Smith et al. 2006).

The strength of physician endorsement was found to be statistically significant with CR engagement ($p = 0.01$) (Sherry L. Grace et al. 2008). However, other factors that are related to referral source to CR such as physician referral intentions and positive physician perception of CR was found not significant by the same study (Sherry L. Grace et al. 2008) . Patients who were referred to CR prior to CABG were 2.3 as likely to engage in CR (OR: 2.27, 95% CI: 1.77 to 2.92, $p < 0.001$) (Smith et al. 2006). Patients with a cardiac event or procedure other than PCI were more likely to engage in CR than those hospitalised for PCI procedure (OR: 1.79, 95% CI: 1.14 to 2.82, $p = 0.01$) (Grace et al. 2010).

2.4.2 Uptake determinants

As mentioned previously, 29 studies (N = 341,989) investigated the determinants of CR uptake as the only outcome while 3 studies investigated both CR uptake and adherence in the same study (N = 22,041). Collectively, the 32 studies included a total of 361,934 participants (ranging from 131 to 267,427). The mean age of participants across all studies was 62.8 years (ranging from 58 to 69 years) with female representation of 29.2% of the total sample (ranging from 15.5% to 48%) whereas 5 studies were investigating CR uptake determinants in female gender only (Sanderson et al. 2010; Mochari et al. 2006; Allen et al. 2004; Missik 1999; Gallagher et al. 2003).

The population diagnosis reported in all studies was MI in 15 studies, ACS in 3 studies, CAD in 3 studies, CHD in 3 studies, and mixed diagnosis in 6 studies. The revascularisation method across studies was PCI, CABG or medical treatment in 12 studies, PCI or/and

CABG in 10 studies, CABG only in 3 studies, PCI only in 1 study and 6 studies failed to report on this item.

With regards to study design, all included studies were observational studies. Among those, 19 studies utilised the prospective approach while 13 studies were conducted retrospectively. Out of the 32 observational investigating CR uptake, 18 studies conducted secondary analysis of other datasets to investigate the study outcome. The results of quality assessment for the 33 included studies in CR uptake is presented in Figure (2.5).

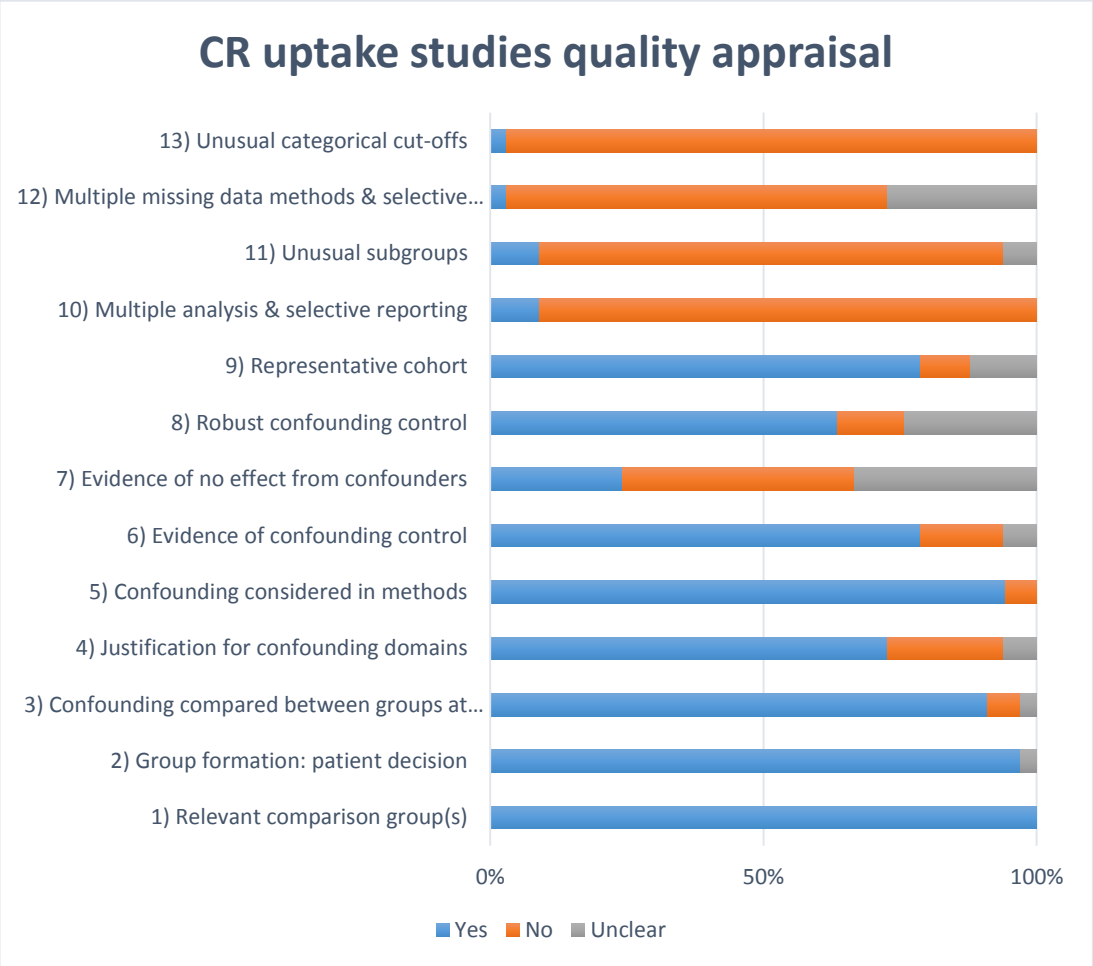


Figure 2.5 CR uptake studies quality appraisal.

A summary of the CR uptake determinants as reported in the investigated studies is displayed in (Figure 2.6). The figure bars are colour coded and labelled as previously described in (Figure 2.4).

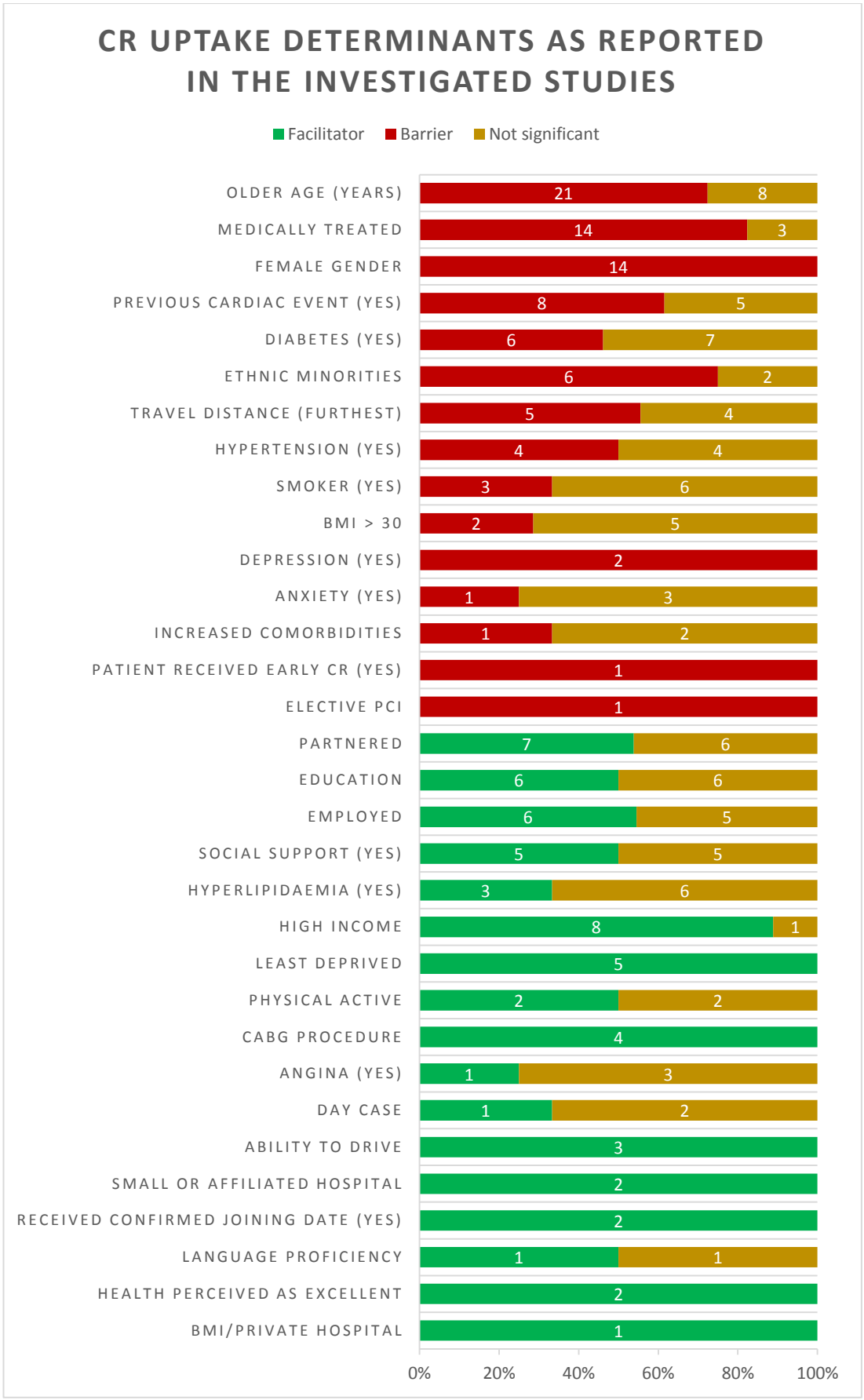


Figure 2.6 Determinants of CR uptake as reported in the investigated studies.

2.4.2.1 Patient's socio-demographics

Out of the 32 studies that investigated CR uptake, 21 studies found age to be a significant determinant, 8 not significant determinant and 3 studies; Harrison & Wardle (2005), Molloy et al (2008) and Lemstra (2013) did not report on age as the aim was to measure a specific determinant. All 21 studies found that younger participants are more likely to start CR compared to older patients. However and in a less robust method, 6 studies computed this finding from a univariate analysis. In the remaining 16 studies, the odds of young patients starting CR ranged from 40% to 72% in studies that measured age as a categorical variable and from 0.95 to 0.99 in studies that measured age as a continuous variable.

The impact of gender was investigated in 21 studies while 4 studies Gallagher et al (2003), Allen et al (2004), Mochari et al (2006) and Sanderson et al (2010) had 100% female participants and 1 study Suaya et al (2007) stratified the sample by gender prior to analysis. The remaining 6 studies didn't report in gender. Out of the 21 studies, 14 studies found that gender is a significant determinant of CR uptake where males are more likely to start CR compared with their female counterparts. The odds of male patients starting CR ranged from 1.11 to 2.86 in 10 studies while 5 studies reported gender as a significant predictor ($p < 0.05$) of CR uptake as only univariate analysis was conducted.

Patient ethnicity as a determinant of CR uptake was investigated in 8 studies. Six studies found that patients from ethnic minorities are less likely to uptake CR (ranging from 58% to 200% less likely). However, 2 studies found ethnicity as a non-significant determinant of CR (Harlan et al. 1995; Sanderson et al. 2010). Subjects' marital status was investigated in 13 studies with 7 studies reporting it as a significant determinant of CR uptake. Overall, partnered subjects were found to be more likely to commence a CR programme compared with single or previously partnered. The odds of partnered patients to start CR ranged from 1.44 to 3.53 more likely.

The role of patient's level of education on CR uptake was investigated in twelve studies. Six studies concluded that patient's level of education is not associated with CR uptake (Lane et al. 2001; Reges et al. 2013b; McKee et al. 2014; Soo Hoo et al. 2016; Allen et al. 2004; Mochari et al. 2006). Three studies found it significant in a univariate analysis ($p < 0.05$) (Evenson et al. 1998; Harlan et al. 1995; Missik 1999). In a multivariate analysis, three

studies found that patients with at least high school education were more likely to start CR (OR: 1.50, 1.81 and 3.32) (Parashar et al. 2012; Dunlay et al. 2009; Sanderson et al. 2010) respectively.

The employment status was investigated in 15 studies. Five studies found that the employment status of a participant is not significant. Four studies found that employment status is a significant determinant of CR uptake by conducting a univariate analysis. The remaining six studies conducted a multivariate analysis and found that patients in full employment are more likely to join CR. The odds of fully employed participants to start CR ranged from 1.52 to 3.07 compared with unemployed or retired participants.

Patient's income was reported as a significant predictor in 8 studies and not significant in 1 study (Sanderson et al. 2010). Two out of the eight studies investigated this determinant in a univariate analysis Harlan et al (1995) and Reges et al (2013) while six studies conducted a multivariate analysis and found out that patients with low income are less likely to start CR ranging from 44% to 77%. Social deprivation was also investigated in five studies and all found it a significant determinant of CR uptake. The least deprived patients were more likely to join (ranging from 17% to 35%) compared with the most deprived patients in three studies while two studies reported this determinant in a univariate analysis ($p < 0.05$).

The role of social support in CR uptake was controversial among the studies reporting this determinant. While five studies found that social support is not a significant predictor, another five studies reported that it is strongly correlated with increase in CR uptake. In those studies reporting social support as a predictor of CR uptake, four studies indicated that subjects reporting enough social support were more likely to attend CR (OR: 1.46, 3.42, 4.26 and 4.5) (Cupples et al. 2010; Chamosa et al. 2015; Molloy et al. 2008; Lane et al. 2001) respectively. The remaining study reported social support as a significant predictor in a univariate analysis ($p = 0.019$) (Beauchamp et al. 2013).

2.4.2.2 Cardiac risk factors

As outlined in Table 2.5), this group contains eight determinants; hypertension, diabetes, high blood cholesterol, family history, being overweight, physical inactivity, anxiety and depression. Hypertension was investigated in eight studies where it was found significant in

four studies (King et al. 2001; Dunlay et al. 2014; Parashar et al. 2012; Evenson et al. 1998) and not significant in four studies (McKee et al. 2014; Lane et al. 2001; Sanderson et al. 2010; Beauchamp et al. 2013). Hypertensive patients were found to be less likely to start CR in two multivariate analysis studies (OR: 0.85 and 0.58) (Parashar et al. 2012; King et al. 2001) while it was significant determinant in two univariate studies (Evenson et al. 1998; Dunlay et al. 2014).

Diabetes as a determinant of CR uptake was investigated in thirteen studies. Seven studies concluded that it was not a significant predictor of CR uptake while six studies proved the opposite. Among those six studies, three studies reported that diabetic patients were less likely to start CR (OR: 0.40, 0.58 and 0.70) (Turk-Adawi et al. 2014; van Engen-Verheul et al. 2013; Dunlay et al. 2009) respectively, and three studies found diabetes is a significant determinant of CR uptake in a univariate analysis ($p < 0.05$) (Evenson et al. 1998; Beauchamp et al. 2013; Dunlay et al. 2014).

Hyperlipidaemia or high blood cholesterol was investigated in nine studies. Two studies found it significant determinant of CR uptake by conducting a univariate analysis (Evenson et al. 1998; Dunlay et al. 2014) and one study reached the same finding by conducting a bivariate analysis controlling for age (OR: 1.90, 95% CI: 1.2 to 3.1) (Nielsen et al. 2008). The remaining six studies found hyperlipidaemia not significant determinant of CR uptake. Family history of cardiac disease was investigated in five studies and was found significant in only one univariate study (Evenson et al. 1998).

Individuals who had BMI > 30 were found to be less likely to start CR in two studies (OR: 0.89) (King et al. 2001) and ($p = 0.002$) (Dunlay et al. 2014). Five studies found no association between BMI and CR uptake (Parashar et al. 2012; McKee et al. 2014; Chamosa et al. 2015; Sanderson et al. 2010; Beauchamp et al. 2013). Individuals performing regular exercise were found more likely to start CR in two studies. Harlan et al (1995) found that performing regular exercise is a significant determinant of CR uptake ($P = 0.03$) (Harlan et al. 1995). While Lane et al (2001) found those who took less frequent exercise prior to MI are less likely to join (OR: 0.85, 95% CI: 0.80 to 0.91) (Lane et al. 2001). However, two studies found this association is not significant (Sanderson et al. 2010; Beauchamp et al. 2013).

Participants levels of anxiety was investigated in four studies and found not significant in three of them (French et al. 2005; Harlan et al. 1995; McKee et al. 2014). In the study conducted by Lane et al (2001) it was found that those who started CR had lower trait anxiety scores (OR: 1.04, 95% CI: 1.01 to 1.06) (Lane et al. 2001). Two studies have found that the presence of depressive symptoms had a large impact on CR uptake. Hoffmann et al (2013) reported that individuals with depressive symptoms are less likely to start CR (OR: 0.26, 95% CI: 0.08 to 0.88) (Hoffmann et al. 2013). This finding was in agreement with another American multivariate study (OR: 0.56, 95% CI: 0.36 to 0.88) (Turk-Adawi et al. 2014). However, three studies found no association between depression and CR uptake (French et al. 2005; McKee et al. 2014; Sanderson et al. 2010).

2.4.2.3 Lifestyle & health status

How patients perceived their health before the cardiac event has been investigated in two studies. Dunlay et al (2009) concluded that patients whom perceived their health as excellent before MI were 7.33 times more likely to uptake CR than those who perceived it as poor (OR: 7.33, 95% CI: 1.38 to 38.88) (Dunlay et al. 2009). Also Harlan et al (1995) found that in a univariate analysis that CR participants were significantly less impaired than non-participants before CABG ($p = 0.001$) (Harlan et al. 1995). Another important indicator of patient's wellbeing is the total number of comorbidities. Sundararajan et al (2004) found that patients with two or more comorbidities are less likely to start CR (OR: 0.82, 95% CI: 0.72 to 0.93) (Sundararajan et al. 2004). This finding differs from Allen et al (2004) who assessed comorbidity by Charlson index score and found that increased number of comorbidities is not associated with CR uptake (OR: 1.16, 95% CI: 0.93 1.45) (Allen et al. 2004). This result is consistent with two later studies (Parashar et al. 2012; Soo Hoo et al. 2016).

The feeling of cardiac symptoms like angina has been investigated as a driver of CR participation. Lane et al (2001) found in a multivariate analysis that patients starting CR were less likely to suffer from angina pectoris (OR: 2.02, 95% CI: 1.16 to 3.50) (Lane et al. 2001). This finding is contrary to that of Nielsen et al (2008) who found that chest pain is a positive predictor of CR uptake (OR: 8.6, 95% CI: 3.0 to 24.8) (Nielsen et al. 2008). However, three studies reported that the presence of angina or chest pain is not associated with CR uptake (Parashar et al. 2012; McKee et al. 2014; Allen et al. 2004).

The association of CR uptake and history of a previous cardiac event was investigated in thirteen studies. Three studies found that a previous MI is a strong barrier against CR uptake (OR: 0.24, 95% CI: 0.09 to 0.65) (Melville et al. 1999), (OR: 0.24, 95% CI: 0.12 to 0.51) (Dunlay et al. 2009) and (OR: 0.62, 95% CI: 0.39 to 0.97) (McKee et al. 2014). Another two studies confirmed this findings by reporting that non-starters are more likely to have a history of MI (OR: 3.04, 95% CI: 1.52 to 6.10) (Lane et al. 2001) and (OR: 1.29, 95% CI: 0.71 to 2.33) (Chamosa et al. 2015). In univariate analysis, three studies also confirmed that previous MI is significantly associated ($p < 0.05$) with CR uptake (Evenson et al. 1998; Missik 1999; Hoffmann et al. 2013). However, this association was not found to be significant in another five studies (French et al. 2005; Parashar et al. 2012; Soo Hoo et al. 2016; King et al. 2001; Reges et al. 2013b).

Smokers were found to be starting CR less likely than non-smokers in two multivariate studies (OR: 0.59; 95% CI, 0.44 to 0.80) (Parashar et al. 2012) and (OR: 0.59; 95% CI, 0.44 to 0.78) (Turk-Adawi et al. 2014). It was also found significant in one univariate analysis ($p = 0.001$) (Dunlay et al. 2014). History of smoking was found to be significant determinant of CR uptake in one univariate study ($p < 0.05$) (Evenson et al. 1998), and not significant in one multivariate study (OR: 1.05, 95% CI: 0.91 to 1.21) (Turk-Adawi et al. 2014). The association of smoking with CR uptake was found not significant in another six studies (Harlan et al. 1995; McKee et al. 2014; Melville et al. 1999; King et al. 2001; Lane et al. 2001; Sanderson et al. 2010).

Transportation distance to CR location has been investigated as potential determinants of CR uptake in six studies. Suaya et al (2207) found that those at the greatest distance from a CR centre (15 – 231 miles) have the least likelihood of CR uptake (OR: 0.29, 95% CI: 0.27 to 0.31) (Suaya et al. 2007). This is in line with Chamosa et al (2015) findings which confirms that patients driving more than 50 km are less likely to start CR compared with those driving less than 10 km (OR: 2.87, 95% CI: 1.29 to 6.41) (Chamosa et al. 2015). Brual et al (2010) also attempted to empirically test the drive time threshold for CR utilization and concluded that only those who have to drive over 80 minutes are less likely to start CR compared to those who drive less than 10 minutes (OR: 0.22, 95% CI: 0.11 to 0.42) (Brual et al. 2010). This association was not evident in univariate analysis conducted in four other studies (French et al. 2005; Cupples et al. 2010; Melville et al. 1999; Sanderson et al. 2010).

In the same context, the ability to drive was associated with increased CR uptake in three studies. Non-drivers were three-folds less likely to start CR than drivers in a secondary retrospective Australian study conducted by Worcester et al (2004) (OR: 3.09, 95% CI: 1.62 to 5.57) (Worcester et al. 2004). This is supported by another primary prospective American study (OR: 0.16, 95% CI: 0.06 to 0.42) (Dunlay et al. 2009). These findings were further confirmed by another study which found out that those who possess driving license are more likely to start CR (OR: 2.42, 95% CI: 1.02 to 5.73) (Reges et al. 2013b). Also the participants' geographic place of residence was investigated in two studies. King et al (2001) found that the odds of those who live in tertiary care centre city were 4.48 times higher than their counterparts (King et al. 2001), while Sundararajan et al (2004) reported that those who live in an accessible geographic place of residence (according to the Australian index of remoteness) were 28% more likely to start CR (OR: 1.28, 95% CI: 1.13 to 1.45) (Sundararajan et al. 2004). The impact of the patient's spiritual beliefs on CR uptake was investigated in one multivariate middle-eastern study and found not to be significant (Reges et al. 2013b).

2.4.2.4 Service level factors

The most influential determinant in this group is treatment type. Whether a patient received CABG, PCI or medical treatment for the index cardiac event seems to have a large impact on his decision to uptake CR. A total of seventeen studies investigated this determinant with only three studies finding it not significant (Parashar et al. 2012; McKee et al. 2014; Sanderson et al. 2010). The remaining fourteen studies, including five univariate analysis studies, concluded that patients who underwent revascularisation procedure are more likely to start CR than those treated medically. Within the revascularisation procedures, patients receiving CABG treatment are even more likely to start CR than those receiving PCI (OR ranging from 2.76 to 58) (Suaya et al. 2007; Sundararajan et al. 2004; van Engen-Verheul et al. 2013; Hoffmann et al. 2013). Also patients having elective PCI are less likely to start CR than those receiving primary PCI (OR: 0.48, 0.41 to 0.56) (van Engen-Verheul et al. 2013).

Patient's length of stay in hospital was investigated in four studies. Dunlay et al (2014) have found that non-starters had longer hospital length of stay ($p < 0.001$) (Dunlay et al. 2014). A more recent study by Soo Hoo and colleagues (2016) conducted a multivariate analysis to

measure CR uptake after 4 weeks and 6 months from the index cardiac event and found out that hospital length of stay is not significant in both time points in patients admitted with ST-elevation MI (p = 0.179 and 0.792) respectively (Soo Hoo et al. 2016). Another study conducted a univariate analysis to investigated this determinant in MI population and found out starting CR was not associated with the number of days stayed at hospital (p = 0.50) (French et al. 2005).

Patients treated in small hospitals (1 - 160 beds) were more likely to start CR (OR: 1.27, 95% CI: 1.11 to 1.46) and patients transferred from long term care or a skilled nursing facilities were less likely to start CR compared with those admitted from home (OR: 0.72, 95% CI: 0.65 to 0.79). Also patients admitted to hospitals affiliated to medical schools were 33% more likely to start CR than hospitals with the opposite characteristics (OR: 1.33, 95% CI: 1.21 to 1.46) (Suaya et al. 2007). This last finding is in line with the findings of a previous study which concluded that patients admitted to private hospitals are 32% more likely to start CR than those admitted to teaching hospitals (OR: 1.32, 95% CI: 1.17 to 1.48) (Sundararajan et al. 2004).

Patients not receiving a confirmed joining CR appointment were found to be less likely to start CR than those who were given an appointment (OR: 0.31, 95% CI: 0.18 to 0.54) (Melville et al. 1999). Also those patients who received a recommendation letter from their physician to start CR were more likely to join than those who didn't (OR: 2.79, 95% CI: 1.51 to 5.14) (Reges et al. 2013b). Those who attended CR previously were found to be less likely to uptake CR again (OR: 0.26, 95% CI: 0.12 to 0.56) (Dunlay et al. 2009). The last determinant in this group was proficiency of the native language which was investigated in only two studies and reported as a significant predictor of CR uptake in a bivariate analysis (p = 0.001) by (Reges et al. 2013b) and as not significant determinant (p = 0.42) by (Beauchamp et al. 2013).

2.4.3 Adherence determinants

A total of 13 studies investigating CR adherence have been identified in this systematic review (N = 48,578). Among which there are ten studies that were looking at CR adherence as the only outcome (N= 28,633) including two RCT's (N = 335). The remaining observational studies were conducted either prospectively (five studies) or retrospectively

(six studies). Secondary analysis of other datasets to investigate the study outcome was utilised in five studies.

Since the definition of 'CR adherence/completion' varies among researchers, it is important to clarify how the term has been used in the included studies. Five studies defined drop out by computing a cut-point based on the number of sessions attended (Worcester et al. 2004; Beckie & Beckstead 2010; Turk-Adawi et al. 2013a; Doll et al. 2015; Beckie et al. 2015). Three studies defined completion of CR by attending 100% of the prescribed sessions (Sarrafzadegan et al. 2007; Lemstra et al. 2013; Armstrong et al. 2014). Two studies marked a participant as a completer relying on feedback from the participant himself or from the CR programme manager (Harrison & Wardle 2005a; Casey et al. 2008). Two studies defined completion by conducting a second CR assessment (Yohannes AM, Yalfani A, Doherty P 2007; S. L. Grace et al. 2016) while the definition of completers in one study was ambiguous (Ananya Tina Banerjee et al. 2007).

The mean age of participants across all studies is 63.3 years (ranging from 55 to 73.5 years) with female representation of 35.7% of the total sample (ranging from 24.0% to 78.5%) whereas 3 studies were investigating CR adherence determinants in female gender only (Beckie & Beckstead 2010; Beckie et al. 2015; S. L. Grace et al. 2016). The population diagnosis reported in all studies was MI in 4 studies, CAD in 1 study, CHD in 1 study, and mixed diagnosis in 7 studies. The revascularisation method across studies was PCI, CABG or medical treatment in 8 studies, PCI or/and CBAG in 4 studies and CABG only in 1 study. The Cochrane risk of bias table for the included RCT's is presented in (Table 2.4) while the nonrandomised studies quality assessment for the included adherence studies is displayed in (Figure 2.7).

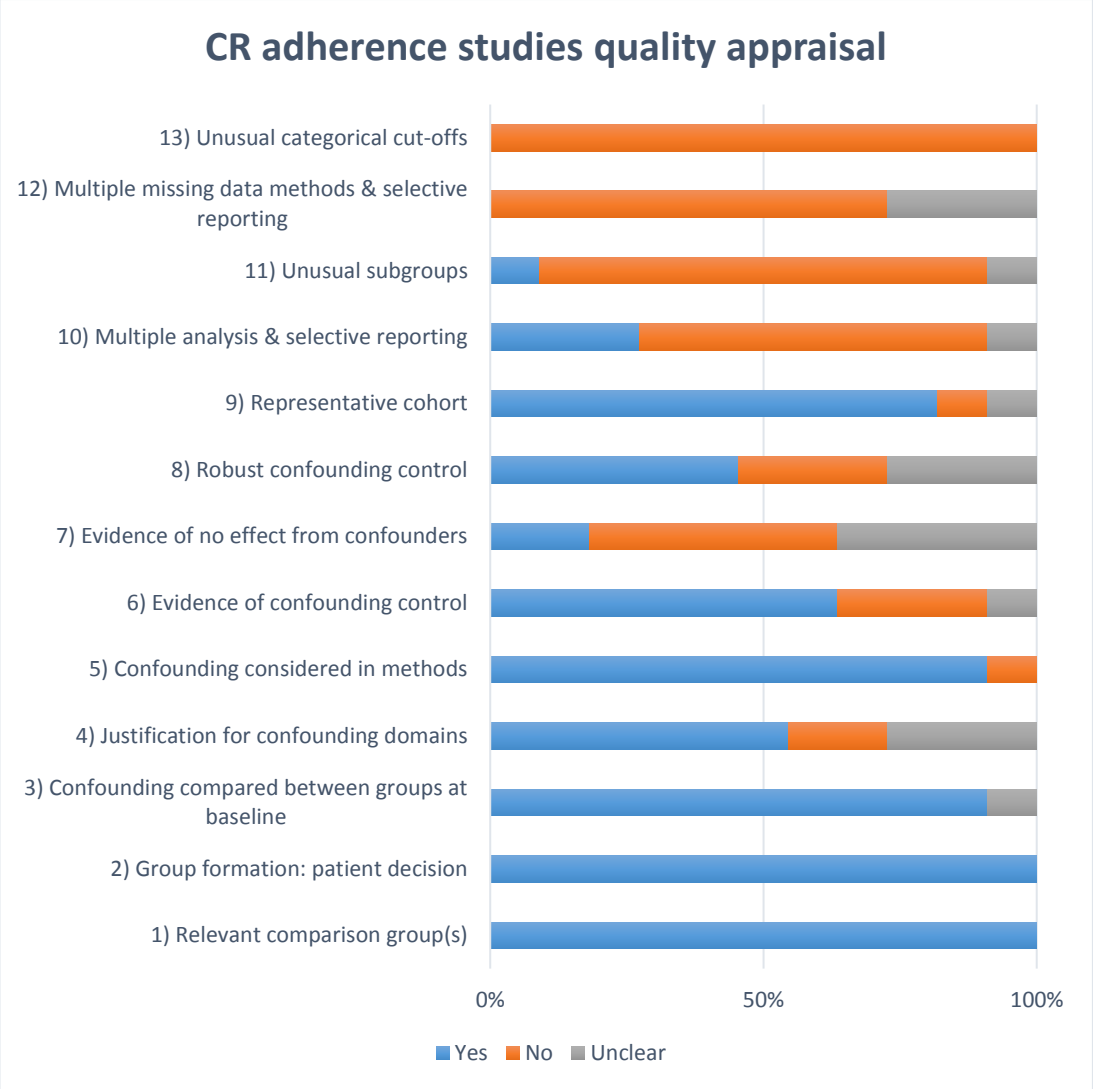


Figure 2.7 CR adherence studies quality appraisal.

A summary of the CR adherence determinants as reported in the investigated studies is displayed in (Figure 2.8). The figure bars are colour coded and labelled as previously described in (Figure 2.4).

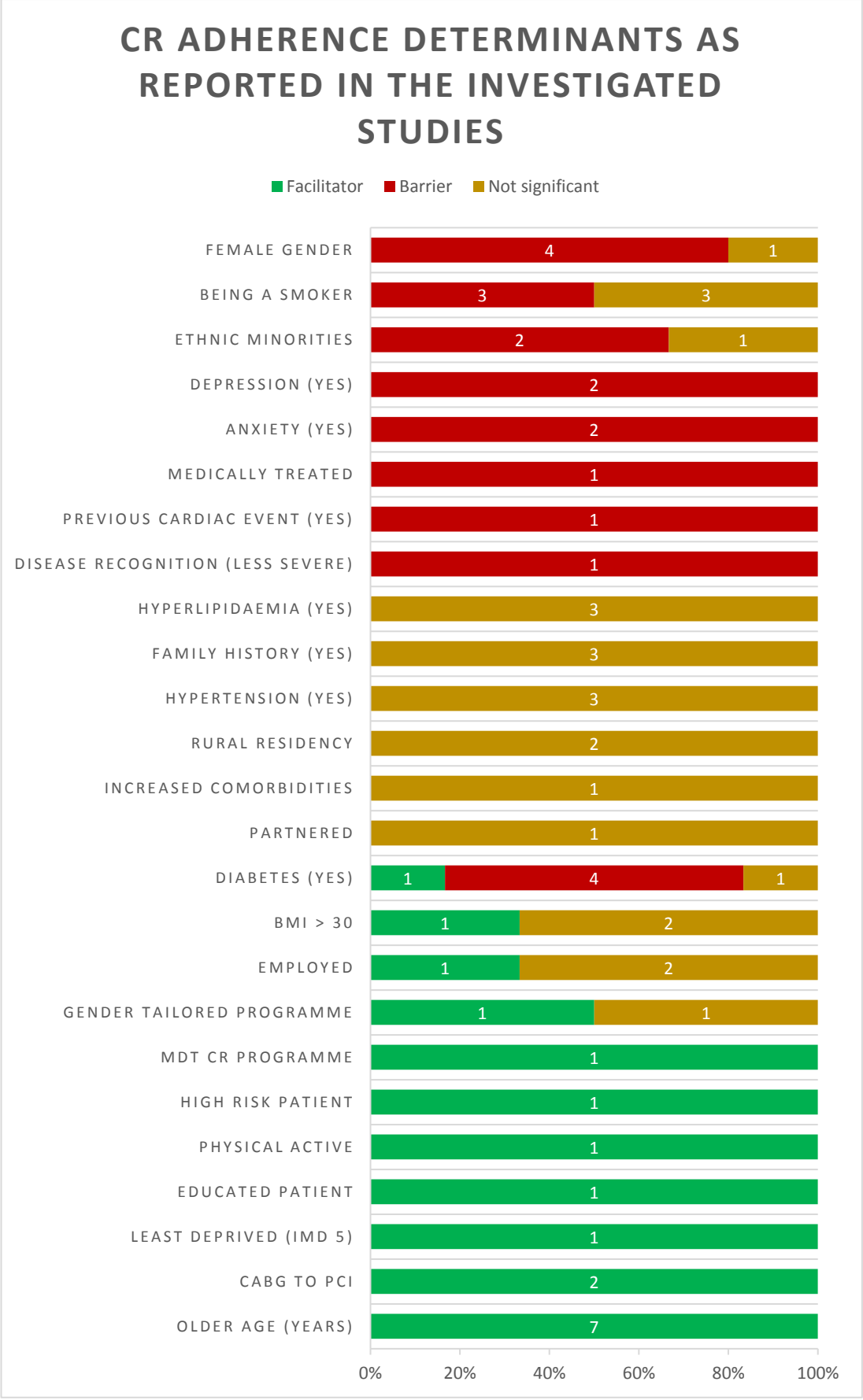


Figure 2.8 Determinants of CR adherence as reported in the investigated studies.

2.4.3.1 Patient's socio-demographics

Seven studies investigated the impact of age on CR adherence and all concluded that younger age is associated with higher dropout rates. Among which, three studies measured age as a continuous variable (in years) while the other three dichotomised age into two groups (≤ 65 and > 65 years). In the latter case, the odds of subjects older than 65 years to complete CR was (1.56, 1.9 and 2.39) (Casey et al. 2008; Turk-Adawi et al. 2013a; Harrison & Wardle 2005a) respectively. Within subjects aged 65 years or older, Doll et al (2015) found no association between age and CR adherence in those aged (65 - 74 years) and those aged (> 75 years) (p = 0.53) (Doll et al. 2015). In studies measuring age in years, Yohannes et al (2007) found out that younger participants are less likely to complete (OR: 0.89, 95% CI: 0.82 to 0.95) (Yohannes AM, Yalfani A, Doherty P 2007). Sarrafzadegan et al (2007) confirmed this finding by reporting that young patients are more likely to drop out (OR: 1.02, 95% CI: 1.00 to 1.03) (Sarrafzadegan et al. 2007). The last study conducted a t-test to compare the mean age of completers (63.5 years) to the mean age of non-completers (55.4 years) which was statistically significant (p < 0.001) (Beckie et al. 2015).

The impact of participants' gender on CR adherence was investigated in five studies. Yohannes et al (2007) and Sarrafzadegan et al (2007) found out that the odds of female participants to drop out early was (5.59 and 1.82) respectively(Yohannes AM, Yalfani A, Doherty P 2007; Sarrafzadegan et al. 2007). Among older participants (> 65), Doll et al (2015) found out that those attending (≥ 26 CR sessions) were more likely to be males (p < 0.001) (Doll et al. 2015). Also a univariate analysis study reported that participant's sex is statistically significant in the overall completion of CR (p = 0.02) (Harrison & Wardle 2005a). However, in a logistic regression analysis controlling for age, BMI, employment status and depression concluded that gender was not found a predictor of CR completion (OR: 1.34, 95% CI: 0.86 to 2.06) (Casey et al. 2008).

Participant's ethnicity was investigated in three studies. An American study concluded that Non-whites were less likely to adhere to CR than Whites (OR: 0.60, 95% CI: 0.41 to 0.88) (Turk-Adawi et al. 2013a). A UK study also revealed that South Asians are less likely than Whites to fully adhere to a 6-month CR program despite equal access and no cost barrier (p =0.04) (Banerjee et al. 2007). Among older American cohort (> 65 years), a study found out that White race is not associated with increased CR adherence (p = 0.79) (Doll et al. 2015).

Marital status was investigated in only one study and found to not to be significant (Sarrafzadegan et al. 2007).

The influence of employment status on CR adherence was investigated in three studies. Worcester et al (2004) revealed that retired and unemployed participants are more likely to drop out early than employed participants (OR: 1.83 and 4.69) respectively (Worcester et al. 2004). This is in contrast of the findings of Iranian study which reported that the number of CR sessions in which the subjects attended did not differ according to job category (Sarrafzadegan et al. 2007). Also a retrospective secondary analysis investigating CR adherence determinants in a mixed population found no association between employment and CR completion (OR: 1.37, 95% CI: 0.78 to 2.40) (Casey et al. 2008). However, CR completion rates are significantly higher in high-income neighbourhoods compared with low-income neighbourhoods as reported by a Canadian secondary retrospective study (OR: 5.40, 95% CI: 1.45 to 20.10) (Lemstra et al. 2013). The last reported determinant in this group is participant's education level which was investigated in only one study. This primary prospective multivariate analysis study, revealed that participants with educational level ranging from diploma to bachelor degree are attending more CR sessions than those with ($\leq$ high school) and those with ($\geq$ master degree) (20.9 ± 1.6 versus 17.2 ± 0.4, $p = 0.004$) (Sarrafzadegan et al. 2007).

2.4.3.2 Cardiac risk factors

The most reported determinant among this group is diabetes mellitus. It has been found statistically significant determinants of CR adherence in five out of six studies investigating this factor. The only two multivariate studies reporting this outcome were controversial. While Turk-Adawi et al (2013) observed higher adherence in patients with diabetes than without diabetes (OR: 1.3, 95% CI: 1.13 to 1.49), a previous study by Worcester et al (2004) reported that having a history of diabetes was associated with drop-out amongst attending men (OR: 3.38, 95% CI: 1.43 to 7.97) (Turk-Adawi et al. 2013a) (Worcester et al. 2004).

In the same vein but with a less robust method, Armstrong et al (2014) revealed that among 7,036 nondiabetic and 1,546 diabetic patients who completed CR, 84.9% of nondiabetic versus 79.6% of diabetic patients completed the 12-wk CR program ($p < 0.001$) (Armstrong

et al. 2014). Also an American secondary retrospective study reported that in patients older than 65 years, those with diabetes attend less number of sessions (≥26 sessions) ($p = 0.04$) (Doll et al. 2015). Similarly another American primary prospective study in a mixed population reported that completers are more likely to be nondiabetic ($p = 0.009$) (Beckie et al. 2015). The only study that couldn't prove this association was a middle-eastern study conducted by (Sarrafzadegan et al. 2007).

The impact of obesity, either reported as a BMI or waist size measurement, on CR adherence has been reported in four studies. A middle-eastern study prospectively investigating CR adherence determinants in MI patients reported that lower BMI (<30) and higher waist-to-hip ratio are significant predictors of CR completion (OR: 0.95, 95% CI: 0.92 to 0.98) and (OR: 12.87, 95% CI: 1.87 to 88.49) respectively (Sarrafzadegan et al. 2007). Conversely, an American prospective study investigating CR adherence determinants in mixed population found that women not completing CR had a larger waist circumference (107.5 ± 15.5 cm versus 99.6 ± 15.5 cm; $p = 0.014$) and reported no significant association between BMI or body weight and CR completion ($p = 0.06$ and 0.07) respectively (Beckie et al. 2015). The same conclusion was reached by another American retrospective secondary analysis studies which found no association between BMI and CR adherence (OR: 0.99, 95% CI: 0.95 to 1.02) and ($p = 0.70$) respectively (Casey et al. 2008; Doll et al. 2015).

Those who have higher psychological distress (anxiety and depression) as measured by Hospital Anxiety Depression (HAD) score were found to have higher drop out ratios (OR: 1.48, 95% CI: 1.21 to 1.82) (Yohannes AM, Yalfani A, Doherty P 2007). This finding is supported by another study which reported that participants who had higher levels of depressive symptoms were less likely to complete CR (OR: 0.96, 95% CI: 0.93 to 0.99) (Casey et al. 2008). Also this study revealed significant differences in anxiety and depression levels among young women and those who dropped out of CR compared with older women ($p < 0.001$) (Casey et al. 2008).

The impact of physical inactivity as a cardiac risk factor on CR adherence has been investigated in one study conducted by (Worcester et al. 2004). This study reported that women who exercise < 6 hours/week are 2.29 more likely to drop out than women exercising ≥ 6 hours/week (OR: 2.29, 95% CI: 0.58 to 9.03) and women who never exercise

are 7.32 more likely to drop out (OR: 7.32, 95% CI: 1.32 to 41.21). Hypertension, hyperlipidaemia and family history of cardiac disease were reported as not significant determinants of CR adherence (Beckie et al. 2015; Doll et al. 2015; Sarrafzadegan et al. 2007).

2.4.3.3 Lifestyle & health status

The most debated determinant in this group is smoking status. It has been found significant determinant of CR adherence in three out of six studies. An Australian primary prospective study reported that former smokers and current smokers are more likely to drop out from CR than those who never smoked (OR: 2.98, 95% CI: 1.07 to 8.27) and (OR: 3.33, 95% CI: 1.50 to 7.39) respectively (Worcester et al. 2004). This is supported by the findings of Iranian study which reported that non-smokers are 78% more likely to complete CR than smokers (OR: 1.78, 95% CI: 1.25 to 2.53) (Sarrafzadegan et al. 2007). Among older people (aged > 65 years), (Doll et al. 2015) reported that current and recent smokers are attending less number of CR sessions than non-smokers ($p < 0.001$). In (Yohannes AM, Yalfani A, Doherty P 2007) study, drop-out patients were more likely to be active smokers than were completers (26.2% versus 16.3%), however, this difference was not statistically significant. Furthermore, two more recent studies revealed no significant association between CR adherence and smoking status (Beckie et al. 2015; Turk-Adawi et al. 2013a).

The patient's risk category for cardiac events during exercise as defined by the American Association of Cardiovascular Pulmonary Rehabilitation (AACVPR) has been investigated in one study (Turk-Adawi et al. 2013a). This study revealed that those in the high risk category attended more CR sessions than the low risk group (OR: 1.42, 95% CI: 1.15 to 1.76) while there was no significant difference between the low and the moderate group (OR: 0.91, 95% CI: 0.68 to 1.22). The same study investigated the impact of different comorbid conditions on CR adherence such as arthritis, pulmonary disease, stroke, back pain… etc. and found no statistical significant association with CR adherence (Turk-Adawi et al. 2013a).

Older patients (> 65 years) who have a history of previous MI, PCI or CABG were found to be less likely to attend more CR sessions (≥ 26) than their counterparts ($p = 0.01$) (Doll et al.

2015). The influence of the participant's geographical location (urban or rural) on CR adherence has been investigated in two studies and found not significant (Harrison & Wardle 2005a; Turk-Adawi et al. 2013a).

2.4.3.4 Service level factors

The study conducted by Turk-Adawi et al (2013) measured CR adherence (≥ 21 sessions) by characteristics of CR facility. Programmes providing diet classes and diet counselling have higher rates of adherence (OR: 1.75, 95% CI: 1.34 to 2.27) and (OR: 1.55, 95% CI: 1.13 to 2.11) respectively. Also programmes offering psychological counselling, medications counselling, relaxation training, lifestyle modification lessons and medical director involvement have higher rates of adherence (OR: 1.49, 95% CI: 1.08 to 2.07), (OR: 1.41, 95% CI: 1.02 to 1.95), (OR: 1.25, 95% CI: 1.01 to 1.56), (OR: 1.32, 95% CI: 1.01 to 1.74) and (OR: 1.76, 95% CI: 1.02 to 3.04) respectively. In addition, those programmes with adequate space, adequate equipment and continuously assessing patients satisfaction have the highest adherence rates (OR: 2.57, 95% CI: 1.65 to 4.00), (OR: 2.03, 95% CI: 1.08 to 3.81) and (OR: 3.32, 95% CI: 1.30 to 8.51) respectively (Turk-Adawi et al. 2013a).

With regards to disease recognition, Yohannes et al (2007) in a primary prospective study reported that participants who consider their illness has less severe consequences are more likely to drop out (OR: 0.61, 95% CI: 0.50 to 0.76) (Yohannes AM, Yalfani A, Doherty P 2007). In the same line, a secondary retrospective revealed that those who underwent CABG are 54% more likely to attend more CR sessions (≥ 21) (OR: 1.54, 95% CI: 1.24 to 1.82) (Turk-Adawi et al. 2013a). Also another secondary retrospective study investigated the impact of the revascularisation strategy (PCI, CABG or medical therapy alone) on CR adherence (≥ 26 sessions) among older patients (> 65 years) and found it significant in a univariate analysis ($p < 0.001$) (Doll et al. 2015).

In a randomised trial, Beckie & Beckstead (2010) tried to compare the impact of two gender tailored programme on CR adherence among women (women's only versus mixed-sex). Overall, the mean number of sessions attended by women in the gender tailored CR was higher than traditional CR ($p < 0.001$) (Beckie & Beckstead 2010). Conversely, Grace et al

(2016) clinical trial concluded that women adhered moderately to all included CR models (supervised mixed-sex, supervised women-only, or home-based CR) (Grace et al. 2016).

2.4.4 Summary of all determinants

This study set out to systematically review the existing literature around the determinants of CR utilisation. As detailed in the previous sections, a total of 46 different determinants have been identified in the investigated studies. Table 2.7 displays an overview of all reported determinants for CR engagement, uptake and adherence. In this table, there are four columns where the first one displays the name of the determinant and the remaining three columns represent each stage of CR utilisation. Each cell of this table has two types of data; (1) a figure to show the total number of studies investigated that determinant (2) a small coloured doughnut chart. The chart reflects the proportion of studies that reported the determinant as a barrier (red colour), facilitator (green colour) or not statistically significant (yellow colour). The benefit of this approach is to give the reader a general overview of the number of studies that investigated each determinant and to show any controversy in the literature about this determinant. However, this table doesn't show the strength nor the quality of the evidence displayed.

Table 2.7 A summary of all reported determinants in the investigated studies.

Variable	Engagement	Uptake	Adherence
Older age	3	29	7
Female gender	1	14	5
Ethnic minority	1	8	3
Least deprived patient	-	5	1
Partnered	3	13	1
Social support (yes)	-	10	-
Employed	1	11	3
Educated	1	12	1
BMI > 30	3	7	3
Physical inactivity (yes)	2	4	1
Smoking (yes)	3	9	6
High income (yes)	2	9	-
Angina (yes)	-	4	-
Diabetes (yes)	2	13	6
Hypertension (yes)	-	8	3
Anxiety (yes)	-	4	2
Depression (yes)	1	2	2
Family history of cardiac disease (yes)	1	-	3
Hyperlipidaemia (yes)	1	9	3
Increased number of comorbidities	1	3	1
Previous cardiac Event (yes)	-	13	1
Elective PCI (yes)	-	1	-
CABG procedure (yes)	2	4	2
Medically treated (yes)	-	17	1
Travel distance (furthest)	2	9	-
First language proficiency (yes)	1	2	-
Ability to drive (yes)	-	3	-
Health perceived as excellent (yes)	-	2	-
Multidisciplinary team centre (yes)	-	-	1
Received confirmed joining date (yes)	-	2	-
Patient received early CR (yes)	-	1	-
Day case PCI (yes)	-	3	-
BMI/Private Hospital	-	1	-
Small or affiliated Hospital (<160 bed)	-	2	-
Automatic referral to CR	2	-	-
Positive physician perception of CR	1	-	-
Physician referral intention	1	-	-
Strength of physician endorsement	1	-	-
Referral prior to CABG	1	-	-
Disease recognition (less severe)	-	-	1
High risk patient (yes)	-	-	1
Rural residency (yes)	-	-	2
Gender tailored programme (yes)	-	-	2

Key: Systematic review (SR) findings = proportion of studies in each category

2.5 Discussion

This study set out with the aim of assessing the determinants of CR engagement, uptake and adherence since CR utilisation rates worldwide are below desirable. A total of 46 studies (N= 398,667) were included in the final review. This is 17 studies more than a recent systematic review conducted to analyse factors affecting CR utilisation (Ruano-Ravina et al. 2016). Included studies were performed in eight different countries, with different study designs, covered mixed diagnoses and different treatment methods. Although these factors may increase heterogeneity among reported results, however, it ensures that the reported determinants are reflecting the real practiced CR worldwide. Despite the sparse controversial disagreements among studies' results, our findings clearly indicate that there is a sort of global homogeneity in CR utilisation determinants.

Although extensive research has been carried out on CR uptake and adherence, researchers have not treated CR engagement in much detail. Our search strategy has identified only four studies that investigated CR engagement where three of them were conducted by the same first author. Patients experiencing automatic referral combined with head-to-head discussion are eight times more likely to engage in CR than patients following usual referral strategy (Grace et al. 2011). The second strongest reported determinants of CR engagement is geographical proximity to CR centre. Those individuals living near a CR centre were found to be three times more likely to engage in CR than those living further away (Smith et al. 2006). Other determinants with relatively high impact on CR engagement were age, gender, language proficiency and treatment type. However, with such a small study number, these data must be interpreted with caution as the findings might not be extrapolated to the whole population.

CR uptake determinants captured the largest share of the included studies in this review, 32 studies with a population of 361,934 participants. Being investigated in 29 studies, patient's age has been the most investigated determinant of CR uptake. Despite discrepancies in the statistical techniques used, 21 studies found younger age to be significantly associated with CR uptake reporting odd ratios between 40-70% in multivariate analysis studies. Similarly, gender has been reported in 14 studies indicating that males are more likely to start CR 11-280%. This phenomena has led to the introduction of studies dedicated to investigate CR

uptake in female population exclusively. Despite the documented critical role played by age and gender in health related behaviours (Thompson et al. 2016; Deeks et al. 2009), only one study has investigated age-gender interaction (Dunlay et al. 2009).

Among the included studies and within the socio-demographic group, 7 out of 13 studies reported marital status as significant determinant, 5 out of 10 for social support and 6 out of 12 for education level. With such controversy in findings, these determinants remain the most debated in regards to CR uptake. It is difficult to explain these contradictory findings, but it might be attributed to the susceptibility of observational study designs to confounding. Particularly, some of these studies utilised amenable statistical techniques, univariate analysis. Moreover, most of these studies were conducted in relatively small studies which may not contain all of the characteristics and variables reported previously in the literature.

Geographic barriers like transportation time, urban/rural differences and the ability to drive are reported as a major determinant of CR uptake. As anticipated, those who live farther away from the CR centre were found to have the least likelihood of starting CR (up to 80% less). Also the ability to drive has increased the likelihood of subjects to start CR by two to three-fold. The overcoming of this type of barriers is usually beyond the scope of clinical practice, however, other types of CR like home-based CR might be a possible alternative. The type of treatment received for the index cardiac event also plays a major role on the patient's decision to start CR. Those who underwent revascularisation procedure, particularly CABG, are more likely to start compared with those treated with medications only. A possible explanation for this might be that those patients treated by medications do not perceive that their condition warrants CR compared to those hospitalised for revascularisation (Grace et al. 2010).

With regard to adherence and unlike uptake, younger age has been found to be a determinant of early dropout in all 7 studies that investigated age. While female gender remained a predictor of poor CR utilisation. Diabetes mellitus was also found to be a factor increasing dropout rates in 4 studies but vice versa in 1study. Also smokers or former smokers are less likely to adhere to CR as reported in three studies. These findings raise a flag to CR directors that current CR programmes are less attractive to those who are in increased risk of having another event.

Service level factors play a major influence on the patient's decision to stay in the programme. The study conducted by Turk-Adawi et al (2013) concluded that some modifiable organisational factors such as assessment of patient satisfaction and having adequate space and equipment can largely improve patients' adherence (Turk-Adawi et al. 2013a). Despite the negative finding by Grace et al (2016) trial, with regards to the introduction of a gender tailored programme which might be attributed to sessions timing. Introducing alternative programme models might increase adherence in the less representative groups as proven by Beckie & Beckstead (2010) trial (Grace et al. 2016; Beckie & Beckstead 2010). However, the data with regards to CR adherence must be interpreted with caution due to the different definitions of CR adherence and completion across studies.

2.6 Limitations

The most important limitation lies in the fact that it was not possible to pool the results through meta-analysis due to the significant heterogeneity of studies included. This heterogeneity resulted from different sample size, different population, study design, statistical analysis and how CR engagement, uptake and adherence are defined across included studies. Another source of weakness is the limited number of studies investigating CR engagement that were included in this review.

2.7 Conclusion

This systematic review analysed data from 46 studies conducted in 8 countries (N = 398,667). This study has identified determinates of CR utilisation from baseline assessment to completing the programme. Taken together, some of the determinants like age and gender are not modifiable and the only way to counter their influence is to understand how CR is offered and seek solutions around how to optimise throughput so that services tackle such inequalities. While other determinants are service related and more work can be done in this area to improve utilisation. As there is a good rationale for increasing CR utilisation, further high quality research is needed to better understand barriers against CR utilisation particularly in the CR engagement stage.

3 Methodology

3.1 Background & aim

Published research in the medical field is being generated at high rates with an aim to increase clinical knowledge and thus better understanding of health related issues. This 'explosion of knowledge' as referred to by many authors, must be accompanied by training on how to critique and conduct robust evidence based clinical research. Therefore, there is a need to quality assure papers so that decisions made about clinical practice are based on valid evidence. This type of evidence is obtained by conducting high-quality research in a systematic and principled way. These methods are distinguished by following a sequential process while obeying explicit rules. These processes and rules form what is known in research as 'methods' which should not be confused with the other term 'methodology'. In fact and strictly speaking, the terms 'methodology' and 'methods' refer to different meanings. Polgar & Thomas in their book 'introduction to research in the health sciences' define methods as the rules used for acquiring and analysing data which lead to establishing evidence in research whereas methodology refers to the critical discussion, comparison and application of different methods (Polgar & Thomas 2013).

As discussed above, there is a need to quality assure papers so that decisions made about clinical practice are based on high-quality research. Hence, the purpose of the first section in this chapter is to conduct a critical discussion on the possible valid methods that can be used to answer the primary research question. This is better achieved by comparing all applicable scientific methods then justifying why a specific method was favoured over the others. The second section of this chapter will attempt to explain how the primary data used throughout this research is collected and managed by the NACR team. The third and last section of this chapter will focus on data analysis and what steps should be followed to obtain robust research findings. This latter section will include a sub-section on how data is prepared prior to being analysed focusing on how to handle missing data and outlier values. Another sub-section about model building, model diagnostics and model validation will close this chapter. However, each study in this thesis will have its own methods section that contains more specific details related to that study.

3.2 Research design

Quality of research can vary considerably due to methodological rigour. Defects in design or the way research is conducted may result in bias and therefore measured effects can be obscured. Research design is defined as the clear statements of how the research data is collected in the study and this design should guide data collection suitable for answering the research question (Polgar & Thomas 2013). This design should also help to give an unbiased estimate of whether one treatment is more effective or safer than another for a particular population (Anglemyer et al. 2014). Bias in the literature has been defined as;

> *"The systematic deviations from the true underlying effect brought about by poor study design or conduct in the collection, analysis, interpretation, publication or review of data"* (Centre for Reviews and Dissemination 2009).

In the field of clinical research, there are different types of research designs that are in use and each type can address different research questions more appropriately. One way to classify different types of research designs is by the strength of evidence they provide. This classification is known as 'evidence hierarchy' (Ligthelm et al. 2007) (Table 3.1).

Table 3.1 Main types of research designs sorted by strength of evidence[6].

Strength of evidence				Bias
	Review	Systematic review &meta-analysis	Collects all previous studies on the topic and statistically combine their results.	
	Experimental	Randomised control trial (RCT)	Randomly assign a group of individuals to receive treatment or placebo.	
		Quasi-experiment	Same as above but without random assignment.	
	Observational	Cohort study	A defined group of participants is followed over time and comparison is made between those who did and did not receive an intervention.	
		Case-control study	Compares histories of a group of people with a condition to a group of people without.	
		Cross-sectional study	Assessing the prevalence of an outcome at one point in time at a broad population.	

As shown in (Table 3.1), research designs can be classified in a hierarchical shape based on their susceptibility to bias and therefore the strength of evidence they provide (Centre for Reviews and Dissemination 2009). Although experimental designs are considered less susceptible to bias than observational, researchers may instead use observational designs in cases that it is unworkable or unethical to use experimental designs. When is it more suitable to use one design over the other and what are the pros and cons of each will be discussed in the following section focusing mainly on RCTs versus cohort observational as these are the main two types used in clinical research (Noordzij et al. 2009). Particularly that these types of design have led to debate in the area of cardiology and CR (e.g. RAMIT and Cochrane RCT only reviews versus CROS observational reviews).

[6] Adapted from Oxford centre for evidence-base medicine.

3.3 Trial vs Observational

Before comparing the two research designs, it is fundamental to understand what each term exactly refers to. RCTs mainly refer to the study design where individuals are randomly assigned into control group or intervention group (or to multiple intervention groups) by the play of chance (randomisation). Another important feature of RCT is concealment which means that the intervention or treatment allocated to groups cannot be known in advance. Although there are different types of RCTs such as parallel RCT, cross-over RCTs and cluster RCTs, they all share these two main features which are conducted to limit the risk of bias (Centre for Reviews and Dissemination 2009). Researchers normally use evidence from RCTs to evaluate the efficacy of an intervention or treatment under ideal settings.

In the other hand, observational designs do not require randomisation and the assignment of individuals is determined by usual practice or 'real world' choices. That means the allocation of individuals into control or intervention groups is outside the control of the researcher (Rosenbaum 2002). In this design, the researcher merely observe in natural settings the differences between those who did and did not receive the intervention. Observational designs can be used to measure the efficacy of an intervention or treatment in non-experimental 'real world' environment at the general population level (Anglemyer et al. 2014). Researchers normally use observational designs for hypothesis generation and highlighting areas for further research (Centre for Reviews and Dissemination 2009). Taken together, observational studies are vital in building clinical evidence, exploring how an intervention is practiced on the ground and understanding disparities in access to and delivery of healthcare services (Carlson & Morrison 2009).

Regardless of the chosen research design, the ultimate goal is to achieve unbiased, reliable and generalisable results. RCTs, when properly conducted, limit the risk of bias more than observational designs. This is because in RCTs the groups being compared are similar in all aspects other than the intervention. Also the groups, in properly implemented RCT, are balanced for both known and unknown factors that might affect the measured outcome. This type of setting limits the influence of any confounding factor that might mediate the results.

Although RCTs are considered the most rigorous method in research designs and level A evidence in the evidence hierarchy by AHA, ACC and ESC (Hannan 2008; Silverman 2009), this method has a number of weaknesses. The tightly controlled environment required for RCTs does not include all the issues faced by clinicians in real world practice. Also the selective process in choosing participants may make the study population less representative of the whole population. These strict selection criteria of environment and participants in RCTs question the generalisability of its findings (Noordzij et al. 2009). Because RCTs are time consuming and expensive in addition to the difficulty in recruiting suitable participants, they may have inadequate statistical power which can make them underpowered to detect important differences in outcomes (Hannan 2008). A major limitation of RCT designs is in cases where it is unethical to randomise patients such as situations where the intervention is believed (but not yet proven) to have a negative effect on participants (Collet 2000). Other situations where RCTs are possible but not appropriate, include the follow up of adverse events that are rare or may take several years to develop (Noordzij et al. 2009). In summary, where a solid evidence of efficacy exists, there is no further need to conduct RCT's. This is why some RCT's, like RAMIT, failed to recruit even a quarter of the planned sample size (Silverman 2009; Doherty & Lewin 2012).

The weaknesses and limitations mentioned above have led to a call for other relevant research design to supplement the important findings achieved by RCTs. This design should complement findings from RCTs by assessing treatment efficacy in a natural real world environment and in larger more diverse population with longer follow up periods. This design should also be capable of identifying clinically important differences among proven treatments which should complement the clinicians' knowledge of available treatments. Moreover, this design should provide data on treatments long-term safety and tolerability. All these features are inherent features of well performed observational designs. It could be argued that observational designs are an important addition to the clinical researcher resources by complementing RCTs findings with information on efficiency, safety and patient clinical behaviour in a real world population. Furthermore, observational studies allow researchers to better understand which factors determine the likelihood of taking up trial based interventions in the real world setting (Silverman 2009).

However, it should be noted that the most serious shortcoming of observational designs is the selection bias which is happening due to the absence of randomisation (Hannan 2008). Selection bias can lead to large unobserved differences between treatment and control groups which may result in false estimates of treatment effects and therefore manipulate the outcomes being measured. These unobserved differences are known as confounders and can be controlled for by robust statistical techniques (Field A. 2013). This effect can also be reduced by conducting the analysis in large high quality database that contains all of the characteristics and variables reported in the literature previously and known to have an effect on the measured outcome (Hannan 2008).

In this thesis, the primary research question is: 'what are the factors that determine CR engagement, uptake and adherence in the PCI population?' This question focuses predominately on determinants and not outcomes which means RCT designs are not appropriate. There is also evidence from the NACR, wider literature and health care policy targets that patients are not utilising evidence based programmes which further legitimates the use of observational studies to help understand how CR utilisation can be improved and how CR can be made more attractive to patients (NACR reports). In addition, cohort observational design will provide a large enough sample of patients to be investigated and followed for longer periods which is a major limitation of the previous studies. Also the NACR dataset with close to a million patient and more than 1,000 variables collected can be analysed using rigours statistical techniques to achieve valid and reliable results.

3.4 Data source

This thesis intends to generate new knowledge and insights on the determinants of CR engagement, uptake and adherence in the PCI population. This will be achieved by conducting a secondary analysis on the NACR dataset aimed at addressing key research questions. The specific objective of this section is to explain what NACR is and how it collects the data.

3.4.1 The National Audit of Cardiac Rehabilitation

Established in 2005 and funded by the BHF, NACR was designed to support cardiovascular prevention and rehabilitation services to achieve the best possible outcomes for patients. The aims of NACR are to increase the availability and uptake of prevention and rehabilitation programmes, and promote best practice and quality improvement in cardiovascular prevention and rehabilitation services by:

- Monitoring and supporting cardiovascular rehabilitation (CR) teams, commissioners and coordinators in delivering high-quality and effective services, to evidence-based standards, for the benefit of all eligible patients;
- Highlighting inequalities and insufficiencies in the delivery of cardiovascular rehabilitation services against key service indicators at strategic clinical network, clinical commissioning group, health board and cardiac network levels for over 308 CR programmes in the UK;
- Designing and implementing research to determine the effectiveness of routinely delivered CR services on patient agreed outcomes, cardiovascular disease risk profiles and health and social care utilisation;
- Using audit and research data generated through the NACR to inform:
    - NICE clinical guidance and service specification development
    - Clinical practice standards from national associations
    - NHS healthcare commissioning processes and decision making
    - The public and cardiac patient groups about how their local services are performing.

NACR is managed by a team based in the Department of Health Sciences at the University of York. Informatics and data management services are provided by the NHS Digital based in Leeds.

3.4.1.1 Data collection

NACR has approval to collect anonymised patient data for a range of clinical variables. The audit collects data for patients who undergo CR in the UK including the following criteria.

- Demographic - gender, date of birth, postcode, ethnic status (national census method). Clinical - blood pressure, weight, height, cholesterol, medication, initiating event (reason for rehabilitation), previous cardiac events, and comorbidities.
- Behavioural - smoking status, activity level, economic activity measures from National Census, physical fitness.
- Health-related quality of life as scored via the Dartmouth Coop questionnaire.
- Mental health - anxiety and depression as scored via the Hospital Anxiety and Depression Scale (HADS).
- Wait time - date of initiating event, date referred to cardiac rehabilitation, date invited to join, date started rehabilitation programme, date finished.
- Uptake - agreed to take part (yes, no) and reason for refusal or being unable to attend.
- Drop-out rates - reason for not completing cardiac rehabilitation, if known.

Some of the data fields are collected via a set of self-reporting questionnaires in which respondents read the question and select a response by themselves without medical staff interference (copy of questionnaires in appendix 9-8). In addition to electronic data collection, staffing details (per centre) were collected from the annual NACR paper survey, which collects data on types of staff, hours worked and numbers of staff per program (NACR 2016).

Information is entered manually into the NACR through a secure online portal, provided by NHS digital. Alternatively, data files of records for multiple patients are uploaded. Data is gathered by clinicians and by purpose-designed questionnaires. Patients complete a questionnaire before, immediately after, and 12 months after attending rehabilitation. The staff of the individual CR programmes distributes the questionnaires themselves, receive the

replies, and submit the data to the NACR database. Postal surveys collect information on organisational elements such as staffing and activity.

The NACR team at York send questionnaires out to the co-ordinators of every cardiovascular prevention and rehabilitation service on the register they maintain, receive the responses, collate the results and include them in the project's annual reports. Electronic-survey is also collected to enable the audit to be sensitive to changes in clinical practice. The York team use the data to produce annual reports and ad hoc reports on request by individual programmes. Programmes can also view and download their data for local analyses.

For all collected data the NACR team record who created them, which centre and the date of creation. Also they the team creates additional variables that can be utilised such as CR duration and variety of waiting times variables. Figure 3.1 below illustrates two different paths of CR collected by the NACR team.

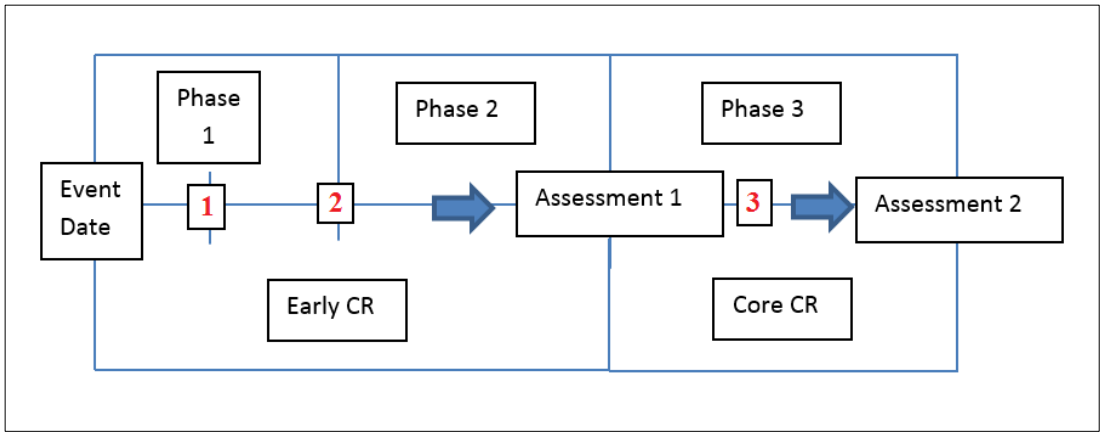


Figure 3.1 Two different paths of CR collected by NACR.

In (Figure 3.1) the red numbers 1, 2, and 3 refer to the following;

Identified on the Ward post cardiac event treatment.

1. Discharge from hospital.
2. Core CR, or outpatient CR, what the NACR report mainly focuses on and lasts for 8-12 weeks, on either side is the Assessments 1 and 2 (pre and post, used in most NACR research).

3. 12 months post CR, this was the community based CR also known as Phase 4, at 12 months on patients are invited to complete questionnaires and come in for the last assessment.

3.4.1.2 Data entry

Data entry is the process of digitising data by keying it into a computer system; manual data entry describes the physical process of typing information into computer software. NACR data collection involves human operators keying in data found on patients' record. The manual process of data entry has a main disadvantage in speed and accuracy. Manual data entry occasionally introduces the possibility of human error. Moreover, workers working under stress or suffering from a lack of concentration or fatigue may make more errors. These entry errors impact the quality of data and may affect the outcome result.

One of the greatest challenges facing any large database managers is how to improve and maintain the quality of their data. NACR has tightened up on data quality procedures to align with NICE guidance and the emerging NHS commissioning and accountability frameworks (NACR 2014). In order to improve the quality of data, two main techniques are usually adopted. The first approach is an automated data auditing and cleaning by adding validations to the entry fields in the portal system to prevent users from keying in extreme values. The second, is by exploratory data analysis and cleaning conducted manually by the person analysing the data (Hellerstein 2008).

3.4.1.3 Ethical & research approval

Gaining patient consent to use their data for national audit purposes is extremely difficult challenge and would create extra burden on staff and services during the management of a heart attack or following a cardiac surgery. This is an issue for many NHS services which has led the UK Government and the NHS to adopt a national process whereby, in certain circumstances and with sufficient safeguards applied, the requirement for patient consent is relaxed. For this reason NHS give exemption from individual consent in such cases. In fact, NACR is authorised from the Health Research Authority's Confidentiality Group (CAG) to collect patient identifiable data without explicit consent from individual patients (under section 251 of the NHS act 2006). However, patients are informed about the purpose of the audit and how their data will be used in face to face communication and through any

questionnaire they fill. They are also told that they can opt out without any effect on their treatment (NACR 2016).

With respect to researchers, NACR data is used for a large number of purposes, including post graduate and PhD theses (NACR Information Sheet 2017). However, before analysing NACR data, the researcher should be aware that NACR has a strict Data Sharing Agreement with NHS Digital and they should adhere to number of regulations all the time. First a researcher must complete and pass the Information Security Training Course arranged by the University of York before being permitted to access the data. The researcher should also be aware of what is permitted and not permitted for the processing and dissemination of the audit data. The following is a list of what is permitted and not permitted as stated in the information sheet about the usage of NACR data (July 2017 update).

First, what is permitted;

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

Second, what is not permitted;

- The data must not be copied or removed from the Department of Health Sciences secure network ("I Drive") in original or altered forms even when using a password protected external storage device.

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

3.4.1.4 Quantitative secondary data analysis

The word quantitative has a direct meaning which refers to data that express a certain quantity, amount or range (numerical data) while the term secondary analysis is more complicated. In the field of clinical research, the difference between the terms primary and secondary data depends on the relationship between the person who collected a dataset and the person who is analysing it. This is an important concept as the same set of data could be

primary in one analysis and secondary in the other (Boslaugh 2007). The term secondary data is used in social science when the data were collected by someone other than the researcher. Several definitions for secondary data analysis appear in the literature with minimal differences. One of the earliest definitions was suggested by Glaser in 1963: "the study of specific problems through analysis of existing data which were originally collected for another purpose" (Long-Sutehall et al. 2011).

Another recent definition was proposed by Hewson in 2006: "the further analysis of an existing dataset with the aim of addressing a research question distinct from that for which the dataset was originally collected and generating novel interpretations and conclusions" (Smith et al. 2008). Secondary data can come from many sources such as large, government-funded datasets, university or college records etc.

Re-using existing data has some major advantages. First, data contains large sample sizes of higher quality data than most researchers could realistically produce themselves, saving time and resources. Second, data represent real populations where low prevalence groups are oversampled which results in increased statistical power and precision. Other advantages include the fact that datasets often contain considerable breadth (hundreds of variables). Researchers can assess change across time using data collected for several years - this would be difficult for one researcher to collect (Cheng & Phillips 2014; Vartanian 2011).

The use of secondary data means study design and data collection has already completed and researchers must be careful to interrogate and explore new questions with caution as the data may not facilitate particular research questions. In addition, users of secondary data should spend some time exploring associated documentation to understand how the data were collected, from whom it was collected and what was done with it after data collection (Vartanian 2011).

Secondary data analysis imposes retrospective analysis of the data. Retrospective analysis is the opposite of prospective analysis where researchers design the study before subjects develop the measured outcome. One advantage of retrospective analysis, using large registries or audits, is that it makes use of existing data, which, compared to prospective studies requiring patient recruitment, means the data collection phase of the study is much

quicker. Subject to having strong statistical support and data modelling expertise retrospective observational studies are also good for studying multiple outcomes and addressing less common exposures which normally requires large cohort in prospective analysis. For instance, this was evidenced in prospective CR studies, such as RAMIT, which struggled to recruit sufficient patients to allow robust analysis (see chapter 2) (Doherty & Lewin 2012). Although there are inherent weaknesses with retrospective studies mainly the disadvantage that the data was originally constructed to measure another outcomes, this can be accounted for as part of the new study design.

The use of large datasets requires in-depth knowledge of statistics and experience in at least one statistical software package, which is not generally provided by basic graduate statistics courses. This is fundamental as the user will need to do some data manipulation in order to structure their chosen dataset into a form appropriate for analysis for each study. The required statistical knowledge includes how to deal with missing data and outliers in an appropriate way as the researcher has no means to access the original dataset. A key aspect of secondary data analysis is the need to behave ethically when using the data. It is important to ensure that the data is used to its full potential, whilst ensuring promises of confidentiality made to the data subjects are kept.

3.5 Data analysis

A well designed study, poorly analysed, cannot lead to reliable results. Data analysis, in general, is defined as '*the process of systematically applying statistical and/or logical techniques to describe and illustrate, condense and recap, and evaluate data*' (Rcr & Project 2008). Data analysis is the stage when researchers manipulate the raw data in a scientific method to convert it into information that inform the answers for research questions, test hypothesis or challenge previous knowledge. The famous statistician John Tukey defined data analysis in 1961 as *'Procedures for analysing data, techniques for interpreting the results of such procedures, ways of planning the gathering of data to make its analysis easier, more precise or more accurate, and all the machinery and results of (mathematical) statistics which apply to analysing data'* (Tukey 1962).

There are several phases in data analysis that can be distinguished. These phases are interrelated and iterative in a way that feedback from later phases may generate extra work in earlier phases (Schutt & O´neil 2014). After data collection the data should be processed or organised for analysis (data structuring). Once the data have been structured, evaluating the data for missingness, duplication and errors will be more plausible. This phase is known as the data preparation phase. After that, data is ready to be explored. Normally the first stage in this phase is to run descriptive statistics to begin to understand the key messages contained in the data (Few 2004). Descriptive statistics, however, may result in additional data cleaning or even additional data collection. Descriptive statistics is an important phase in data analysis as it helps the researcher to visualise the data by expressing it in graphical format or in mathematical format such as averages and medians.

The following phase in data analysis is to identify relationships among the analysed variables, such as correlation, by applying mathematical formulas or models called algorithms (Judd & McClelland 1989). This phase is usually conducted with the aid of sophisticated software statistical packages such as SPSS or STATA. These packages will help the researcher to conduct statistical modelling such as regression in which an outcome variable is predicted by a combination of one or more predictor variables (Field A. 2013). The final stage of data analysis is validating the obtained results to decide whether these results are acceptable as discerptions of the data analysed.

In order to meet the required statistical skills to answer the research question, the author of this thesis has successfully completed basic and advanced statistics modules provided by the department of Health Sciences at the University of York. In addition, the NACR research team provides senior statistical support to its researchers. Furthermore, Dr Nils Gutacker (second supervisor) has provided valuable advice and assistance on data preparation, analysis and modelling.

3.5.1 Data preparation

Data preparation plays a critical role in secondary data analysis. Research findings and hypothesis testing can go profoundly wrong if data preparation has been overlooked. In order to conduct a robust secondary data analysis, the researcher should prepare the data appropriately to decrease error rates and increase both the power and replicability of results.

This includes learning the necessary skills on how to deal with missing values and outliers in a methodological way as the researcher has no means to access the original dataset. Missing values and outliers arise in almost all secondary statistical analysis. They have been always a threat to the validity of clinical research (Langkamp et al. 2010; Kwak & Kim 2017; Cheng & Phillips 2014).

3.5.1.1 Missing values

When no data value is stored for a covariate in an observation we say there is a missing data or missing values in the dataset. In the field of statistics, various definitions of missing values are found. One definition of missing values in the literature is *'the values that are not available and that would be meaningful for analysis if they were observed'* (Dupont 2011). Missingness in the data can occur for several reasons such as non-respondents in a survey or dropout subjects in longitudinal studies. Missing values are unavoidable in clinical research but their potential to impact the analysis has often been overlooked in the medical literature (Wood et al. 2004).

Large data sets are full of legitimately missing data, and researchers need to be thoughtful about handling this issue in an appropriate methods (Osborne 2012). Due to the nature of how NACR collects its data, there is a considerable number of missing data. Although timely NACR data entry has improved and is prompt for some programmes, it can be behind by months due to working processes, waiting times or lack of data entry clerks. In addition, the electronic update of the NACR database is performed every three months while the survey data is only updated once per year. However, NACR team has made enormous efforts to improve the quality of the data collected which can be easily noted when comparing recent data quality to those five years ago.

Researchers in health sciences usually address missing data by excluding incomplete cases in the analysis (Sterne et al. 2016). This practice has been adopted for two possible reasons. First, it has commonly been assumed that if data are missing at random, the analyses will tend to be unbiased, although based on a smaller sample size than the original data set (Higgins & Green 2011). Second, statistical techniques that can handle missingness in the data have, until recently, not been readily accessible to medical researchers (Sterne et al. 2016). However, research findings using only complete data should be based not only on

observed data values but should also take account of why data are missing (Seaman et al. 2013). Understanding the causes of data missingness is vital to appropriately tackle the incomplete data. If values are missing completely at random, the collected data sample may still represent the population. But if the values are missing in a systematic pattern, the analysis may generate biased findings (Adèr & Mellenbergh 2008).

When we say values in a dataset are missing completely at random (MCAR) that means missingness is independent on the response or any of the other observed data, i.e. missingness occur entirely at random (unsystematic). The analysis conducted on MCAR data is unlikely to be biased, however, data are rarely MCAR (Hosmer, Lemeshow 2013; Polit & Beck 2012). A less stringent assumption is that data missingness is not random (systematic) but it can be entirely explained by other observed variables. For example, respondents in service occupations were less likely to report their income. Data that meets this assumption is known as data missing at random (MAR) (Bhaskaran & Smeeth 2014). Complete cases analysis in MAR data is more vulnerable to bias compared with MCAR, however, exclusion of subjects with incomplete data may increase the loss of precision and power in the analysis (Sterne et al. 2016). The third type of missingness is known as missing not at random (MNAR). This is when data missingness is systematic even after the observed data are taken into account. To extend the previous example, respondents with high income were less likely to report their income. In this situation, complete data analysis will definitely generate biased results (Little, R.J.A., Rubin 1987).

If we assume data are MAR, then unbiased and statistically more powerful analyses can generally be done by including subjects with incomplete data. A range of simple techniques are commonly used to deal with missing values. One of which is replacing the missing values with imputed values from the observed data e.g. the mean of the observed values. Another techniques is replacing missing values with the last measured value (last value carried forward). Unfortunately, none of these simple techniques is statistically valid nowadays because they can lead to biased results. This is due to the fact that single imputation of missing data techniques usually cause standard errors to be very small, since it doesn’t account for our uncertainty about the missing values (Sterne et al. 2016). Other more sophisticated techniques are available to handle missing data such as weighting the analysis to allow for the missing data and maximum likelihood estimation technique. However, in the

modern era of statistical computing, more robust method of dealing with missing data is available ‘multiple imputation’ (Hosmer & Lemeshow 2013; Osborne 2015; Sterne et al. 2016; Molenberghs, G 2007).

Since its introduction in 1978, multiple imputation has become an influential technique in handling missing data in statistical analysis. The literature around this technique continues to grow including experimental studies and systematic reviews (Molenberghs, G 2007). The key idea of multiple imputation is to replace each missing value with a set of multiple plausible values (determined by the analyst). Each replacing value is drawn from a conditional distribution of the missing value given the observed value. Normally, multiple imputation involves three steps. Starting with an analysis of the complete dataset to define and quantify the missingness patterns. Secondly, the imputation step which creates a predefined number of complete datasets. Finally pooling the results of the multiple data sets (Hosmer & Lemeshow 2013).

Multiple imputation technique has potential to strengthen the validity of medical research outcomes (Sterne et al. 2016). One great strength of multiple imputation technique is that the researcher can compare the results of the original and imputed datasets (Molenberghs, G 2007). However, the validity of the generated results from multiple imputation depends on careful and appropriate implementation of the technique and it shouldn’t be applied at the push of a button. In 2007, a prospective cohort study reported the development of CVD risk prediction tool based on a large clinical database (Hippisley-Cox et al. 2007). The authors reported difficulties with missing values in the analysed database so they utilised multiple imputation technique. In their published final model they couldn’t prove significant correlation between cholesterol and CVD risk which was surprising. However, when the authors subsequently restricted their analysis to complete cases (excluded cases with missing value) there was a significant association between cholesterol and CVD risk. Furthermore, when a revised improved imputation technique was conducted, a similar result was obtained (Sterne et al. 2016).

Another drawback of multiple imputation is the inability of current statistical packages to run hybrid sophisticated statistical techniques for the same dataset. For example conducting multiple imputation and bootstrapping in one statistical test or multiple imputation with

multilevel modelling. As result, the researcher should make a balanced choice on what technique to use based on the analysed dataset and the tested hypothesis. Throughout this thesis, all analyses will be conducted using the multiple imputation technique as the NACR dataset suffers from a considerable number of MAR data.

3.5.1.2 Outliers

In statistics, an outlier is a data point that deviates considerably from the remaining data as to flag suspicions that it was generated by a different mechanism (Aggarwal 2013). Outliers may be due to extreme measurements or may indicate data entry error. Data entry is the process of digitising data by keying it into a computer system; manual data entry describes the physical process of typing information into computer software. NACR data collection involves human operators keying in data found on patients' record. The manual process of data entry has a main disadvantage in speed and accuracy. Manual data entry occasionally introduces the possibility of human error. Moreover, workers working under stress or suffering from a lack of concentration or fatigue may make more errors. These entry errors impact the quality of data and may affect the outcome result.

One of the greatest challenges facing any large database managers is how to improve and maintain the quality of their data. NACR has tightened up on data quality procedures to align with NICE guidance and the emerging NHS commissioning and accountability frameworks (NACR 2014). In order to improve the quality of data, two main techniques are usually adopted. The first approach is an automated data auditing and cleaning by adding validations to the entry fields in the portal system to prevent users from keying in extreme values. The second, is by exploratory data analysis and cleaning conducted manually by the person analysing the data (Hellerstein 2008). In this study, three steps of data cleaning were adopted;

1. Checking that all data entries fall within the cut-points of the NACR portal system.
2. Manually removing any clinically non-meaningful numbers such as height over 2.3 meters.
3. Deleting any values outside three standard deviations of the mean (3 SD rule).

3.5.2 Statistical modelling

A model is a scaled-down version of a real-world phenomenon. A real-world phenomenon can be any incident deserving of inquiry and investigation, especially events that are particularly unusual or of distinctive importance (Sandywell 2011). Scientists have been always attracted to explain and discover real-world phenomenon. Whatever phenomenon they desire to explore, they collect sample data from real world to represent this phenomenon as they cannot have access to every subject of the population. The collected data will then be used to test a hypothesis they previously developed about the phenomenon under investigation. Testing a hypothesis involves building statistical models which are a smaller representation of the data collected. A statistical model is normally shaped by mathematical equations to express the relationships among number of variables and therefore statistical model can be looked at as 'a formal representation of a theory' (Adèr & Mellenbergh 2008). However, any statistical model we construct should enable us to make predictions or inferences about the real world that are as accurate as possible based on the observed data. The degree to which a statistical model represent the collected data, is known as the fit of the model (Field A. 2013). A good fit model, therefore, is an excellent representation of the real-world situation and vice versa. Consequently, all statistical models can be represented by the following equation:

$$Outcome = (model) + error$$

In fact, statistical models are used in daily life without necessarily realising it. When we summarise a set of numerical data into a mean or when we represent categorical data in proportions then we are using statistical modelling. Any model we chose to represent our observed data, will vary depending on our study design, type of collected data and what we are trying to measure (Field A. 2013). Respectively, models can also vary in its complexity.

As discussed above, the choice of a statistical model is guided by number of factors. This is because every modelling tool answers specific questions. For example, if we want to determine whether there are any statistical significance differences between the means of two or more independent groups, we can use a one-way analysis of variance model (ANOVA). While if our study purpose is to make predictions about the value of an outcome variable based on the value of independent variables then we use linear regression model.

The choice of a statistical model can also be informed by the shape of the relationships between the dependant and independent variables. Sometimes the shape of the relationship is best described by a non-linear relationship e.g. polynomial or curved. This is best explored in descriptive statistics by graphical representation between the investigated variables.

Whatever statistical model we chose to represent our observed data, a critical part of the process involves checking to make sure that the data we want to analyse can actually be represented using this model. In fact, inferring conclusions about any tested population almost always requires some background assumptions. Those assumptions must be considered carefully as violating assumptions can risk the model validity which could generate incorrect conclusions. For example, all parametric tests assume that the sample data are drawn from a normally distributed population. While non-parametric tests make assumptions about random and independence of sampling.

As previously stated, for any statistical model we construct we have to assess the goodness of fit, i.e. how much does it represent the population. A simple way to check the fit of any statistical model is to assess the deviance between the observed values and the expected values generated by the constructed model. This deviance can be used to assess the total error in any model (Davis 2008). A large deviance indicates large error in the model and therefore a lack of fit. The process of quantifying the amount of error in any model is known as model diagnostics. Model diagnostics is possibly the most important tool in the modelling building process (Molenberghs, G 2007). As a result, many statistical tools have been developed for model diagnostics. These tools can be primary tools such as graphical residual analysis or sophisticated numerical methods such as lack-of-fit tests. The choice of the appropriate tool will mainly depend on the type of model constructed as primary tools are often difficult to interpret due to constraints on the residuals imposed by the estimation of the unknown parameters.

The central thesis of this work is to investigate the factors that will predict CR engagement, uptake and adherence in the PCI population. This will be achieved by conducting a retrospective secondary analysis of the UK National Audit of Cardiac Rehabilitation for patients who underwent PCI from 2013 to 2016. Three themed studies will be conducted each concerned with a different outcome. The first study seeks to investigate the factors that

are associated with CR engagement measuring a dichotomous outcome (engaged / not-engaged). The second study will examine the factors associated with starting CR measuring a dichotomous outcome (started / not-started). In the third study the factors that lead patients to complete CR programme will be evaluated measuring a binary outcome (completed / not-completed). Since we are predicting a binary outcome in all three studies, then the statistical model of choice will be a binomial logistic regression model. Binomial logistic regression model (often referred to as just logistic regression) attempts to predict the likelihood of an observation falling into one of two categories of a dichotomous dependent variable (outcome) based on one or more independent variables (predictors) that can be either continuous or categorical (Field 2013).

Although other types of logistic regression can deal with ordinal and multinomial outcomes, here we will limit our discussion to binomial logistic regression. More about logistic regression model, its assumptions and its validation tools it will be discussed briefly in the following section.

3.5.2.1 Logistic regression

The appropriate statistical model to choose when predicting an outcome that can only take a value of two categories (0 or 1) is logistic regression (Davis 2008). Logistic regression in health sciences is used when predicting a binary dependant variable such as the probability of a patient to have a characteristic or experience the event (code 1) or else (code 0) based on observed characteristics of the patient (age, sex, body mass index, results of various blood tests, etc.) or other factors (Freedman 2005). Although the dependant variable can only take values of 0 and 1, the predicted value generated by the model take the form of probabilities based on the values of the independent variables. The higher the predicted value, the more chance this patient will have the characteristic or experience the event measured (Newman 2000).

Although logistic regression and linear regression are both a special case of the generalised linear model, they are based on different assumptions. A key difference between the two models can be seen in two different features of logistic regression. First, logistic regression is used for modelling categorical dependant variable while linear regression is used for modelling continuous variables. Second, in logistic regression the predicted values are

restricted to (0, 1) and displayed as the probability of particular outcomes while linear regression predicted values of the dependent variable based on different values of the independent variables (Freedman 2005).

Probit regression uses similar techniques as logistic regression with a difference that that probit regression uses cumulative normal distribution while logistic regression employs cumulative logistic distribution to estimate the probabilities of the outcome. In fact, the cumulative logistic and normal distributions have almost similar shape. However, the cumulative logistic distribution has heavier tails (higher kurtosis), which often increases the robustness of analyses based on it compared with using the cumulative normal distribution (Menard 2010).

3.5.2.2 Model assumptions

As was pointed out previously, a critical part of constructing a model involves checking for assumptions. In fact, logistic regression has seven assumptions that must be met. Meeting those assumptions will allow us to ensure the accuracy of our model and test how our model fits the observed data (Lund, M., Lund 2015). The first four assumptions relate to the study design which includes; binary outcome variable, two or more predictors, independence of observations and there should be at least 15 observations per predictor. The rest three assumptions relate to the nature of the collected data. First, there must be a linear relationship between a continuous predictor and the logit transformation of the outcome. Second, the data shouldn't show multicollinearity. That is, predictor inserted in the models are not highly correlated with each other. Finally, there should be no significant outliers, high leverage points or highly influential points. These terms refer to observations in the data that are in some way unrealistic and may have a very negative impact on the regression equation (Lund, M., Lund 2015).

3.5.2.3 Model diagnostics

The validity of inferences drawn from a model depends on satisfying the assumptions. Once the prediction model is fitted to the data, it is essential to check that this model is actually a valid model. A good model is one that 'fits' the data well, in the sense that the values predicted by the model are in close agreement with those observed. A careful evaluation of the extent to which the constructed model provides a good representation of the observed

data is vital. A main purpose of model diagnostics is to identify subjects who are problematic under the constructed model (David Hosmer, Stanely Lemeshow 2013).

To test if each predictor is adding to the model goodness of fit we use Wald test. This test evaluates the statistical significance of the coefficient of each predictor. If the coefficient of a certain predictor is statistically not significant then we assume that removing the variable from the model will not substantially harm the fit of that model. Another method to assess the goodness of fit for a model is to check the residuals. Residuals in any model are the differences between the observed values in the data and the predicted values from the final model. If the residuals are randomly distributed that suggests a good fit. On the other hand, if non-random structure is evident in the residuals, it is a clear sign that the model fits the data poorly.

A logistic regression model is preferable over another model if it provides a better fit to the data with fewer predictors. This can be achieved by conducting a procedure called the likelihood ratio test between two or more models. This test compares the likelihood of the data under the full model against the likelihood of the data under another model with less predictors. Obviously, the log likelihood of a model (how well it fits the data) will be lower if a predictor is removed, however, this test assesses if the observed difference between the two models is statistically significant. Pseudo R^2 in logistic regression model is a good representation of the log likelihood ratio where it divides the log likelihood ratio of the fitted model over the log likelihood ratio of the null model (without predictors). The Pseudo R^2 measure is expressed in values ranging from 0 to 1, with values closer to zero indicating that the model has no predictive power (Menard 2010).

Another test to determine the data goodness of fit is the Hosmer-Lemeshow test. This test shows how close the predicted probabilities are to the observed data. This is done segmenting the observed data with similar predicting probabilities into the same groups. A Pearson chi-square test is then conducted to evaluate if the difference between predicted values and observed values is statistically significant. Not statistically significant p-value of the Hosmer-Lemeshow test indicates that the model fits data well. However, it has been noted that this rule might be difficult to achieve if working with large datasets (David Hosmer, Stanely Lemeshow 2013).

The receiving operating characteristics curve (ROC curve), is a measure of how correctly the model classifies cases. Using the ratio of positive data points which are correctly classified as positive and the ratio of negative data points that are incorrectly classified as positive, a graph is produced to show the trade-off between the proportions of values correctly predicted compared with the proportion of values incorrectly predicted. Ultimately, the area under the ROC curve, or AUROC is the most meaningful measure in this graph. That metric ranges from 0.50 to 1.00, and values above 0.80 indicate that the model has a good predictive power (Hernández-Orallo 2013).

3.5.2.4 Model validation

Any statistical model developed for prediction needs validation (Miller et al. 1991). Model validation is conducted to ensure that the predicted values generated by the model are likely to predict outcomes on future subjects or subjects not used to develop the model. Model validation is an important step to ascertain that predicted values fairly represent the collected data and to ensure they are generalisable to other populations. The two main methods of model validation are external validation and internal validation (Harrell 2015).

External validation involves testing the final developed model in subjects external to those used for model development (Riley et al. 2016). External validation can explore genuine differences in the characteristics of subjects used to develop the model and those used to test it in addition to testing how well the model performs (Collins et al. 2014). External validation can vary in stringency. Testing the developed model in another population extracted from another country is considered the most stringent form of external validation while testing the model in same geographic area but from different settings is a less stringent form of external validation. The least stringent form of external validation is what is known as data-splitting. This is when part of the data is not used to develop the model but as a test sample (Harrell 2015).

Although external validation is a useful tool to validate prediction models, it is commonly unused. In 2010, a systematic review of 78 studies used external validation method concluded that '*there is a dearth of well-conducted and clearly reported external validation studies*' (Riley et al. 2016). There are two likely causes for that, first, data-splitting technique results in lower precision and power of the model due to the reduced sample size.

Second, evaluating prediction models on other datasets by different researchers is rare due to insufficiencies in the reported methodology of the majority of published validation studies (Collins et al. 2014).

Internal validation involves fitting and validating the model by carefully using one series of data (Harrell 2015). Resampling methods can be utilised to compute unbiased estimates of the prediction model performance without scarifying the sample size. The most efficient internal validation technique is claimed to be bootstrapping technique (Steyerberg et al. 2001). Bootstrapping is a more sophisticated approach to data-splitting which is achieved by computer-intensive resampling techniques. In bootstrapping, repeated random samples are drawn from the estimation sample (commonly 1000 iterations) thereby creating artificial datasets on which models are estimated. Based on these coefficient estimates, events are predicted in the estimation sample (Gutacker et al. 2015). A drawback of this technique is its limitation when used with other computerised techniques such as multiple imputation (see section 3.5.1).

4 Engagement study

4.1 Abstract

4.1.1 Background and Aims

Despite the proven benefits of cardiac rehabilitation (CR), utilisation rates remain below recommendation in the percutaneous coronary intervention (PCI) cohort in most European countries. Although extensive research has been carried out on CR uptake, no previous study has investigated the factors that lead patients to attend the initial CR baseline assessment (CR engagement). This paper attempts to provide new insights into CR engagement in the growing PCI population.

4.1.2 Methods and Results

In total, I analysed data on 59,807 patients who underwent PCI during 2013 to 2016 (mean age 65 years; 25% female). 20 factors were hypothesized to have a direct impact on CR engagement and they were grouped into 4 main categories; namely socio-demographic factors, cardiac risk factors, medical status and service-level factors. A binary logistic regression model was constructed to examine the association between CR engagement and tested factors. All but one of the proposed factors had a statistically significant impact on CR engagement. Results showed that CR engagement decreases by 1.2% per year of age (OR 0.98) and is approximately 7% lower (OR 0.93) in female patients, while patients are 4.4 times more likely to engage if they receive a confirmed joining date (OR 4.4). The final model achieved 86.6% sensitivity and 49.0% specificity with an area under the receiver operating characteristic curve of 0.755.

4.1.3 Conclusion

The present results highlight the important factors of the likelihood of CR engagement. This implies that future strategies should focus on factors that are associated with CR engagement.

4.2 Introduction

Cardiac rehabilitation (CR), which is defined as a structured multidisciplinary intervention for cardiovascular risk assessment and management, advice on structured exercise training, psychosocial support and the appropriate prescription and adherence to cardio-protective drugs, is the most investigated form of secondary prevention interventions (Piepoli et al., 2016b). CR has been established as one of the most clinically and cost-effective intervention in cardiovascular (CVD) disease management (Dalal, Doherty and Taylor, 2015). CR improves clinical outcomes by modifying cardiac risk factors and is cost saving through a reduction in unplanned re-admissions for cardiac problems (NICE, 2013). Participation in a CR programme for patients hospitalized for an acute coronary event or revascularization is therefore recommended by European guidelines (class 1 level A) (Piepoli et al., 2016a). However, despite the proven benefits of CR it remains underutilised in many healthcare systems, with major inequities in access for certain patient groups such as the elderly and female patients (Sumner, Grace and Doherty, 2016). Furthermore, it has previously been observed that utilisation rates are lower than expected in patients undergoing percutaneous coronary interventions (PCI) in most European countries (Humphrey, Guazzi and Niebauer, 2014).

Although extensive research has been carried out on CR uptake (e.g. proportion of eligible patients starting core CR), researchers have not investigated the factors that are associated with patients attending an initial CR baseline assessment (CR engagement), which informs the design of the tailored CR programme. Not all patients who attend the initial CR baseline assessment take part in the core CR programme, and not all patients that are eligible engage with CR at all. European guidelines continue to recommend CR initial assessment as a minimum standard and core component of CR (Windecker et al., 2014).

According to the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) this baseline assessment could commence on a ward prior to discharge, or at an outpatient clinic or when they first attend the outpatient programme. It is only deemed complete when a formal assessment of lifestyle risk factors (smoking, diet, fitness and physical activity status), psychosocial health status, medical risk factors (blood pressure, lipids and glucose) and use of cardio-protective therapies has taken place (BACPR, 2017).

This paper aims to provide new insights into the factors that lead patients in the PCI population to attend their initial CR baseline assessment. I hypothesised that CR engagement is not a single patient decision but also related to service level initiatives.

4.3 Methods

This study investigates factors that will predict patient engagement with CR among PCI patients. Logistic regression model will be constructed to identify predictors of CR engagement among the selected population.

4.3.1 Data source

The NACR is operated in collaboration with NHS Digital to monitor the quality of and outcomes from cardiovascular secondary prevention and rehabilitation services in the UK. NACR has approval that is gained on an annual basis (under section 251 of the NHS act 2006) to collect anonymised patient data for a range of clinical variables without the explicit consent from individual patients (NACR, 2016). Data are gathered by clinicians through validated questionnaires that are completed via a secure online system hosted by NHS Digital. The secure online data include details of patients' demographic characteristics, clinical condition and lifestyle. NACR has shown to be representative of CR provision in the UK with 72% of all CR programmes entering data electronically using the NACR online system (NACR, 2016).

To investigate the impact of social deprivation on CR uptake, the Index of Multiple Deprivation (IMD) 2010 was linked to NACR data set. The IMD is the official measure of relative deprivation for small areas (or neighbourhoods) in England (DCLG, 2015). The IMD scores are based on 8 distinct domains of deprivation with respect to 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 generate an approximate overall deprivation score for each individual patient according to their small area of residence (Sumner, Grace and Doherty, 2016).

4.3.2 Design and inclusion criteria

This is a retrospective observational study using data retrieved from the NACR dataset for the period 1st April 2013 to 31st March 2016. Although NACR collects data for three countries (England, Northern Ireland and Wales), only patients in England were included in the study as the IMD is only available for English small areas. In addition, patients were included in the analyses if they had any type of PCI treatment during the study period and were referred to CR (Figure 4.1). Referral to a CR programme in England is usually conducted while the patient is still admitted or shortly after discharge for day case PCI patients (Sumner, Grace and Doherty, 2016).

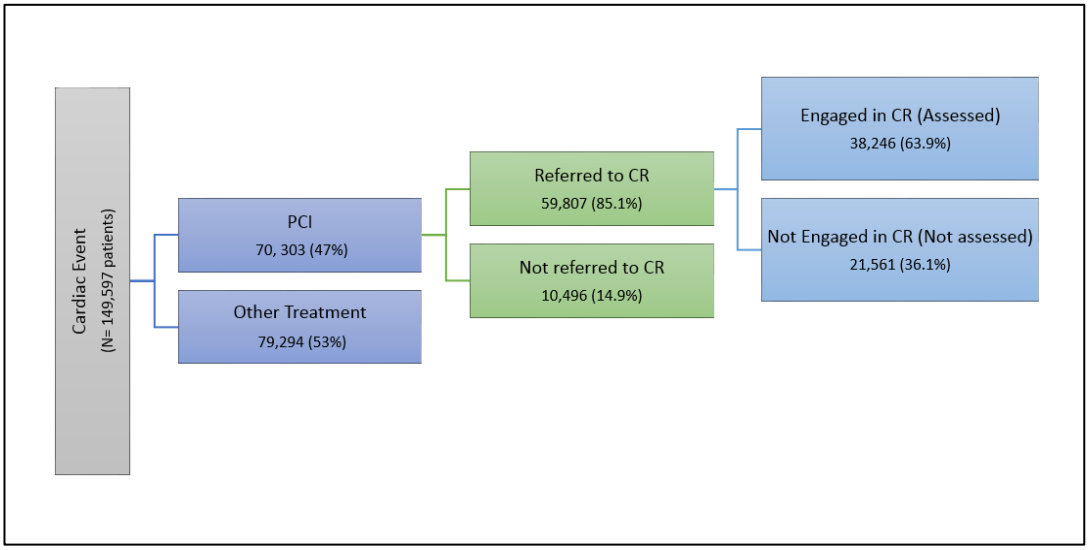


Figure 4.1 Study Flow and sample size.

4.3.3 Factors investigated

Twenty factors from the primary data set were hypothesised to have a direct impact on patients' decision to engage in CR based on the wider literature on CR uptake (Balady et al., 2011; Clark et al., 2012; van Engen-Verheul et al., 2013; Grace et al., 2008; Gravely-Witte et al., 2010; Karmali et al., 2014) (Table 4.1). Predictor variables were either categorical or continuous depending on the method of data collection in NACR. The IMD score was grouped into 5 equal-sized quintile groups where the first quintile includes the most-deprived patients and the fifth quintile includes the least-deprived patients.

Table 4.1 Hypothesised predictors for CR engagement.

	Socio-demographic factors	Cardiac risk factors	Patient's medical status	Service level factors
1	Age	High blood pressure	Total number of comorbidities	Referred to CR by
2	Sex	Diabetes	Previous cardiac event	Venue of Source of referral to CR
3	Ethnicity	High blood cholesterol	Angina	Hospital length of stay
4	Marital status	Anxiety		Received confirmed joining date
5	Index of multiple deprivation (IMD)	Depression		PCI type
6		Family history		Patient received early CR

A detailed explanation of the investigated factors and their subcategories can be found in (Appendix 9.4).

4.3.4 Data analysis

Descriptive statistics were calculated to compare differences in baseline characteristics between engaged and non-engaged patients. I used t-test for continuous variables and chi-square tests for categorical variables with p-values < 0.05 considered to be statistically significant.

A binary logistic regression model was constructed to predict the probability of CR engagement and to examine the association among the research variables. I followed a backward selection process in which all variables were entered simultaneously in the model and variables with p-value > 0.05 were removed. This process was repeated until all variables had $p<0.05$. I also used forward selection techniques, beginning with a simple model including patients' socio-demographic factors only, to which the other three blocks of predictors (Table 4.1) were then added in sequence to create three additional, increasingly more complex models. The four models were then tested against each other on the basis of log likelihood and variance explained (Pseudo-R2).

Since age and gender were reported in the literature as a major determinant of CR accessibility and outcomes (Thomas et al., 2014; NACR, 2016; Al Quait and Doherty, 2016), age and gender-specific interaction was tested by inserting a 2-way age and gender interaction term in the model as a separate variable. To account for other interactions in the model between gender and any other tested variable, the analysis was repeated for males and females separately (stratified analysis).

The final model's goodness-of-fit was evaluated using a Hosmer and Lemeshow test (Field, 2013). To validate the model predictive power, a receiver operating characteristic (ROC) curve was plotted and model accuracy was measured by the area under the ROC curve (AUC) (Hajian-Tilaki, 2013).

Under the assumption that missing values are missing at random, all variables with > 5% missingness were handled by multiple imputation using 20 imputed data sets. The resulting estimates were pooled using Rubin's rule. All analyses were performed using SPSS version 24.

4.4 Results

The analysis sample included 59,807 patients. The baseline characteristics of both groups (engaged and not-engaged) are illustrated in (Table 4.2).

Table 4.2 Baseline characteristics of both groups.

Factor	Engaged	Not-engaged	P value
N	38,246 (63.9%)	21,561 (36.1%)	<0.001
Mean age (SD)	64.16 (11.7)	65.36 (12.4)	<0.001
% Female	24.7%	25.6%	0.012
Ethnicity (White)	85%	81%	<0.001
Marital Status (single)	23.3%	25.9%	<0.001
IMD* score (5)[7]	25.4%	19.3%	<0.001
% Comorbidities (+3)	30.1%	23.6%	<0.001
% Elective PCI procedure	35 %	32.6%	<0.001
% Day case procedure	15.9%	18.4%	<0.001

[7] Ratio of least deprived patients in the cohort

In (Table 4.3) a comparison of the summary statistics for the four models created as explained in the methods section.

Table 4.3 summary statistics for the four models created by forward stepwise regression.

Model	-2 Log likelihood ratio	Pseudo R	Correctly classified cases
Model 1[8]	77226.16	0.02	63.9%
Model 2[9]	73698.13	0.03	64%
Model 3[10]	72608.09	0.05	64.8%
Model 4[11] (final)	63847.12	0.25	73.1%

The final model was statistically significant, χ^2 (32) = 11928.8, $p < 0.0005$. The model explained 25% (Nagelkerke R^2) of the variance in CR engagement and correctly classified 73.1% of cases. Sensitivity was 86.6%, specificity was 49%, positive predictive value was 75.1% and negative predictive value was 67.3%. The ROC curve test indicates that the final model has a good predictive ability with AUC of 0.755 (SE = 0.002, 95% CI, 0.751 to 0.759) (Figure 4.2).

[8] Socio-demographic factors only.
[9] Model 1 plus risk factors.
[10] Model 2 plus patient's medical status.
[11] Model 3 plus service level factors.

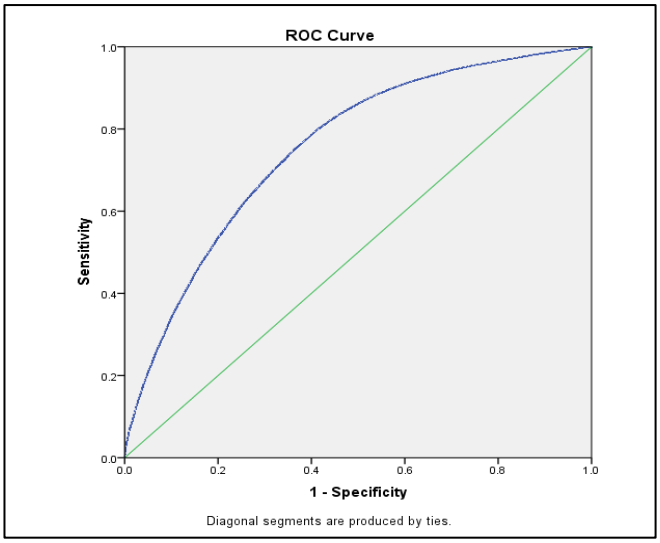


Figure 4.2 ROC curve of the final CR engagement model.

To assess the model for influential cases, Cook's distance test and leverage values were computed. There were no unusually high values in both tests (all < 1). Hosmer and Lemeshow test in the final model is not statistically significant (p = 0.349) indicating that the model is not a poor fit. Of the twenty predictors tested, only hypertension was found to be not statistically significant (Table 4.4). Splitting the data into male and female groups to account for gender related interaction with other variables did not reveal any significant change in the reported results.

Table 4.4 Pooled estimates of the logistic regression model predicting likelihood of CR engagement.

Factor[12]	***Categories***	***P value***	***Odds ratio***	***95% CI for OR***	
				Lower	*Upper*
Age	*In years*	*0.000*	*0.988*	*0.987*	*0.990*
Sex (male)	*Female*	*0.002*	*0.929*	*0.885*	*0.974*
Ethnicity (White)	*Ethnicity Black*	*0.222*	*1.239*	*0.878*	*1.749*

[12] Predictor with base category in brackets.

	Ethnicity South Asian	*0.001*	*0.866*	*0.792*	*0.946*
	Ethnicity Other	*0.000*	*0.757*	*0.712*	*0.804*
Marital status (Single)	*In partnership*	*0.000*	*1.223*	*1.144*	*1.307*
	Previously partnered	*0.000*	*1.250*	*1.153*	*1.355*
IMD rank (1 most deprived)	*IMD rank (2)*	*0.480*	*1.029*	*0.951*	*1.113*
	IMD rank (3)	*0.000*	*1.190*	*1.101*	*1.288*
	IMD rank (4)	*0.000*	*1.240*	*1.155*	*1.331*
	IMD rank(5)	*0.000*	*1.464*	*1.363*	*1.572*
Cardiac risk factors (no)	*Hypertension*	*0.407*	*0.977*	*0.923*	*1.033*
	Diabetes	*0.000*	*0.877*	*0.822*	*0.935*
	Depression	*0.000*	*1.561*	*1.374*	*1.774*
	Hypercholesterolemia	*0.000*	*0.787*	*0.743*	*0.834*
	Family History	*0.005*	*1.093*	*1.027*	*1.162*
	Angina	*0.000*	*1.225*	*1.144*	*1.312*
	Anxiety	*0.000*	*1.435*	*1.257*	*1.639*
Number of comorbidities (0)	*Comorbidity < 3*	*0.000*	*1.589*	*1.477*	*1.710*
	Comorbidity > 3	*0.000*	*1.802*	*1.586*	*2.048*
History of previous cardiac event (no)	*Previous event*	*0.000*	*0.749*	*0.715*	*0.786*

Patient refereed by (consultant)	*Cardiac nurse*	*0.000*	*0.902*	*0.854*	*0.953*
	GP	*0.467*	*1.791*	*0.348*	*9.204*
	Primary care nurse	*0.056*	*1.391*	*0.992*	*1.953*
	Other	*0.085*	*1.097*	*0.987*	*1.219*
Venue of source of referral (NHS Trust)	*General Practice*	*0.000*	*9.302**	*7.803*	*11.091*
	BMI/Private Hospital	*0.035*	*0.810*	*0.667*	*0.985*
Hospital length of stay (overnight stay)	*Day Case*	*0.000*	*0.736*	*0.691*	*0.784*
Received confirmed joining date (no)	*Yes*	*0.000*	*4.443*	*4.239*	*4.656*
PCI type (primary)	*MI*	*0.000*	*1.111*	*1.060*	*1.165*
	Elective	*0.000*	*1.211*	*1.146*	*1.278*
Patient received early CR (no)	*Yes*	*0.000*	*0.533*	*0.509*	*0.558*
Constant	-	*0.000*	*5.602*	*3.830*	*8.194*

*The effect inflated by small sample size.

4.5 Discussion

This is the first study to investigate the determinants of CR engagement in patients following PCI treatment. In this retrospective secondary analysis, it was found that the probability of CR engagement decreases by 1.2% (OR 0.98, 95% CI 0.987 to 0.990) per additional year of patient age, and is approximately 7.1% lower (OR 0.929, 95% CI 0.885 to 0.974) for female patients compared to male patients. These novel results, obtained from routine clinical data support the findings of earlier systematic reviews and meta-analyses which indicate that

existing CR programmes are more attractive to middle-aged male patients, thus perhaps being less attractive for the elderly or female patients (Windecker et al., 2014; Wenger, 2008; Anderson et al., 2016; Menezes et al., 2014).

The recent European guidelines on cardiovascular disease prevention have emphasised that minority ethnic groups like South Asians have a higher risk of CVD but are less represented in CR programmes (Piepoli et al., 2016a; Karmali et al., 2014). Our results support this and suggest that South Asians are less likely to engage in CR compared to the majority ethnic white patient population (OR 0.866), thereby identifying a potential mechanism that leads to differential uptake of CR programmes. Also, CR engagement was significantly correlated with the index of social deprivation as measured by IMD where CR engagement increased from the most deprived to the least deprived patients (except for the first two most deprived deciles). Current European and international guidelines have called for equal access for all MI patients, including those from minority ethnic groups and socially deprived groups, and our results question the extent to which this has been achieved. (National Institute for Health and Care Excellence, 2013; Graham et al., 2007; Balady et al., 2011). In addition, single patients are less likely to be engaged in CR compared to partnered or previously partnered patients (22% and 25 % respectively). This may be because couples facilitate attendance by providing social support, transportation to CR centres or communication with health professionals (Clark et al., 2012). However, note that previously partnered patients are the most engaged CR group.

The current study found that cardiac risk factors play a major role in CR engagement. Diabetes (OR 0.88), hypercholesterolemia (OR 0.79) and history of previous cardiac event (OR 0.749) are associated with reduced CR engagement while hypertension was not found to be a significant predictor of CR engagement (P = 0.404). Other risk factors such as angina (OR 1.22), anxiety (OR 1.43), depression (OR 1.56) and family history of cardiac disease (OR 1.09) were found to increase the likelihood of patients' engagement in CR. One unanticipated finding was that the number of comorbidities was not found to be in itself a barrier to CR engagement. This finding contradicts a retrospective analysis conducted in the Netherland (van Engen-Verheul et al., 2013) and another Canadian qualitative study (Grace et al., 2009) although these studies were investigating uptake to core CR not CR

engagement, i.e. the initial baseline assessment that may take place before or at the very beginning of core CR sessions.

If patients had a life-saving PCI (primary PCI) they were less likely to engage in CR compared to MI/PCI and elective PCI (OR = 1.21 and OR = 1.11). Having PCI as a day case procedure also reduced the likelihood of CR engagement by 27%. This result may be explained by the fact that a day case procedure reduces the time window to identify and recruit patients to CR thus requiring programmes to be more innovative in contacting patients (Sumner, Grace and Doherty, 2016). Another finding that was contrary to expectations is that patients who took part in early phase 1 CR sessions (either inpatient or home-based programmes) were less likely to start the core CR programme (OR = 0.533).

One of the most telling findings to emerge from the analysis is that patients who were given a firm date to attend the initial CR assessment were over 4 times more likely to engage in CR (OR 4.443). Also, patients who have been referred from a general practice were more than 9 times more likely to attend the assessment session compared to patients referred from hospital setting (OR 9.30). The primary route of referral in our sample was through a hospital cardiac nurse (74.7% of patients), and these patients were significantly less likely to engage in CR compared to patients referred by consultant, general practitioner (GP) or primary care nurse (OR 0.902). It is difficult to explain this result, however the strength of healthcare professional endorsement for CR is known to play a significant role in CR uptake (Grace et al., 2008).It has been also reported in several studies that nurses have been shown to be more successful coordinators of secondary preventive programmes (Jennings and Astin, 2017).

The analysis of CR engagement undertaken here has extended our understanding of the determinants of low CR utilisation rates in England. Although age and gender are significant determinants of CR engagement, which is also true for CR uptake, (Table 4.4) illustrates how service level factors play a major role in CR engagement. These findings highlight that service level initiatives, such as providing a firm date to attend the initial CR baseline assessment, play an important part in promoting initial CR engagement. Further research should be undertaken to investigate the differences and determinants between those patients who start CR and those who drop out.

4.6 Study limitations

The definition of CR engagement is novel and required the use of a combination of NACR data fields, which will benefit from repeat studies in other CR datasets to further validate this approach. In addition, the NACR dataset is setup to evaluate service quality and outcomes so some other relevant factors influencing CR engagement may have been missed. Also, while I evaluated the type of PCI as a determinant of engagement, it is likely that these correlate with unobserved clinical factors, so that our estimate of the effect of PCI type may be subject to confounding.

4.7 Conclusion

This is the first study on CR engagement from a nationally representative cohort of patients. This paper provides new insights into the factors that lead patients to attend their CR initial baseline assessment (CR engagement) in the growing PCI population. The most obvious finding to emerge from this study is that CR engagement is not a single patient decision but is also related to service level factors, over which healthcare systems have more direct control. The findings should make an important contribution to our understanding of the relatively low CR utilisation rates in this cohort despite the known benefits of CR.

5 Uptake study

5.1 Abstract

5.1.1 Background

Cardiac rehabilitation (CR) uptake rates are still below recommendations in most European countries. Age and female gender have been identified in the literature as barriers against CR uptake. This study evaluated the extent by which age and gender determine the likelihood of CR uptake among percutaneous coronary intervention (PCI) patients in England.

5.1.2 Methods

I analysed routine clinical data from the UK National Audit of Cardiac Rehabilitation for patients who underwent PCI in 2013 to 2016 and had completed a baseline CR assessment. A hierarchical logistic regression model, using multiple imputation as appropriate, assessed the impact of age and gender on CR uptake while accounting for patients' characteristics and service level factors.

5.1.3 Results

The sample consisted of 38,246 patients (64.2 ±11.7 years, 75.3% male), of which 28,263 (73.9%) patients started CR (63.6 ±11.4 years, 76% male). The likelihood of starting CR decreases with patient age (OR: 0.98, 95% CI: 0.98 to 0.99) and is higher for women than men (OR: 1.58, 95% CI: 1.11to 2.25). There was significant interaction revealing that younger women (≤ 57 years) are more likely to start CR compared to younger men (OR: 0.98, 95% CI: 0.98 to 0.99) while older women were found to be less likely to join compared to younger/middle age women or older men (> 57 years).

5.1.4 Conclusion

Strategies to increase CR uptake in PCI patients should consider age in the context of gender when offering CR and deploy tailored support to enable patients to progress from assessment to starting CR.

5.2 Introduction

Since the first PCI procedure was conducted by Andreas Gruentzig in 1977, this revascularisation technique has significantly developed and nowadays represents the first choice of treatment for CAD. This huge success of PCI procedures is underpinned by improved rates of survival and more attention should be made towards improving patients' quality of life and preventing secondary cardiac events. This goal can be achieved by offering patients a comprehensive CR programme which has been evidenced to reduce mortality, hospital readmissions and improve quality of life (Anderson et al., 2016; Rauch et al., 2016; Sumner, Harrison and Doherty, 2017). The proven efficacy of CR has made it (Class 1 level A) recommendation by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology (Ruano-Ravina et al., 2016).

However, rates of CR uptake in the PCI population remain low despite guideline recommendations. The UK National Audit of Cardiac Rehabilitation (NACR) report in 2016 has shown low uptake in the English cohort of patients following myocardial infarction (MI) (40%) and elective PCI (45%) compared to the world-leading uptake rate in the CABG population (58%). This is of major concern since PCIs now constitute the vast majority of revascularisation procedures in the UK (96,143 compared to 17,513 CABG procedures in 2014) (Townsend et al., 2015) and, as a result, around 50,000 eligible patients were not accessing vital CR services to improve their chance of recovery and reduce the risk of suffering another cardiac event (NACR, 2015).

A large and growing body of literature analyses health care-seeking behaviours and the determinants of health services utilisation to understand how people engage with the healthcare systems. Several lines of evidence suggest that health care-seeking behaviour is influenced by many patient characteristics such as patient demographics and socio-economic status (Thompson et al., 2016). Existing research specifically recognises the critical role played by age and gender in health related behaviours (Deeks et al., 2009; Thompson et al., 2016). Similarly, two recent systematic reviews of determinants of CR uptake identified age and gender as important independent factor (Ruano-Ravina et al., 2016; Karmali et al., 2014).

One criticism of the existing literature on CR uptake is that most studies have been limited by their small sample size, particularly for minority groups in their population such as females and older patients. Also the rapid advances in the technology and applicability of PCI in addition to changes in patients' health behaviours over time require continuous re-evaluation of CR uptake determinants. This study sought to provide updated estimates of CR uptake determinants. It will also investigate the impact of age and gender effects on CR uptake using a large routine clinical data for patients who underwent PCI and test whether the age gradient in uptake varies by gender, i.e. whether there is an inter-relationship (interaction) between age and gender.

5.3 Methods

5.3.1 Design and inclusion criteria

This is a retrospective observational study where data retrieved from the NACR dataset for the period 1st April 2013 to 31st March 2016. Patients were included in the analyses if they had any type of PCI treatment in England during the study period, were referred to CR and had attended a pre-CR assessment session (Figure 5.1). Although NACR collects data for three countries (England, Wales and Northern Ireland), only patients residing in England were included to allow for consistent measurement of social deprivation using the English Index of Multiple Deprivation (IMD). Referral to a CR programme in England is usually conducted while the patient is still admitted or shortly after discharge for day case PCI patients while the pre-CR assessment is implemented on a ward prior to discharge, or at an outpatient clinic in CR phase 2 or when they first attend a core CR (outpatient) programme (Sumner, Grace and Doherty, 2016; BACPR, 2017).

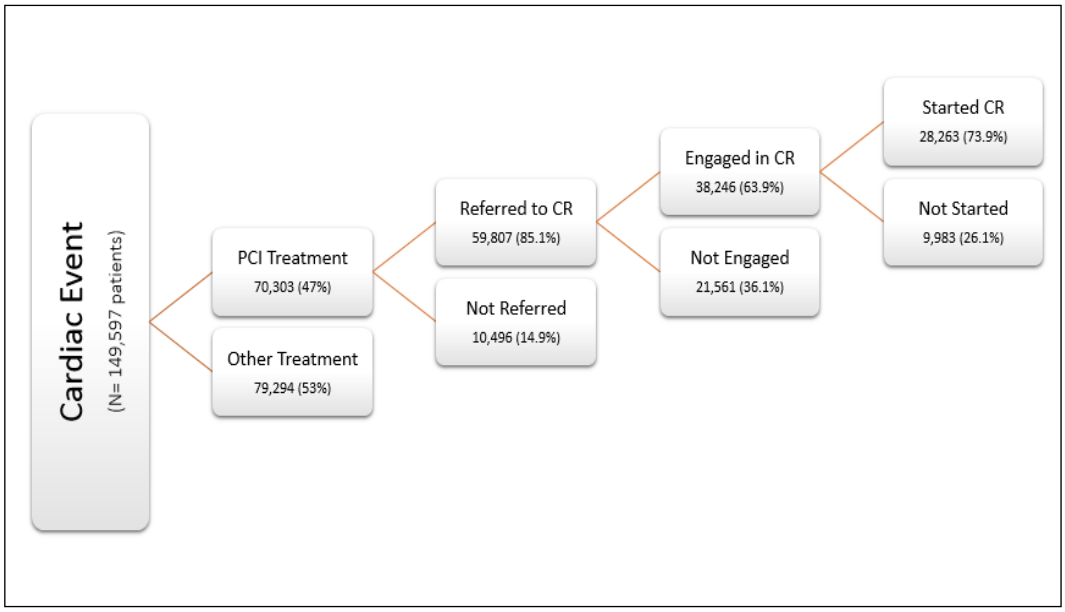


Figure 5.1 Study flow and sample size.

5.3.2 Data source

In collaboration with NHS Digital and British Heart Foundation (BHF), NACR monitors the quality and outcomes of cardiac rehabilitation services in the UK. NACR has been approval by NHS Digital under section 251 of the NHS Act 2006 to collect anonymised patient data for a set of clinical variables via a secure online portal. These data are gathered by clinicians through specifically designed and validated questionnaires and include details of patients' demographic characteristics, clinical conditions and lifestyles (NACR, 2016). In 2016, the total number of CR programmes delivering core CR in the UK and participating in NACR was 318. With nearly 90% survey response rate in 2015, NACR dataset is considered highly representative of CR provision in the UK (NACR, 2015).

To take account of the impact of social deprivation on CR uptake, the Index of Multiple Deprivation (IMD) 2010 reported at the Clinical Commissioning Group (CCG) level, was linked to NACR data set. 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 for each individual patient (Sumner, Grace and Doherty, 2016). Patients were assigned to one of five equal-sized groups according to the quintiles of the distribution of IMD scores, with the first quintile group representing the most-deprived patients.

5.3.3 Measures

CR uptake in this study was defined as starting the CR exercise-based programme (outpatient CR) by attending at least one outpatient CR session (Suaya et al., 2007; Karmali et al., 2014). Noting that only patients who had a baseline assessment (engaged) were included in the analysis. This study also attempts to explore the impact of age and gender as independent and inter-related factors informing CR uptake. Twenty-six other factors were included in the analysis to adjust for their potentially confounding influence on uptake (Table 5.1).

Table 5.1 the factors that impact CR uptake classified into 4 main categories.

	Patient's socio-demographics	**Cardiac risk factors**	**Lifestyle & Medical status**	**Service level factors**
1	Ethnicity	High blood pressure	Physical fitness	Referred to CR by
2	Marital status	Diabetes	Being overweight	Source of referral to CR
3	Employment	Physical inactivity	Social support	Hospital length of stay
4	Index of multiple deprivation (IMD)	High blood cholesterol	Alcohol intake	Time from event to baseline assessment
5	Age*gender (interaction term)	Anxiety	Smoking	Received confirmed joining date
6		Depression	Total number of comorbidities	PCI type
7		Family history	Previous cardiac event	Patient received early CR
8			Angina	

Those factors were selected based on the existing literature and the data fields collected in NACR. A number of factors were identified in previous studies as determinants of CR uptake but not collected in NACR (e.g. transportation, place of residence, religion, etc.) and were therefore not considered in our analysis. The control factors were grouped into four main categories (blocks), namely socio-demographic factors, cardiac risk factors, lifestyle & medical status and service-level factors. Detailed explanation of the selected factors and their subcategories are shown in (Appendix 9.5).

5.3.4 Data analysis

I first calculated descriptive statistics and compared baseline characteristics between starters and non-starters using t-tests for continuous variables and chi-square tests for categorical variables, with a p-value < 0.05 considered statistically significant.

Binary logistic regression model was developed to predict the probability of starting CR and to examine the association among the research variables. The first set of models were created following a backward selection process where all variables entered simultaneously, variables with p-value > 0.05 were removed and the process was repeated until no variables had p-value > 0.05. I also conducted forward stepwise regression in which variable were entered as blocks. A simple model with patient's age, gender and their interaction term was first constructed. Then a second more complex model was created by adding socio-demographics to the first model. A third, fourth and fifth models were built alternately by adding the three remaining sets of variables in (Table 5.1), i.e. cardiac risk factors, lifestyle & medical status and service level factors. The five constructed models were then tested against each other to find the best model in explaining the highest variance of the outcome.

The final model goodness-of-fit was tested using a Hosmer and Lemeshow test (Field, 2013). To validate the model predictive power, a receiver operating characteristic curve (ROC curve) was plotted and model accuracy was measured by the area under the curve (AUC) (Hajian-Tilaki, 2013).

I used multiple imputation for variables containing missing data. This was done under the assumption that values are missing at random, i.e. the probability of a value to be missing is a function of observable patient characteristics and random chance, not the value of the

variable itself. 20 imputed data sets were created and the resulting estimates were pooled using Rubin's rule. All analyses were performed using SPSS version 24.

5.4 Results

The sample included 38,246 patients. The baseline characteristics of both groups (starters and non-starters) are illustrated in (Table 5.2).

Table 5.2 Baseline characteristics of both groups.

Patient characteristic	Starters (N=28,263, 73.9%)	Non-starters (N=9,983, 26.1%)	P-value
Mean age (SD)	63.59 (11.4)	65.79 (12.3)	<0.001
% Female	24%	26.6%	<0.001
Ethnicity (White)	84.5%	86.5%	<0.001
Employment (Retired)	35.3%	29%	<0.001
% Smokers	8.7%	13.8%	<0.001
% Comorbidities (+3)	44.1%	55.9%	0.242
% Elective PCI procedure	34.2%	37.3%	<0.001
% Moderate physical activity[13]	27.9%	18.2%	<0.001
% Day case PCI	14.6%	13.7%	0.006

[13] Ratio of patients taking moderate physical activity for 150 minutes per week.

A binomial logistic regression was performed to ascertain the impact of the 28 predefined patient and clinical factors on the likelihood of patients joining a CR programme. The final model was statistically significant, χ^2 (10) = 7145.26, $p < 0.0005$. The model explained 25% (Nagelkerke R^2) of the variance in CR uptake and correctly classified 78.9% of cases. With a cut-value set at 0.5 the Sensitivity was 94.4%, specificity was 35.2%, positive predictive value was 80.5% and negative predictive value was 68.8%. Table 5.3 presents the summary statistics of these five models constructed by means of forward selection.

Table 5.3 summary statistics for the five models created by forward stepwise regression.

Model	-2 Log likelihood ratio	Pseudo R	Correctly classified cases
Model 1[14]	43518.53	0.011	73.9%
Model 2[15]	43079.71	0.028	73.9%
Model 3[16]	42750.83	0.040	73.9%
Model 4[17]	41981.18	0.068	74.1%
Model 5[18] **(final)**	36663.74	0.250	78.9%

In the final model, out of the twenty-eight predictor variables only five were not statistically significant: BMI, depression, social support, alcohol input and physical fitness ($p > 0.05$).

[14] Age, gender and interaction term only.
[15] Model 1 plus Socio-demographic factors
[16] Model 2 plus risk factors.
[17] Model 3 plus patient's medical status.
[18] Model 4 plus service level factors.

The remaining twenty-three variables were all statistically significant in the final model ($p < 0.05$). Table 5.4 displays the results of all investigated determinants in the model.

Table 5.4 Results of all investigated determinants in the model.

Factor	Categories	P value	Odds ratio	*95% CI for OR*	
				Lower	Upper
Age	In years	0.003	0.989	0.981	0.996
Sex (Male)	Female	0.007	1.625	1.139	2.320
Interaction term	Age*Sex	0.004	0.992	0.987	0.998
Ethnicity (White)	Black	0.597	1.129	0.719	1.772
	South Asian	0.017	0.862	0.763	0.974
	Other	0.279	1.051	0.960	1.151
Patient received early CR	Yes	0.000	0.809	0.761	0.860
IMD rank (1 most deprived)	IMD rank (2)	0.000	1.305	1.180	1.444
	IMD rank (3)	0.000	1.436	1.300	1.585
	IMD rank (4)	0.000	1.487	1.341	1.649
	IMD rank(5)	0.000	1.819	1.644	2.013
Comorbidities	Hypertension	0.000	1.141	1.068	1.220
	Diabetes	0.000	0.860	0.796	0.929
	Physical activity	0.001	1.151	1.065	1.245

	Hypercholesterolemia	0.012	1.098	1.021	1.180
	Family History	0.000	1.217	1.133	1.306
	Angina	0.000	0.772	0.713	0.836
	Anxiety	0.001	1.311	1.122	1.531
	Depression	0.097	0.887	0.771	1.022
BMI Assessment 1	> 30	0.574	1.021	0.948	1.100
History of previous cardiac event	Yes	0.000	0.769	0.722	0.820
Employment (employed)	Unemployed	0.275	1.072	0.945	1.215
	Retired	0.020	1.142	1.022	1.277
Marital Status (Single)	In partnership	0.004	1.146	1.044	1.257
	Previous partnership	0.289	1.063	0.950	1.190
Social support	Yes	0.758	1.018	0.910	1.138
Alcohol intake	≤14 units/week	0.102	0.921	0.834	1.017
Smoking status	Smoker	0.000	0.599	0.549	0.653
Physical fitness	Yes	0.196	1.047	0.977	1.122
Number of comorbidities (0)	Comorbidity < 3	0.131	0.944	0.876	1.017
	Comorbidity > 3	0.009	0.862	0.770	0.964
	Cardiac nurse	0.000	1.300	1.214	1.392

Patient refereed by (consultant)	GP	0.041	2.312	1.037	5.155
	Primary care nurse	0.000	5.093	2.878	9.010
	Other	0.000	1.287	1.120	1.478
Hospital length of stay (overnight stay)	Day Case	0.000	1.202	1.106	1.306
Source of referral (NHS Trust)	General Practice	0.000	0.290	0.249	0.338
	Source of Referral (BMI/Private Hospital)	0.295	0.819	0.559	1.199
Received confirmed joining date	Yes	0.000	2.137	1.965	2.324
PCI type (primary)	PCI Type (MI)	0.001	0.892	0.835	0.954
	PCI Type (Elective)	0.000	0.779	0.724	0.838
Waiting time from cardiac event to pre-CR assessment (2 Weeks)	4 Weeks	0.000	1.832	1.705	1.968
	6 Weeks	0.000	2.265	2.094	2.451
	8 Weeks	0.000	2.471	2.212	2.760
	> 8 Weeks	0.000	2.495	2.279	2.733
Constant		0.000	5.413	3.004	9.756

In addition, a significant interaction term was found between age and sex (OR = 0.993, 95% CI 0.987 to 0.998) (Figure 5.2).

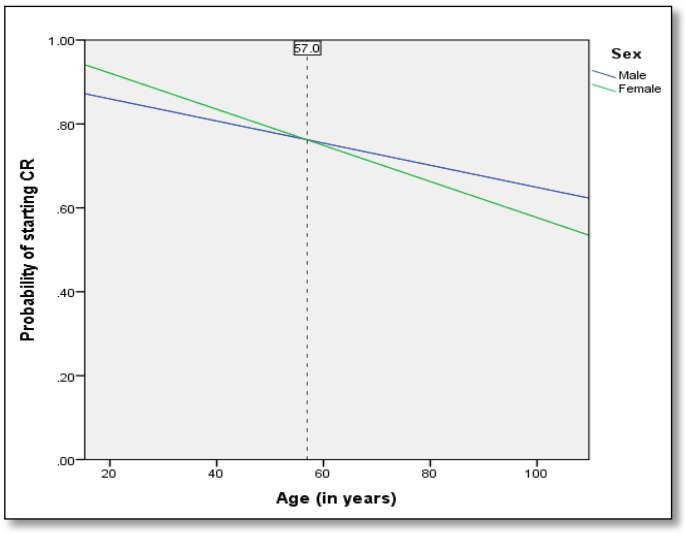


Figure 5.2 Age by sex interaction term.

In order to account for potential outliers and influential cases in the final model, Cook's distance test and standardised residuals were assessed (Field, 2013). There were no unusually high values of Cook's distance (all < 1) and the standardised residuals with < 5% of the values > ±3. The final model also proved to be a good predictor of the outcome variable (Hosmer and Lemeshow test: p = 0.231) indicating that the model is not a poor fit (Tabachnick and Linda Fidell, 2007). The ROC curve test indicates that the model has a good predictive ability with AUC of 0.76 (SE = 0.003, 95% CI: 0.75 to 0.77).

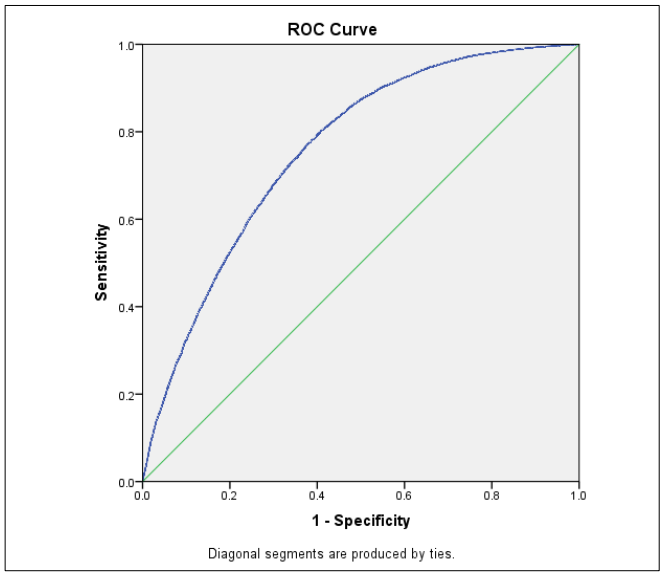


Figure 5.3 ROC curve for the final CR uptake model.

5.5 Discussion

Prior to discussing the findings of the results, a note on emphasis is important as unlike most of the literature, which has focused on uptake from all eligible patients, I have focused on what determines uptake for those patients who had completed a baseline CR assessment (Al Quait et al., 2017). In this secondary analysis of the NACR dataset, the likelihood of starting CR decreased statistically significantly with age (OR 0.98, 95% CI 0.98 to 0.995) and women were 63% more likely to start CR compared to men (OR 1.63, 95% CI 1.14 to 2.32). Also there is a significant interaction term between age and gender. In statistics, we say there is an interaction term when the value of an independent variable in the tested model differs significantly depending on the level of another independent variable (Field 2013). This age-gender interaction term is showing that younger women (< 57 years) are more likely to start CR than younger men (OR 1.6, 95% CI 1.1 to 2.2) while older women were found to be less likely to join compared to younger/middle age women or older men (> 57 years old) (Figure 5.2). These results seem to be consistent with other research conducted in health seeking behaviour which found that men aged 45-65 are less likely to utilise medical services (Cook et al., 1990). However, other researchers in the same field have shown no significant difference in health seeking behaviour between genders (Galdas, Cheater and Marshall, 2005). This discrepancy in the literature could be attributed to the widespread differences in study design and samples investigated. These findings builds on those observed in earlier CR systematic reviews and meta-analyses which collectively support the idea that existing CR programme designs are possibly informed by randomised trial studies where the dominant population was middle-aged patients hence it is not attractive for the elderly especially old female patients (Windecker et al., 2014; Wenger, 2008; Anderson et al., 2016; Menezes et al., 2014).

A number of other factors besides age and gender were statistically significant determinants of CR uptake. One important factors is the source of referral to CR. Multiple healthcare professionals, with a broad range of expertise, are usually involved in patient treatment after a cardiac event. Each profession should, in its own way, encourage patients to participate in CR after hospital discharge (Arena et al., 2012). Particularly, the strength of physician endorsement to CR plays a significant role in CR endorsement (Grace et al., 2008). This analysis has shown that patients who were referred from a primary care setting (GP or

primary care nurse) were more likely to start CR compared to patients referred from a hospital settings (consultant or cardiac nurse). These differences may be explained in part by the stronger relationship between patients and their GP's due to continual nature of primary care. Another important finding was that patients who were given a firm date to start CR by a phone call, letter or email were twice as likely to start CR (OR 2.1, 95% CI: 1.9 to 2.3).

A Cochrane systematic review has shown that minority ethnic groups were under-represented in CR programmes (Karmali et al., 2014). This is in agreement with the findings presented here as South Asians were found less likely to start CR compared to British White (OR 0.87, 95% CI:). Also, CR uptake decreased with increasing relative socio-economic deprivation. These findings points to inequalities in access to care and potential discrimination. Partnered patients tend to be more likely to join CR than single and previously partnered patients (p = 0.028, OR 1.1). This finding align with other qualitative research which indicated that couples are facilitating attendance by providing social support, transportation to CR centres or communication with health professionals (Clark et al., 2012). In the literature, there is a debate whether social support is a predictor of CR enrolment. For example, the presidential advisory of the American Heart Association (AHA) has identified the lack of social support as a barrier against CR attendance (Balady et al., 2011) but it did not prove to be a predictive factor in a prospective multisite qualitative study conducted by Grace et al (Grace et al., 2008). The current study confirms the lack of association between social support and CR uptake in PCI patients.

CR programmes in the UK and elsewhere are predominantly exercised based. Therefore it is anticipated that patients with higher physical fitness are more likely to join. NHS guidelines for adults aged from 19-64 recommends at least 150 minutes of moderate physical activity per week (NHS, 2015). Those patients who follow the guidelines and answered 'Yes' to the question 'Do you take regular physical activity of at least 30 minutes duration on average 5 times a week?' in the NACR questionnaire were found to start CR more frequently (OR 1.2). Also hypertensive, patients with hyperlipidaemia and family history of heart disease were found to be more likely to start CR than the others (OR = 1.1, OR = 1.1, OR = 1.2) respectively. However this analysis further supports the idea that CR programmes are still not attractive to certain patient groups like smokers and diabetic patients, or that the health service fails to engage with these patient groups sufficiently. This study found that smokers

are less likely to start CR by 40% (OR 0.6). This result may help to reveal part of the uncertainty reported by Murray et al (Murray et al., 2012) in their systematic narrative review of quantitative observational studies which found that smoking produced conflicting results with regards to CR uptake. Finally the number of comorbidities was identified as a barrier in CR uptake in this analysis. This finding is consistent with a retrospective analysis conducted in the Netherlands (van Engen-Verheul et al., 2013) and another Canadian qualitative study (Grace et al., 2009).

For improved CR outcomes, the UK National Institute for Health and Care Excellence (NICE) in line with national guidelines suggests that pre-CR assessment should start within 24 days of cardiac event (NICE commissioning guides, 2013). However, the findings of the current study suggests that early assessment may impact negatively on CR uptake. For example, patients being assessed 8 weeks after the event were 2.5 times (95% CI) more likely to start CR compared to those assessed in the first 2 weeks of the event.

Although uptake rates in PCI patients in the UK far exceed those seen in other European countries (47% compared to an average rate of 30% across Europe) they are still below the target rate of 65% across all treatment groups specified in the national clinical guideline (DH Cardiovascular Disease Team, 2013). However, CR uptake in the UK continues to rise and the percentage of MI+PCI patients attending CR has increased in 2014 and now stands at 58% (NACR, 2016). Being the largest national CR database in Europe, NACR is an essential part of the international quality assurance network which monitor the extent to which CR programmes perform against key service indicators and achieve expected patient outcomes.

5.6 Study limitations

The generalisability of these results is subject to certain limitations. For instance, patients were considered to start CR if they had a baseline assessment (engaged) and attended at least one outpatient CR session. Also the primary dataset is setup to evaluate final outcomes but not CR uptake, therefore it is likely that some other factors previously reported in the literature influencing CR uptake and not collected in NACR dataset have been missed (e.g. travel distance and patient's level of education). Also while I evaluated the type of PCI as a

determinant of uptake, it is likely that these correlate with unobserved clinical factors, so that our estimate of the effect of PCI type may be subject to confounding.

5.7 Conclusion

Improving CR uptake in PCI patients remains a significant challenge for healthcare professionals. Future strategies to increase CR uptake in PCI cohort should not consider age and gender as entirely independently determinants but should also consider age in the context of gender. Approaches to increase uptake may therefore be differentiated by age and gender profile of the target population. These findings enhance our understanding of determinants of CR uptake and suggests that some of the theoretical expectations about CR uptake are not substantiated by analyses of large, routine clinical datasets.

6 Adherence study

6.1 Abstract

6.1.1 Background

Cardiac rehabilitation (CR) adherence rates in clinical practice are far from optimal in most European countries particular in the Percutaneous Coronary Intervention (PCI) cohort. Previous research proposed variations in the mode of CR delivery as a potential solution to high dropout rates.

6.1.2 Purpose

This study has two main objectives, first to investigate the determinants of cardiac rehabilitation (CR) adherence in the percutaneous coronary intervention (PCI) cohort. Second, to assess variations in the mode of CR delivery in the UK and its impact on adherence rates.

6.1.3 Methods

I adopted a mixed prospective retrospective research methodology to answer the study objectives. First, I analysed routine clinical data from the UK National Audit of Cardiac Rehabilitation (NACR) for patients who underwent PCI in 2013 to 2016 and had started CR. Second, an online survey was administered to 296 CR programmes across the UK to assess characteristics in the mode of CR delivery. Finally, I merged the data to assess different factors on CR adherence rates by constructing a hierarchical logistic regression model, using multiple imputation as appropriate and cluster-robust sandwich estimator.

6.1.4 Results

The sample consisted of 28,263 patients nested in 141 CR programmes across the UK (63.6 ±11.4 years, 76% men and 84.5% Whites) of which 22,173 (78.5%) patients completed the CR programme. The final analytical model had 13 significant predictors of CR dropout. Among which, the likelihood of completing CR decreases if the patient was younger, smoking at baseline, socially deprived and unemployed. I also concluded that there was no significant differences in adherence rates between home-based and group-based programmes either on patients' level or centre level.

6.1.5 Conclusion

It is evidently clear from the findings that different modes of CR delivery have the similar adherence rates. These data support further clinical development of CR programmes to be more attractive to all patient groups.

6.2 Introduction

Accounting for 45% of all deaths, cardiovascular disease (CVD) causes 3.9 million deaths in Europe alone. Gender-adjusted mortality rates show 1.8 million deaths in men (40% of all deaths) and 2.1 million deaths in women (49% of all deaths). In addition, approximately 11.3 million new cases of CVD have been registered in 2015 making the total number of Europeans living with this disease at ~85 million patients. This high prevalence of CVD has an estimated cost to the European economy of €210 billion annually. The economic burden of CVD is not limited to production losses of those of working age, but also extend to the amount of money that carers sacrifice to provide unpaid care for their partners, parents or relatives suffering from CVD (Wilkins et al., 2017). Moreover, European age-adjusted mortality rates have decreased indicating that people are living longer with cardiovascular conditions and the challenge now is to optimise their quality of life (Bjarnason-Wehrens et al., 2010).

On the other hand, Cardiac Rehabilitation (CR) has been proven to be one of the most clinically and cost-effective intervention in the management of CVD (BACPR, 2017). It is now well established that, from a variety of high quality research, CR reduces mortality, hospital readmission and improves quality of life (Anderson et al., 2016; Rauch et al., 2016; Sumner, Harrison and Doherty, 2017). As a result, participation in a CR programme following a cardiovascular event is class 1 level A recommendation by the European Society of Cardiology (ESC) and several other national and international regulating bodies worldwide (Ruano-Ravina et al., 2016). Despite the proven benefits, delivery of routine practice CR still has considerable challenges with referral, uptake and adherence remaining unresolved and implicated in the underutilisation of CR in most European countries (Humphrey, Guazzi and Niebauer, 2014).

The next challenge after facilitating patients' attendance to the outpatient CR, is to maintain adherence to the programme. This is particularly important since CR national registries and audit data have shown wide range of dropout rates (24% to 77%) of patients who start the outpatient CR programme (Turk-Adawi et al., 2013; NACR, 2016). Causal factors leading to these high dropout rates remain speculative since they mainly come from trials via systematic reviews while dropout rates are measured in routine clinical data. Considering the

intrinsic differences in population between trials and registry data, higher quality research based on routine clinical data should be directed towards investigating this persistent problem. A recently published systematic review on CR participation and adherence reported that the information on which factors impede CR adherence is scarce despite the high dropout rates (Ruano-Ravina et al., 2016).

This study therefore set out to assess the determinants of CR adherence in the growing percutaneous coronary intervention (PCI) cohort. PCI population has been specifically selected since it represents the first choice of treatment for coronary artery disease (CAD) in the last decade (Diletti et al., 2014). The second objective of this study is to assess variations in the mode of CR delivery in the UK and its impact on adherence rates. The latter objective was set since there is some evidence that supporting patient preference in the mode of CR delivery proposed as a potential solution to high dropout rates (Dalal, Doherty and Taylor, 2015). This is of interest particularly after the updated Cochrane systematic review which concluded that home- and centre-based CR programmes seem to be similarly effective in improving clinical and health-related quality of life for cardiac patients (Anderson et al., 2017a; Ruano-Ravina et al., 2016).

6.3 Methods

The methodological approach taken in this study is primarily retrospective research design with an additional prospective approach to address the two main objectives of the study. This paper uses routinely collected data retrieved from the UK National Audit of Cardiac Rehabilitation (NACR) dataset to investigate the determinants of CR adherence. The study also employed a prospective survey in order to gain insights into the mode of CR delivered within the UK.

6.3.1 Retrospective approach

The study used a routine clinical data retrieved from the NACR dataset for the period 1st April 2013 to 31st March 2016. The decision to use an observational design was based on its ability to allow the researcher to observe ‘in natural settings’ the differences in how interventions are delivered (Anglemyer, Horvath and Bero, 2014). Moreover, observational designs are vital in building clinical evidence, exploring how an intervention is practiced on

the ground and understanding disparities in access to and delivery of healthcare services (Carlson and Morrison, 2009). In addition, the population captured in a comprehensive routine audit is more representative than volunteer participants within RCTs particularly with regards to mean age and female representation. The data source, inclusion criteria and ethical approval have been described elsewhere (Al Quait et al., 2017).

6.3.1.1 Measures

The primary dependent variable in this study is CR adherence. It is a binary variable with two categories: completers and dropouts. A patient is considered a completer if he or she satisfies two conditions: first, performing a CR assessment at the end of the outpatient programme (assessment 2). Second, marked as a completer by a CR programme staff member. Otherwise, they are considered as a dropout (Figure 6.1).

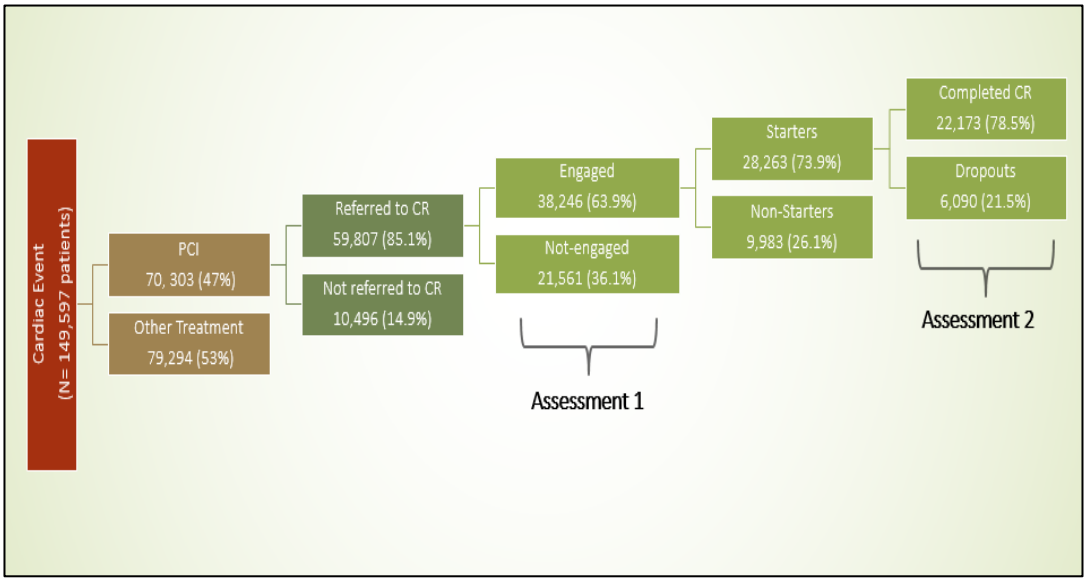


Figure 6.1 Study flow and sample size.

With regards to the independent variables, 28 factors were hypothesised to have a potential direct impact towards CR adherence. This is based on the searched literature and according to its availability in the primary analysed dataset (Table 6.1). These factors were either continuous or categorical depending on the method of data collection in NACR.

Table 6.1 Hypothesised factors for CR adherence.

	Socio-demographic factors	Cardiac risk factors	Life style & Health status	Service level factors
1	Age	Hypertension	Alcohol intake	CR centre prescribed dose
2	Gender	Hyperlipidaemia	Smoking	Group/alone core CR
3	Ethnicity	Diabetes	Physical fitness	Supervised/self-delivered
4	IMD Score	Physical inactivity	Comorbidities	MDT centre
5	Marital status	Being overweight	Previous cardiac event	BACPR certified centre
6	Social support	Anxiety	Family history	PCI type
7	Employment	Depression	Angina	Waiting time

To investigate the impact of social deprivation on CR uptake, the Index of Multiple Deprivation (IMD) 2010 was linked to NACR data set. The IMD is the official measure of relative deprivation for small areas (or neighbourhoods) in England (DCLG, 2015). The IMD scores are based on 8 distinct domains of deprivation with respect to 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 generate an approximate overall deprivation score for each individual patient according to their small area of residence (Sumner, Grace and Doherty, 2016). A detailed explanation of the investigated factors and their subcategories can be found in (Appendix 9.6).

6.3.1.2 Statistical analysis

To begin this process, descriptive statistics were generated for a set of variables to compare differences in baseline characteristics between completers and dropouts. Independent sample t-tests were computed for continuous variables and chi-square tests for categorical variables. A p value <0.05 was considered statistically significant. Under the assumption that missing values are missing at random, all variables with > 5% missingness were handled by multiple imputation using 20 imputed data sets. The resulting estimates were pooled using Rubin's rule.

As the primary dependent variable is binary (completed/dropout), a binary logistic regression model was developed to predict the probability of CR adherence and to examine the association among the research variables. A backward selection technique was followed in which all variables were entered simultaneously in the model and variables with p-value > 0.05 were removed. This process was repeated until all variables had $p \leq 0.05$. Since age and gender were reported in the literature as major determinants of CR accessibility and outcomes, (Thomas et al., 2014; Al Quait and Doherty, 2016) age and gender-specific interaction was tested by inserting a 2-way age and gender interaction term in the model as a separate variable.

Due to the nested nature of the primary dataset, patients are clustered within CR centres. This meant that it was not possible to assume the independency of observations within groups i.e. residuals might be correlated within but not across groups. To account for this issue, the cluster-robust sandwich estimator was used (Rogers, 1993; Williams, 2000). To validate the model's predictive power, a receiver operating characteristic (ROC) curve was plotted and model accuracy was measured by the area under the ROC curve (AUC) (Hajian-Tilaki, 2013). Data management, descriptive statistics and multiple imputation was performed using SPSS software (version 24) while the logistic regression model and diagnostics were conducted using STATA SE (version 15).

6.3.2 Prospective approach

Our survey sought to clarify variation in the mode of delivery as part of routine outpatient clinical practice, at a programme level, and use this to complement the main study (Berkwits and Inui, 1998; Morgan, 1998). This was the first time NACR survey questions designed to

capture the diversity of the mode of delivery in routine CR were developed in partnership with the NACR team and clinical lead. This was sent out to all 296 CR users currently on the CR registry as of August, 2017. Although all survey responses were used to help the NACR build programme level data when evaluating the impact of variations in the mode of CR delivery on adherence rates, only survey responses being linked with the NACR patient level data will be analysed. A Pearson correlation analysis was conducted in order to assess the association between mode of CR delivery and adherence rate. The example of the survey is shown in (Appendix 9.7).

6.3.2.1 Population

The survey was sent to primary contacts at CR programmes that consisted of 296 recipients. The primary contacts were assigned as each programme registered with the NACR and were entered onto the online registry. In the cases where the CR team enter NACR data these have also been approved by the Caldicott guardian at the local trust.

6.3.2.2 Questionnaire

The survey was completed as an online questionnaire through Survey Monkey (https://www.surveymonkey.co.uk/). The survey asked programmes whether their mode of CR delivery consisted of group-based or mixture of group and home-based, once the programme stated their mode of delivery a series of questions specific to their response was asked. These included type of home-based, supervision level with a final question, where relevant, on the reasons for not offering a particular mode such as home-based.

6.4 Results

The first set of analyses examined the determinants of CR adherence. Table 6.2 compares the baseline characteristics of completers and dropouts. A total of 28,263 patients clustered in 141 CR programmes across England (63.6 ±11.4 years, 76% men and 84.5% Whites) were analysed.

Table 6.2 Baseline characteristics of both groups.

Factor	Completed	Dropouts
Sample size	22,173 (78.5%)	6,090 (21.5%)
Mean age (SD)	64.03 (11.1)	61.99 (12.4)
% Female	23.4%	26.3%
Ethnicity (White)	85.3%	81.5%
Employed	25.5%	23.2%
IMD score (5)[19]	25.5%	16.7%
Comorbidities (+3)	29.0%	33.3%
Physical inactivity[20]	29.3%	22.7%
Smokers	7.1%	14.6%
Waiting time[21]	42.3	41.9

6.4.1 Adherence determinants

Out of the 28 determinants tested in the first logistic regression model, 15 turned out to be not statistically significant including the age by sex interaction term ($p > 0.05$) (Table 6.3). This first model was statistically significant with χ^2 (27.44) = 3829876.4, $p < 0.001$.

[19] Ratio of least deprived patients in the cohort.
[20] Ratio of patients taking moderate physical activity for 150 minutes per week at baseline assessment.
[21] Mean waiting time from index event to starting CR in days.

Table 6.3 First model with all independent variables inserted.

Variable	Odds Ratio	[95% CI]		P value
Age (years)	1.011	1.005	1.017	0.000
Sex (male)	1.279	0.853	1.916	0.233
Age by Sex interaction	0.995	0.989	1.001	0.132
Ethnicity (White)				
Black	0.909	0.581	1.422	0.676
South Asian	0.840	0.685	1.030	0.094
Other	0.803	0.698	0.924	0.002
IMD (1 most deprived)				
2	1.316	1.143	1.516	0.000
3	1.407	1.181	1.676	0.000
4	1.526	1.278	1.823	0.000
5	1.917	1.594	2.304	0.000
Marital (single)				
Partnered	1.093	0.949	1.260	0.217
Previous partnership	0.891	0.758	1.047	0.162

Social support (y/n)	1.153	1.038	1.281	0.008
Employment (employed)				
Unemployed	0.823	0.724	0.937	0.003
Retired	0.955	0.864	1.057	0.373
BMI	0.842	0.781	0.907	0.000
Physical inactivity (150 min/week) (y/n)	1.210	1.100	1.331	0.000
Physical fitness (self-reported) (y/n)	1.114	1.008	1.231	0.035
Smoking (y/n)	0.496	0.446	0.552	0.000
Alcohol intake (y/n)	1.037	0.929	1.158	0.514
Angina (y/n)	0.973	0.841	1.126	0.717
Diabetes (y/n)	0.892	0.808	0.984	0.022
Hypertension (y/n)	1.072	0.972	1.183	0.165
Anxiety (y/n)	1.074	0.919	1.255	0.368
Depression (y/n)	0.711	0.607	0.834	0.000
Family History (y/n)	0.952	0.834	1.087	0.467
Hyperlipidaemia (y/n)	1.003	0.880	1.145	0.959

Comorbidities number				
≤ 2	1.110	0.847	1.454	0.451
> 3	0.973	0.729	1.299	0.852
Previous cardiac Event (y/n)	0.866	0.761	0.987	0.031
PCI Type				
MI PCI	0.920	0.832	1.018	0.105
Elective PCI	0.961	0.853	1.083	0.517
CR dose (sessions/weeks)	1.552	1.255	1.919	0.000
Group CR delivery (alone)	1.167	0.979	1.390	0.084
Supervised CR delivery (unsupervised)	0.868	0.644	1.171	0.355
Time from event to Core CR (days)	0.999	0.995	1.003	0.652
BACPR Certified Centre (y/n)	0.946	0.701	1.276	0.716
Multidisciplinary team centre (y/n)	1.180	0.840	1.659	0.340

After removing the 15 variables with $p > 0.05$ the test was run again and only 1 variable turned out to be not statistically significant, previous cardiac event ($p = 0.071$) (Table 6.4). This second model was also statistically significant with χ^2 (33.38) = 1913544.8, $p < 0.001$.

Table 6.4 Second model with all significant variables in the first model.

Variable	Odds Ratio	[95% CI]		P value
Age (years)	1.009	1.003	1.014	0.002
Ethnicity (White)				
Black	0.946	0.606	1.476	0.805
South Asian	0.866	0.698	1.074	0.189
Other	0.826	0.722	0.945	0.005
IMD (1 most deprived)				
2	1.329	1.139	1.551	0.000
3	1.428	1.176	1.734	0.000
4	1.552	1.271	1.895	0.000
5	1.962	1.582	2.432	0.000
Social support	1.187	1.073	1.312	0.001
Employment (employed)				
Unemployed	0.818	0.718	0.933	0.003
Retired	0.943	0.853	1.044	0.259
BMI (y/n)	0.841	0.780	0.906	0.000

Physical inactivity (150 min/week)	1.218	1.108	1.339	0.000
Physical fitness (self-reported) (y/n)	1.124	1.014	1.246	0.026
Smoking (y/n)	0.486	0.437	0.540	0.000
Diabetes (y/n)	0.888	0.800	0.986	0.026
Depression (y/n)	0.699	0.586	0.832	0.000
Previous cardiac event (y/n)	0.867	0.743	1.012	0.071
CR dose (Sessions/weeks)	1.561	1.261	1.933	0.000

After removing the previous cardiac event variable the test was run again and all remaining 12 variables were significant (Table 6.5). This final model was statistically significant, χ^2 (34.23) = 1811961.6, $p < 0.001$.

Table 6.5 Significant determinants in the final CR adherence model.

Variable	Odds Ratio	[95% CI]		P value
Age (years)	1.008	1.003	1.014	0.004
Ethnicity (White)				
Black	0.939	0.606	1.454	0.777
South Asian	0.857	0.694	1.059	0.154
Other	0.825	0.722	0.943	0.005
IMD (1 most deprived)				

2	1.330	1.140	1.551	0.000
3	1.433	1.182	1.738	0.000
4	1.555	1.275	1.896	0.000
5	1.968	1.590	2.436	0.000
Social support	1.191	1.076	1.317	0.001
Employment (employed)				
Unemployed	0.818	0.717	0.934	0.003
Retired	0.940	0.849	1.040	0.230
BMI > 30 (y/n)	0.839	0.779	0.903	0.000
Physical inactivity (150 min/week) (y/n)	1.217	1.107	1.338	0.000
Physical fitness (self-reported) (y/n)	1.126	1.016	1.248	0.024
Smoking (y/n)	0.487	0.438	0.541	0.000
Diabetes (y/n)	0.870	0.775	0.976	0.017
Depression (y/n)	0.687	0.573	0.824	0.000
CR dose (Sessions/weeks)	1.566	1.265	1.938	0.000

The model had a pseudo R2 over imputed data equal to 0.046. The ROC curve test indicates that the model has a good predictive ability with AUC of 0.65 (Figure 6.2).

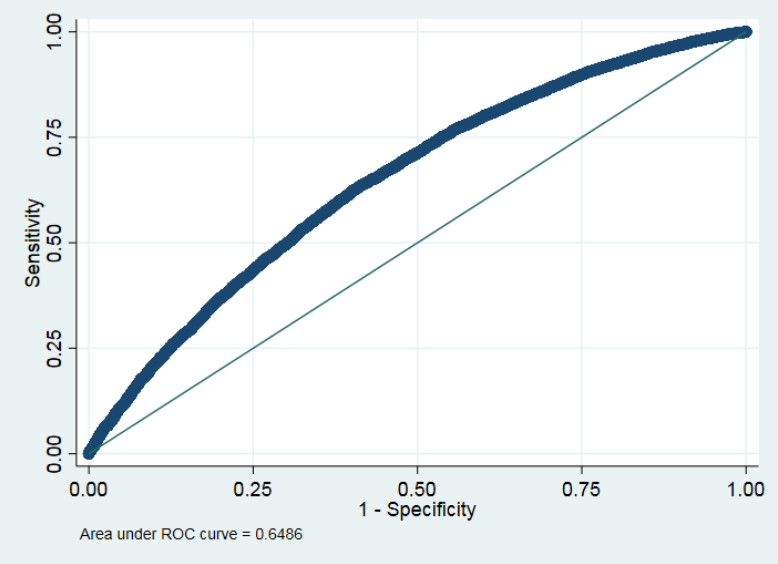


Figure 6.2 ROC for the third model.

6.4.2 Survey results

The total number of CR programmes delivering core CR in the UK is 301 while the total number of programmes entering data electronically in the NACR portal is 224 (74%) (NACR 2017). The questionnaire was sent to 296 programmes and a total of 167 programmes (56.4%) responded, 118 programmes (70.7%) are NACR users and 49 programmes (29.3%) are not. Figure 6.2 provides a flow diagram of the response rate for CR teams, these are split into NACR users and non NACR users. This is due to the survey responses being linked with routine patient level data to provide an extra level of analysis for adherence to CR.

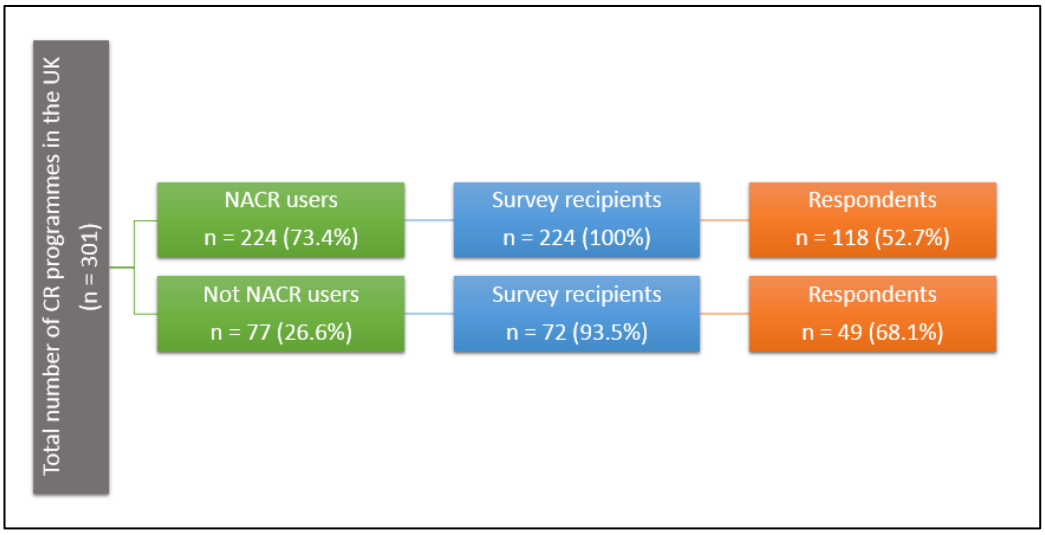


Figure 6.3 Survey respondents flow chart.

Out of the 167 respondent programmes, 104 (62.3%) programmes were delivering CR in both settings and 61 (36.5%) programmes delivered CR in group-based setting only while 1 (0.6%) programme were delivering CR as home-based only and 1 (0.6%) programme delivering acute hospital ward CR only. The responses to the other survey questions is displayed in (Table 6.6). Finally, the Pearson Chi-square test revealed no significant association between mode of CR delivery and adherence rate (p = 0.53, OR: 0.93, 95% CI: 0.87 to 1.01).

Table 6.6 Responses to survey questions.

Mode of Delivery	Mode specific questions	Responses		
			Count	%
Programmes delivering CR as home- & group-based (104 responses)	Home Question 1, do you deliver Heart Manual?	No	67	64.4%
		Yes	37	35.6%
	Home Question 1, do you deliver Angina Plan?	No	96	92.3%
		Yes	8	7.7%
	Home Question 1, delivered as Individual Patient Programme Supervised?	No	52	50%
		Yes	52	50%
	Home Question 1, do you deliver Individual Patient Programme Not Supervised?	No	43	41.3%
		Yes	61	58.7%
	Home Question 1, do you deliver Individual Other (such as home visits, face to face)?	No	104	100%
		Yes	0	0%
Programmes delivering CR as group based only (61 responses)	Group Question 1, why don't you deliver Home based no Funding?	No	14	22.9%
		Yes	47	77.1%
	Group Question 1, why don't you deliver Home based provided elsewhere?	No	56	91.8%
		Yes	5	8.2%
	Group Question 1, why don't you deliver Home based no staff?	No	41	67.2%
		Yes	20	32.8%
	Group Question 1, why don't you deliver Home based no demand?	No	57	93.4%
		Yes	4	6.6%

6.5 Discussion

The present study was designed to investigate the factors influencing CR adherence, including mode of CR delivery, in the PCI cohort. A mixed prospective retrospective methodological approach was adopted to better serve the goals of the study. The retrospective cohort consisted of 28,263 patients with a mean age of 63.6 years (±11.4). Within the cohort, 24% were women and 15.5% from minor ethnic groups. The investigated cohort were nested in 141 CR centres across the UK and 78.5% managed to complete the core CR programme.

With respect to the first objective of the study, our routine clinical data have shown that younger age is associated with higher dropout rates (odds ratio (OR) 1.008, 95% CI 1.003 to 1.014) confirming similar findings in previous cohort studies (Casey et al., 2008; Yohannes AM, Yalfani A, Doherty P, 2007; Sarrafzadegan et al., 2007; Harrison and Wardle, 2005; Turk-Adawi et al., 2013). This study has been unable to demonstrate that gender is a predictor of CR completion. This outcome is contrary to a previous UK study which conducted a multivariate analysis in a smaller cohort (n = 203) recruited from a university teaching hospital (Yohannes AM, Yalfani A, Doherty P, 2007). Also another middle-eastern study found that the odds of female participants to dropout early is 1.82 compared to male participants (Sarrafzadegan et al., 2007). However, in a logistic regression analysis controlling for age, BMI, employment status and depression (Casey et al. 2008) concluded that gender is not a predictor of CR completion (OR: 1.34, 95% CI: 0.86 to 2.06). The possible interference of interaction between age and gender was also tested in this study and found to be not significant.

In contrast to earlier finding by a previous UK study (Banerjee, Gupta and Singh, 2007) which revealed that South Asians are less likely than Whites to adhere to CR, this study found that South Asians and Black patients are not statistically different than Whites in CR adherence rates. However, participants from other ethnic minorities were found to be 17% less likely to adhere to CR compared with Whites (OR: 0.825, 95% CI: 0.722 to 0.943). This result seems to be in part consistent with an American study which found that Non-whites were less likely to adhere to CR than Whites (OR: 0.60, 95% CI: 0.41 to 0.88)(Turk-Adawi et al., 2013).

The most obvious finding to emerge from patient's demographic determinants is the significant correlation between the index of social deprivation as measured by IMD and CR adherence. The current results show that low CR adherence is associated with the most deprived and increases in the least deprived patients. These results builds on those of a Candian retrospective study (N = 18,980) which also found that CR completion rates in a mixed CABG/PCI population are significantly higher in high-income neighbourhoods compared with low-income neighbourhoods (Lemstra et al., 2013). Participant's marital status in this study had no significant influence on adherence rates which is in accordance with Sarrafzadegan et al. (2007) study (Sarrafzadegan et al., 2007). Nevertheless, those patients who reported having 'enough social support if they needed and wanted it' were found to be more likely to adhere to CR than their counterparts (OR: 1.191, 95% CI: 1.076 to 1.317).

Our results display lower adherence rates in unemployed participants compared to those employed or retired (OR: 0.818, 95% CI: 0.717 to 0.934). This finding is partially in line with an older prospective smaller size Australian study (N = 652) which found that retired and unemployed MI patients are more likely to drop out early than employed participants (OR: 1.83 and 4.69) respectively (Worcester et al., 2004). This is in contrast of the findings of a prospective Iranian study which reported that the number of CR sessions in which the subjects attended did not differ according to job category (Sarrafzadegan et al., 2007).

Among studies investigating CR adherence, diabetes mellitus as an adherence determinant is also one of the most reported cardiac risk factor. Our findings show that diabetic patients are 13% less likely to complete the CR programme compared to non-diabetic patients (OR: 0.870, 95% CI: 0.775 to 0.976). Two previous multivariate studies reporting diabetes were controversial. While an American retrospective secondary analysis study observed higher adherence rates in patients with diabetes than non-diabetics (OR: 1.3, 95% CI: 1.13 to 1.49) (Turk-Adawi et al., 2013), a primary prospective Australian study reported that male diabetic patients have higher dropout rates (OR: 3.38, 95% CI: 1.43 to 7.97) (Worcester et al., 2004). In the same vein but with a less robust method, Armstrong et al. (2014) reported that 84.9% of non-diabetic patients versus 79.6% of diabetic patients completed the 12-weekk CR programme ($p < 0.001$).

The impact of obesity, either reported as a BMI or waist size measurement, on CR adherence has been reported in previous studies. Our results show that patients with BMI > 30 are less likely to complete CR compared to those < 30 (OR: 0.839, 95% CI: 0.779 to 0.903). This builds on the findings of Sarrafzadegan et al. (2007) who reported that patients with BMI > 30 were significantly more likely to dropout (OR: 0.95, 95% CI: 0.92 to 0.98) (Sarrafzadegan et al., 2007). This result differs from an American retrospective secondary analysis study that found no significant association between BMI or body weight and CR completion(Casey et al., 2008). Two other studies that investigated BMI in women and older patients (> 65 years) reached the same conclusion.

The impact of physical inactivity as a cardiac risk factor on CR adherence has been investigated in this study and found to be significant. Those patients performing ≥150 minutes of moderate exercise per week were found to be 22% more likely to complete the core CR programme (OR: 1.217, 95% CI: 1.107 to 1.338). This finding is similar to that reported in a previous prospective Australian study which found that women who exercise < 6 hours/week are 2.29 more likely to drop out than women exercising ≥ 6 hours/week (OR: 2.29, 95% CI: 0.58 to 9.03) and women who never exercise are 7.32 more likely to drop out (OR: 7.32, 95% CI: 1.32 to 41.21) (Worcester et al., 2004). The last significant factor in the cardiac risk factor group is depression. I found that patients with the comorbidity of depression are less likely to complete CR (OR: 0.687, 95% CI: 0.573 to 0.824). This finding is supported by Casey et al. (2008) who reported that participants who had higher levels of depressive symptoms were less likely to complete CR (OR: 0.96, 95% CI: 0.93 to 0.99) (Casey et al., 2008).

Another important finding was that smokers were less likely to adhere to CR than non-smokers (OR: 0.487, 95% CI: 0.438 to 0.541). This result reflects those of Worcester et al. (2004) and Sarrafzadegan et al. (2007) who also found that former smokers and current smokers are more likely to drop out from CR than those who never smoked (Worcester et al., 2004; Sarrafzadegan et al., 2007). Also Doll et al. (2015) who investigated CR adherence among older patients (> 65) reported that current and recent smokers are attending less number of CR sessions than non-smokers (Doll et al., 2015). However, three other studies revealed no significant association between CR adherence and smoking status (Beckie et al., 2015; Yohannes AM, Yalfani A, Doherty P, 2007; Turk-Adawi et al., 2013).

One of our most telling findings is that CR adherence rate increases as the number of sessions per week increases (CR dose). I found that patients who were attending more CR sessions per week are more likely to stay in the programme. The adherence rate increases 57% for each extra session attended per week (OR: 1.566, 95% CI: 1.265 to 1.938). Our analysis also revealed that those patients who were able to perform at least 2 minutes of moderate to very heavy physical activity are 13% more likely to complete a CR programme than their counterparts (OR: 1.126, 95% CI: 1.107 to 1.338).

An important concept that emerged from our multivariate analysis was that there is no significant association between adherence rate and how CR was delivered. This study is the first to have created two binary patient level variable that measures if CR was delivered in group-based or individual-based and a second binary variable measuring if CR was delivered under supervision of CR team or it was self-delivered. Although both variables were significant ($p < 0.05$) at the univariate level, this association failed to hold at the final multivariate analysis. This finding is contrary to the limited evidence found by a recent Cochrane systematic review of a small increase in the level of completion with home-based compared with centre-based programmes (Anderson et al., 2017b). This discrepancy in findings could be attributed to differences in population characteristics between routine clinical studies and randomised control trials. For example, the population mean age in this study is 63.6 years with 24% women while the Cochrane review had a younger mean age of 56 years with only 19% women.

With regard to survey results, the overall response to the survey was good (56.4%). This high response rate, 169 programme out of 301, enables us to confidently describe how CR is delivered across the UK. From this data, 62.3% of programmes are capable of delivering CR in both settings (group-based and home based) while 36.5% deliver CR as group-based only. Lack of funding and appropriate staff were the main two reasons for not being able to offer home-based CR as reported by the surveyed programmes. While half of the programmes delivering CR as home based deliver it without any form of supervision (Table 4). What stands out when merging survey results with patients' data is that adherence rates are not influenced by the mode of CR delivery. These results draw our attention to the importance of considering expanding the utilisation of home-based CR.

6.6 Study limitations

Since the primary investigated dataset is setup to evaluate final outcomes but not CR adherence, there is uncertainty whether some other factors influencing CR adherence have been missed. For instance, other factors that has been reported to influence CR adherence rates such as rural residency and education level were not included in the analysis. Furthermore, it has been previously reported that adherence rates in programme delivered by a multidisciplinary team are higher than other programmes (Turk-Adawi et al., 2013), however, the amount of time contributed from each discipline in the programme was not included in this analysis. Also the sample size in the adherence study was the smallest of all three retrospective NACR based studies, which means that the population that complete may not be representative of all CR patients. For example, baseline analysis found that the percentage of single patients in the adherence group is only 8.2% of the total marital status cohort compared to 23.3% in the engagement group and 8.9% in the uptake group (Table 7.2).

6.7 Conclusion

This is the first comprehensive study to investigate CR adherence rates in the growing PCI population. The key strengths of this study are the mixed prospective retrospective methodology approach adopted and the relatively large sample size obtained from a routine clinical dataset. The findings from this study make several contributions to the current literature. First, our multivariate analyses revealed that current CR programmes are not attractive to smokers, unemployed and socially deprived patients. The second major finding was that adherence rates between group-based and home-based programmes are similar despite the recent evidence from a Cochrane systematic review. This was confirmed by our survey results which found no significant adherence rate differences between programmes delivering CR as group-based only and those delivering CR in both settings.

7 Synthesis study

7.1 Introduction

A patient journey through modern comprehensive CR programme is a multifaceted highly variable process. However, CR pathway is made up of key stages that need to occur to enable patients to achieve meaningful clinical outcomes and long-term behavioural change. These key stages begins with patient presentation following a cardiac event and ends up with discharge and transition to long-term management (Figure 1.4) (BACPR, 2017). Such planned and structured pathway of care ensures continuity in treatment of heart disease and the ability to tailor CR to the individual needs of patients. CR also provide safe and predictable methods of disease management which enables a multi-disciplinary team of healthcare professionals to provide a unified evidence-based treatment to all patients (Giuliano et al., 2017).

The CR pathway commonly consists of three main phases (inpatient, outpatient and long-term maintenance) (Piepoli et al., 2016). The outpatient CR, also known as core CR, is a cornerstone phase in the delivery of CR to patients whether delivered as hospital based, community based or home based. Patients' participation in outpatient CR is globally considered the main determinant of optimal CR utilisation. Extensive research, both qualitative and quantitative, have been utilised to understand factors associated with poor patients utilisation of outpatient CR (Murray et al., 2012; Clark et al., 2012; Karmali et al., 2014; Ruano-Ravina et al., 2016). However, as this thesis has shown, research varies in terms of design, targeted population and era which might be a significant source of heterogeneity when conducting a synthesis of literature.

Although the previous four chapters in this thesis independently explored the determinants of CR engagement, uptake and adherence in the literature and in a routine clinical dataset, there is an added benefit to be gained from pulling together data and findings from each of those four chapters. This study therefore set out to combine a number of different pieces into a whole which should allow for a higher level of evaluation and understanding of the findings. It will concisely summarise and link different sources of data in order to enhance our understanding of CR low participation rates in the PCI cohort. This study will also

challenge our previous theoretical expectations and conventional evidence about barriers in CR utilisation and substantiate this approach using routine clinical data. Moreover, it will provide a framework that will map an intervention with respect to identified barriers to promote CR along the patient journey in the PCI population.

7.2 Methods

All studies in this thesis are retrospective observational studies using data retrieved from the NACR dataset for the period 1st April 2013 to 31st March 2016. Although NACR collects data for three countries (England, Northern Ireland and Wales), only patients in England were included in the studies as the IMD is only available for small areas in England. In all three themed studies in the thesis plus the systematic review, the researcher attempted to keep the investigated factors as consistent as possible to facilitate data synthesis among studies (Table 7.1). Nevertheless, evaluating all these variables in all studies was subject to their availability in the primary NACR dataset or in the investigated studies included in the systematic review. Also service level factors varied among the three studies, particularly in the adherence study, to better serve the research outcome in each case.

This chapter will start by evaluating the number of patients interacting with each key stage of CR pathway from the initiation of the cardiac event to completing the outpatient CR programme during the study period. This approach will allow us to identify; (1) number of eligible patients missing out on this effective treatment at each stage (2) identify which key stage has the highest dropout rate. This chapter will also compare differences in baseline characteristics across all three groups (engagement, uptake and completion). Since the analysis will involve three different groups, analysis of variance test for continuous variables and chi-square tests for categorical variables will be used. A p-values < 0.05 will be considered statistically significant.

Table 7.1 Unified tested variables in all studies (service level factors from adherence study).

	Socio-demographic factors	Cardiac risk factors	Life style & Health status	Service level factors
1	Age	Hypertension	Alcohol intake	CR dose
2	Sex	Hyperlipidaemia	Smoking	Group/alone core CR
3	Ethnicity	Diabetes	Physical fitness	Supervised/self-delivered
4	IMD Score	Physical activity	Comorbidities	MDT centre
5	Marital status	Being overweight	Previous cardiac event	BACPR certified programme
6	Social support	Anxiety	Family history	PCI type
7	Employment	Depression	Angina	Time from event to starting CR

Furthermore, this chapter will attempt to analyse individual patterns of change in cohort characteristics among those engaged, started and completed CR in a routine clinical dataset. These changes will then be compared to the existing scientific evidence derived from various study designs (systematic review in chapter 2).

7.3 Results

7.3.1 Patient flow

During the study period, a total of 149,597 cardiac events were recorded in the NACR dataset (Figure 7.1). Out of this cohort 70,303 (47%) patients underwent a PCI procedure. Due to the adoption of automatic referral strategy for all patients groups eligible to CR in England, all patients who are likely to benefit from CR were referred (85.1%).

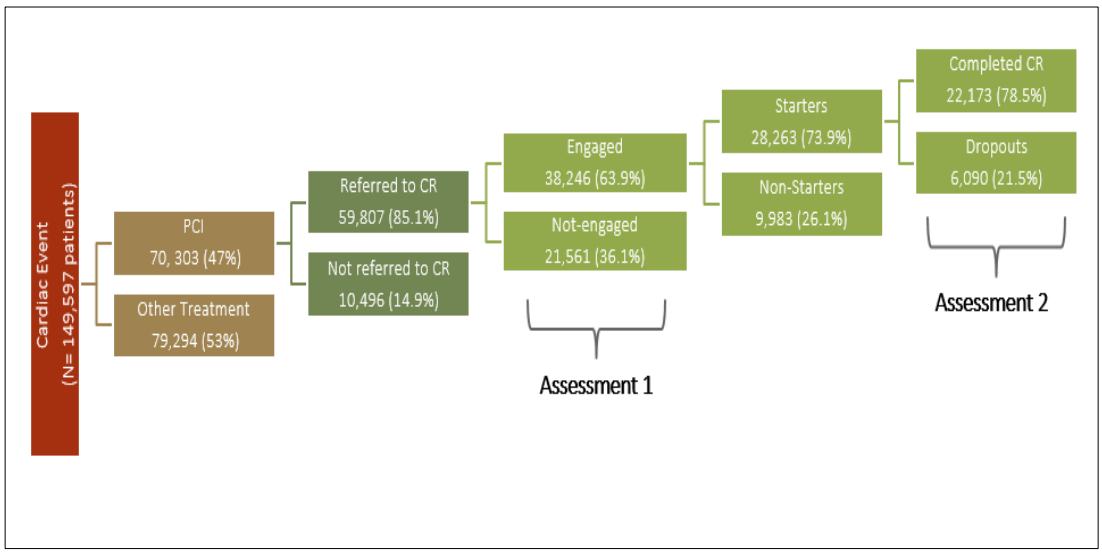


Figure 7.1 Patient flow chart during study period.

As can be noted, all described stages in this journey -so far- are less influenced by the patient's decision to participate in CR. However, post CR referral stages are strongly impacted by informed patient's decision. For patients agreeing to engage, a baseline CR assessment is conducted (assessment 1) (Figure 7.1). Approximately 64% of eligible CR patients engaged with CR at this stage. In other words, 21,561 eligible CR patients decided not to utilise this treatment at this early stage. Of those engaged in CR, 73.9% started the outpatient CR programme while 78.5% of starters completed the programme.

Based on the data presented in (Figure 7.1), a total of 59,807 PCI patients were eligible to receive CR in the specified study period. Despite this, only 22,173 (37.1%) completed the programme while 37,634 (62.9%) patients decided not to join CR at different stages. Approximately half of those patients (57%) were denied CR participation at the first point of contact with outpatient CR (CR engagement).

7.3.2 Baseline characteristics

In this section, a comparison of differences in baseline characteristics among patients in the three studies will be presented. Table 7.2 presents temporal changes in baseline characteristics while (Figure 7.2) displays changes of trends in the same context.

Table 7.2 Baseline characteristics of all groups.

Factor	Engaged	Started	Completed	p - value
N	38,246 (63.9%)	28,263 (73.9%)	22,173 (78.5%)	0.001
Mean age (SD)	64.16 (11.7)	63.59 (11.4)	64.03 (11.1)	0.001
% Female	24.7%	24%	23.4%	0.001
% Ethnicity (White)	85%	84.5%	85.3%	0.001
% Marital Status (single)	23.3%	8.9%	8.2%	0.001
% IMD* score (5)[22]	25.4%	27%	28.9%	0.001
% Comorbidities (+3)	30.1%	44.1%	29.0%	0.001
% Elective PCI procedure	35 %	34.2%	34.3%	0.001

[22] Ratio of least deprived patients in the cohort

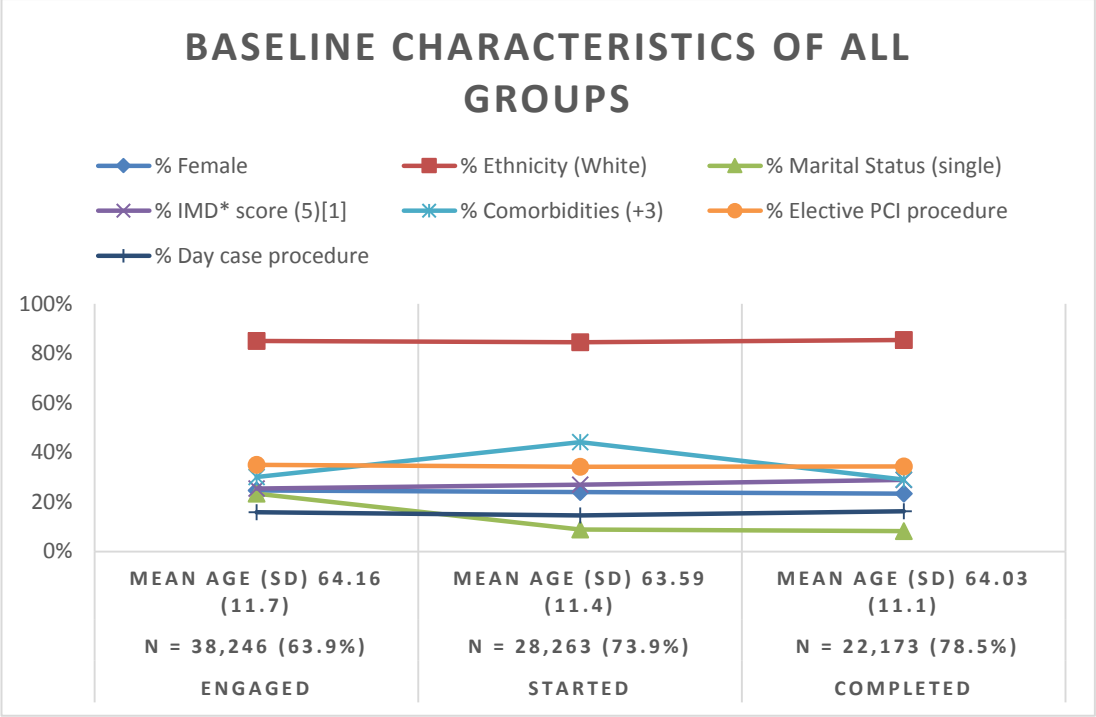


Figure 7.2 Trend changes in baseline characteristics among groups.

7.3.3 Determinants synthesis

The three themed studies in this thesis investigated CR engagement, uptake and completion by testing a predefined set of determinants as shown in (Table 7.1). In this section, all investigated determinants will be displayed in one table to map the role of each determinant in every interaction stage of outpatient CR. In (Table 7.3) there are four columns where the first one displays the name of the determinant and the remaining three columns represent each interaction stage of outpatient CR. Every cell in this table has two types of data; (1) a ratio to show the effect size of that determinant on each stage (2) a small coloured arrow. The arrow reflects the role of that determinant in outpatient CR where red colour means it is a barrier, green colour indicates it is a facilitator and yellow colour indicates that this determinant is not statistically significant at this stage.

Table 7.3 Pooled investigated determinants as reported in all three studies.

Variable	Engagement	Uptake	Adherence
Older age (years)	1.2% ↓	1.2% ↓	1.1% ↑
Female gender	7% ↓	58% ↑	⟺
Age by gender interaction	⟺	1% ↓	⟺
Ethnicity (White)			
Black	⟺	⟺	⟺
South Asian	13% ↓	15% ↓	⟺
Other	24% ↓	⟺	20% ↓
IMD (1 most deprived)			
IMD 2	⟺	31% ↑	32% ↑
IMD 3	19% ↑	44% ↑	41% ↑
IMD 4	24% ↑	50% ↑	53% ↑
IMD 5	46% ↑	84% ↑	92% ↑
Marital (single)			
Partnered	22% ↑	15% ↑	⟺
Previous partnership	25% ↑	⟺	⟺
Social support (yes)	-	⟺	15% ↑
Employment (employed)			
Unemployed	-	⟺	18% ↓
Retired	-	13% ↑	⟺
BMI > 30	-	⟺	16% ↓
Physical inactivity (150 min/week) (yes)	-	16% ↑	21% ↑
Physical fitness (self-reported) (yes)	-	⟺	11% ↑
Current smoker	-	40% ↓	50% ↓
Increased alcohol intake	-	⟺	⟺
Angina (yes)	23% ↑	23% ↓	⟺
Diabetes (yes)	22% ↓	24% ↓	11% ↓
Hypertension (yes)	⟺	15% ↑	⟺
Anxiety (yes)	44% ↑	24% ↑	⟺
Depression (yes)	56% ↑	⟺	29% ↓
Family History (yes)	9% ↑	22% ↑	⟺
Hyperlipidaemia (yes)	21% ↓	10% ↑	⟺
Comorbidities number			
Comorbidities ≤ 2	59% ↑		

Variable	Engagement	Uptake	Adherence
Comorbidities > 3	80% ↑	15% ↓	⟺
Previous cardiac Event (yes)	25% ↓	23% ↓	⟺
PCI Type (Primary)			
MI PCI	11% ↑	10% ↓	⟺
Elective PCI	21% ↑	22% ↓	⟺
CR dose (sessions/weeks)	-	-	55% ↑
Group CR delivery (alone)	-	-	⟺
Supervised CR delivery (unsupervised)	-	-	⟺
Waiting Times between stages	-	26% ↑	⟺
BACPR Certified Centre (yes)	-	-	⟺
Multidisciplinary team centre (yes)	-	-	⟺
Received confirmed joining date (yes)	444% ↑	214% ↑	-
Patient received early CR (yes)	47% ↓	19% ↓	-
Day Case	26% ↓	21% ↑	-
Venue of source of referral (NHS Trust)			
General Practice	930% ↑	71% ↓	-
BMI/Private Hospital	19% ↓	⟺	-
Patient refereed by (consultant)			
Cardiac nurse	10% ↓	30% ↑	-
GP	⟺	230% ↑	-
Primary care nurse	⟺	509% ↑	-
Other	⟺	29% ↑	-
Key: (↓= barrier, ↑= facilitator, ⟺ = no effect)			

7.3.4 Pooled determinants merged with evidence

What follows is an attempt to compare findings derived from clinical data with more conventional evidence. This will be achieved by merging (Table 7.3) with (Table 2.7). This approach will allow the reader to quickly identify agreements and disagreements between the literature and routine clinical data. A note of caution is due here since the table does not display the quality nor the strength of the systematic review evidence. For the systematic review rows, each cell denotes two types of data; (1) a figure to show the total number of studies investigated that determinant (2) a small coloured doughnut chart. The chart reflects

the proportion of studies that reported the determinant as a barrier (red colour), facilitator (green colour) or not statistically significant (yellow colour). The same colour coding and legends described previously are adopted in (Table 7.4). Only variables reported in both sources are displayed.

Table 7.4 Investigated determinants merged with systematic review evidence.

Variable	Source	Engagement	Uptake	Adherence
Older age	Audit	1.2% ↓	1.2% ↓	1.1% ↑
	SR	3	29	7
Female gender	Audit	7% ↓	58% ↑	↔
	SR	1	14	5
Ethnic minority	Audit	19% ↓	15% ↓	20% ↓
	SR	1	8	3
Least deprived	Audit	46% ↑	84% ↑	92% ↑
	SR	-	5	1
Partnered	Audit	22% ↑	15% ↑	↔
	SR	3	13	1
Social support (y/n)	Audit	-	↔	15% ↑
	SR	-	10	-
Employed	Audit	-	13% ↑	18% ↓
	SR	1	11	3
BMI > 30	Audit	-	↔	16% ↓
	SR	1	12	1
Physical inactivity (yes)	Audit	-	16% ↑	21% ↑

[23] Audit = NACR data / SR = systematic review data

	SR	2	4	1
Smoking (yes)	Audit	-	40% ↓	50% ↓
	SR	3	9	6
Variable	**Source**	**Engagement**	**Uptake**	**Adherence**
Angina (yes)	Audit	23% ↑	23% ↓	↔
	SR	-	4	-
Diabetes (yes)	Audit	22% ↓	24% ↓	11% ↓
	SR	2	13	6
Hypertension (yes)	Audit	↔	15% ↑	↔
	SR	-	8	3
Anxiety (yes)	Audit	44% ↑	24% ↑	↔
	SR	-	4	2
Depression (yes)	Audit	56% ↑	↔	29% ↓
	SR	1	2	2
Family history of cardiac disease (yes)	Audit	9% ↑	22% ↑	↔
	SR	1	-	3
Hyperlipidaemia (yes)	Audit	21% ↓	10% ↑	↔
	SR	1	9	3
Increased number of comorbidities	Audit	80% ↑	15% ↓	↔
	SR	1	3	1
Previous cardiac Event (yes)	Audit	25% ↓	23% ↓	↔
	SR	-	13	1
Elective PCI (yes)	Audit	21% ↑	22% ↓	↔

	SR	-	1	-
Multidisciplinary team centre (yes)	Audit	-	-	↔
	SR	-	-	1
Variable	**Source**	**Engagement**	**Uptake**	**Adherence**
Received confirmed joining date (yes)	Audit	444% ↑	214% ↑	-
	SR	-	2	-
Patient received early CR (yes)	Audit	47% ↓	19% ↓	-
	SR	-	1	-
Day case PCI (yes)	Audit	26% ↓	21% ↑	-
	SR	-	3	-
BMI/Private Hospital	Audit	19% ↓	↔	-
	SR	-	1	-
Key: ↓ = barrier, ↑ = facilitator, ↔ = no effect, Systematic review (SR) findings: = proportion of studies in each category				

7.4 Discussion

This is the first study to investigate the three key interaction stages (engagement, uptake and completion) in outpatient CR for the PCI population. It is also the first study to synthesise evidence from routine clinical data to what is known in the literature.

7.4.1 Patient Flow

This study utilised a patient flow perspective summarised in Figure 7.1 which clearly indicates that the majority of patients decided not initiate CR in an earlier stage (engagement). Our analysis, of the earlier parts of the patient journey, differs substantially from previous studies, which have largely investigated in CR uptake (Karmali et al., 2014; Ruano-Ravina et al., 2016). This finding reflects the importance of the CR engagement study conducted in this thesis as being the first from a nationally representative cohort of

PCI patients providing new insights into the factors that lead patients to attend their CR initial baseline assessment.

7.4.2 Baseline characteristics

The second result presented in this study is changes in baseline characteristics among key stages in outpatient CR (Table 7.2) and (Figure 7.2). With regards to ratios of those who interact with each stage we can see an upward trend as the ratio of engagers (63.9%) is lower than starters (73.9%) and completers (78.5%). A possible explanation for this phenomena is that those who overcome the barriers in engagement are more likely to continue until the end of the outpatient programme especially as some of those barriers are common among all stages. With regards to age, we see that the mean age of starters is significantly less than the mean age of engagers and completers ($p < 0.001$) while there is no significant statistical difference between engagers and completers ($p = 0.179$). A downward trend in the ratio of females progressing through the three stages can be easily spotted (24.7% to 24% to 23.4%) ($p < 0.001$).

As far as ethnicity is concerned, Whites are less likely to start CR compared with those engaging or completing CR. Although this difference is statistically significant ($p < 0.001$), it might be related to the large sample size (large degrees of freedom). The ratio of single patients engaging in CR (23.3%) is relatively higher than singles starting or completing the programme (8.9% and 8.2%) respectively. This may be because couples facilitate attendance by providing social support, transportation to CR centres or communication with health professionals (Clark et al., 2012; Al Quait et al., 2017).

In general, CR utilisation seems to be significantly correlated with the index of social deprivation. An upward trend can be drawn as the proportion of least deprived patients steadily increases with each stage of outpatient CR (25.4%, 27% and 28.9%) respectively. The proportion of patients with 3 or more comorbidities is higher in the starting group (44.1%) compared with those engaged (30.1%) and those completing the programme (29%) ($p < 0.001$). The final reported factor in this analysis is the proportion of elective PCI procedures. The analysis shows that the proportion of patients entering each three elements of the patient journey were very similar at 35%, 34.2% and 34.3% for engagement uptake and completing CR respectively. Although this factor is statistically significant in favour of

more elective PCI patients engaging in CR, than the other stages, this level of difference (<1%) is not of clinical importance due to the small generated effect size.

7.4.3 Determinants synthesis

This topic is best discussed in groups according to the classification reported in Table 7.1 - Socio-demographic, cardiac risk factors, Life style & Health status and Service level factors. In addition, it is appropriate, for the sake of clarity, that (Table 7.3) and (Table 7.4) are discussed together in this section.

7.4.3.1 Socio-demographic factors

The study findings shows that older age is associated with decreased CR engagement and uptake. However, this is not the case in CR adherence as older patients are more likely to complete the programme than younger patients. Although our results are in line with the investigated studies in the systematic review this is the first time this has been established in the PCI population using routine clinical data.

The role of participants' gender on the three stages of CR utilisation was found to be inconsistent. With respect to engagement, women are 7% less likely to engage in CR than men. This finding is supported by the only study reporting on this factor which was also a secondary retrospective analysis study (Smith, Harkness and Arthur, 2006). As far as uptake is concerned, the data shows an unexpected finding by stating that women are 57% more likely to start CR than men which is contrary to most of the previous studies in the literature investigating determinants of uptake. This rather contradictory finding may be explained by the fact that this is the first study to test for the impact of age-gender interaction on uptake in the PCI population. With regards to CR adherence, the analysis revealed that gender is not a significant determinant. This finding is in contrast to four studies in the systematic review and in line with one retrospective secondary analysis study (Casey et al., 2008). The discrepancies between routine clinical data and systematic review data with regards to gender might be attributed to the smaller number of females in studies used in systematic reviews of CR. This is because data provides a large enough sample of patients (including minorities) to be investigated and followed for longer periods which is a major limitation in most of the literature.

Patients from ethnic minorities are less likely to utilise CR as per the data. This finding is partially supported by the systematic review results (Banerjee, Gupta and Singh, 2007; Parashar et al., 2012; Reges et al., 2013a; Turk-Adawi et al., 2013). The same can also be said about social deprivation where the least deprived patients are more likely to utilise CR in both data sources. Being in relationship also promotes CR engagement and uptake as reported from the data. However this determinant was found to be not significant with regards to CR adherence. Social support can enhance CR adherence but not CR uptake as found in the audit data while being employed in full or part time will enhance uptake but decrease adherence rates by 18%. Nevertheless, most studies in the systematic review report social support and employment as not significant determinants (Missik, 1999; Parashar et al., 2012).

7.4.3.2 Cardiac risk factors

The analysis found that obesity (measured by BMI > 30) is a barrier against CR adherence. However this association is not significant in CR uptake. With regards to engagement, this measure is not reported in the audit data at this early stage as patients have not carried out an assessment. The only study investigating this at this stage was in a systematic review and it found risk factors not to be significant determinants of engagement. Subjects reporting they are physically active are more likely to uptake and complete CR as per the audit data. This finding is supported by three studies in the systematic review. Again this determinant is not reported in the clinical data with regards to engagement and the only study investigating it in a systematic review was not significant.

The data further supports the idea that current CR programmes are not attractive to smokers and diabetic patients, or that the health service fails to capture these patient groups sufficiently. Hypertensive patients were more likely to uptake CR by 15% although this association was found not significant in the other two stages. This finding is not supported by the systematic review data as four studies found hypertension a barrier against CR uptake and another four found it not significant. Hyperlipidaemia was a barrier against CR engagement (21%) a facilitator in CR uptake (10%) and not significant in CR adherence.

Subjects with a family history of cardiac disease were slightly more likely to engage in CR by 9% and more likely to uptake CR by 22%. This association was not significant in CR

adherence which are in agreement with three studies from the systematic review. Anxious patients engage and take up CR more than non-anxious patients as revealed by the data analysis. With regards to CR adherence, this association was not significant despite anxiety being reported as a barrier against CR adherence in two studies in the systematic review. The association between depression and CR utilisation stages was not consistent as depressed patients are more likely to engage (56%), less likely to complete (29%) and not significantly associated with uptake. The latter result contradicts with the two studies from the systematic review which classified depression as a barrier against CR uptake.

7.4.3.3 Life style & Health status factors

Patients suffering from angina pectoris are 23% more likely to engage in CR but also 23% less likely to start it as the data display. With respect to adherence, the association was found to be not significant. However, the feeling of cardiac symptoms like angina or chest pain was not associated with CR uptake as reported in three studies included in the systematic review. While one Danish retrospective study (N = 206) found that chest pain is a positive predictor of CR uptake. Patients with an experience of a previous cardiac event were less likely to utilise CR in engagement and uptake but not adherence. This finding is partially consistent with other research investigating CR uptake.

Another important indicator of patient's wellbeing is the increased number of comorbidities (≥ 3). This determinant was not found to be in itself a barrier to CR engagement. This finding is supported by the only study (N = 1268) reporting on this determinant in the systematic review which found it also not significant. With regards to uptake, increased number of comorbidities was reported as a barrier in the clinical practice data. This is in line with an Australian retrospective analysis study which found that patients with two or more comorbidities are less likely to start CR. Nevertheless, there was no significant association between CR adherence and increased number of comorbidities in clinical and systematic review data.

7.4.3.4 Service level factors

Patients who underwent an elective PCI procedure were more likely to engage in CR by 21% and less likely to take up CR by 22%. Only one large secondary retrospective analysis

study (N = 35,752) reported on this determinant and supported the clinical data results with regard to CR uptake. Surprisingly, patients who took part in early phase 1 CR sessions (either inpatient or home-based programmes) were less likely to engage in CR (47%) and also less likely to start it (19%). The systematic review data on this determinant comes only from one small (N = 179) primary prospective study which concluded that early CR is a barrier against CR uptake. In the same context, patients who underwent a day case procedure were 26% less likely to engage in CR but 21% more likely to uptake it. Three studies from the systematic review found this association not significant in CR uptake while only one American secondary retrospective analysis study was in agreement with the audit finding.

One of the most telling findings to emerge from (Table 7.4) is that patients who were given a firm date to engage or start CR were much more likely to utilise CR (444% and 214%) respectively. Only two studies from the systematic review investigated the impact of this determinant on CR uptake. A UK secondary retrospective study (N = 508) concluded that patients not receiving a confirmed joining CR appointment were found to be less likely to start CR than those who were given an appointment (OR: 0.31) (Melville et al., 1999). Also an Israeli primary prospective study (N = 420) reported that patients who received a letter to start CR were more likely to join than those who didn't (OR: 2.79) (Reges et al., 2013b).

Type of hospital where the patient was referred from has been labelled as a significant determinant in CR engagement. Clinical audit data results show that patients who were referred from a private/BMI hospital are 19% less likely to engage in CR compared to patients referred from a NHS trust. However, this determinant was found not significant in CR uptake although an Australian retrospective secondary analysis reported that patients admitted to private hospitals are 32% more likely to start CR than those admitted to teaching hospitals (Sundararajan et al., 2004). The routine clinical audit data has been unable to demonstrate that delivering CR by a multidisciplinary team can improve CR adherence. This finding is contrary to an American secondary retrospective analysis (N =4,412) which concluded programmes delivering CR by a multidisciplinary team have higher rates of adherence (Turk-Adawi et al., 2013). It is difficult to explain this discrepancy in findings between the two studies especially both has similar study design (secondary retrospective analysis) and statistical techniques (clustered regression). However, the American study used forward stepwise regression while the thesis study used backward stepwise regression.

Forward stepwise regression is normally used when multicollinearity is a problem which was not the case in the thesis study (Jennvich, 1977). Another possible explanation for this inconsistency in findings is the way CR adherence is defined between the two studies. While the outcome variable in the American study is defined as attending at least 21 exercise sessions, a patient is considered a completer in the NACR data if he or she satisfies two conditions: first, performed a CR assessment at the end of the outpatient programme. Second, marked as a completer by a CR programme staff member. Noting that the median national number of CR sessions attended in 2016 in the UK was 18 sessions (NACR, 2016).

7.5 Limitations

Due to the fact that CR and the way it is developed vary a lot between countries and between centres, there are some discrepancies between factors reported in the audit data and what is concluded from the systematic review. Also there is a considerable heterogeneity between similar factors reported in both data sources. It could be argued that the external validity of studies based on national audits might be limited to that country.

7.6 Conclusion from the synthesis study

This is the first synthesis study to investigate CR utilisation at the three key interaction stages in outpatient CR from a nationally representative cohort of PCI patients. This synthesis has also the added benefit of comparing this synthesised evidence to a systematic review results. The findings from this study make several contributions to the current literature. First, this chapter has demonstrated that decisions about determinants of CR utilisation should take account of all relevant study designs (e.g. trial and retrospective observational studies) that capture the complexity of the cardiology patient journey. Another telling finding to emerge from this study is that CR engagement is the stage where most patients fail to achieve. Also this study reveals that current CR programmes are not attractive to those from most deprived areas, diabetics and smokers. The research has also shown that CR utilisation is not a single patient decision but is also related to service level factors, over which healthcare systems have more direct control.

8 Conclusion of the thesis

8.1 Summary

Despite its well established evidence, CR remains underutilised in many healthcare systems. Also previous research has shown major inequities in CR access for certain patient groups such as the elderly and socially deprived patients. Furthermore, it has previously been observed that CR utilisation rates are lower than expected in patients undergoing PCI procedures in most European countries. These findings question the extent of implementation of national, European and world guidelines which suggest that CR should be equally accessible and relevant to all patient groups after an MI event (Graham et al., 2007; Balady et al., 2011; NICE, 2015).

There were two primary aims of this PhD thesis: first, to systematically review the available literature around the determinants of optimal CR utilisation in the eligible PCI population. Second, this thesis aimed to assess the extent to which those determinants identified in the literature are applicable to the CR population in England by conducting a retrospective secondary analysis of the NACR dataset. In general, the objective of this thesis was to contribute to the growing area of CR research by exploring those determinants in the PCI population and validating them against routinely collected clinical data.

8.2 Key findings

This is the first detailed research to investigate CR utilisation at the three key interaction stages in outpatient CR from a nationally representative cohort of PCI patients. The findings from this research make several contributions to the current literature. These findings also enhance our understanding of the determinants of CR utilisation and suggests that some of the theoretical expectations about CR uptake are not substantiated by analyses of large, routine clinical datasets. The main findings of this thesis can be listed as follows:

- A systematic review of the literature around CR utilisation revealed few studies investigating CR engagement although the majority of patients decide not to initiate CR

at this early stage. Most of the current research has been directed to investigate CR uptake and adherence which have relatively higher utilisation rates than CR engagement.

- The analysis of CR engagement undertaken in this thesis has extended our understanding of the determinants of low CR utilisation rates in England. Although age and gender are significant determinants of CR engagement, which is also true for CR uptake, service level factors play a major role in CR engagement.
- With regards to CR uptake, there was significant interaction revealing that younger women (≤ 57 years) are more likely to start CR compared to younger men while older women were found to be less likely to join compared to younger/middle age women or older men (> 57 years).
- In terms of CR adherence, the results suggest that there was no significant differences in adherence rates between home-based and group-based programmes either on patients' level or centre level.
- Taken together, the findings propose that current CR programmes in England are not attractive to those who are socially deprived, diabetic and smokers.

8.3 Limitations

Despite the implementation of robust statistical techniques and conducting the analysis in large high quality database that contains all of the characteristics and variables, observational studies remain susceptible to selection bias. Selection bias, as explained in chapter 3, can lead to large unobserved differences between treatment and control groups which may result in false estimates of treatment effects (confounding) and therefore manipulate the outcomes being measured. In addition, the analysed dataset was designed to monitor how CR is delivered in the UK but not CR utilisation. Therefore, some other relevant determinants influencing CR utilisation that were reported in previous studies and not collected in the primary dataset have been missed. It is unfortunate that the analyses did not include determinants like patient's education level, transportation time and English language proficiency.

One of the greatest challenges when using large datasets is how to deal with missing data and outliers in an appropriate way as the researcher has no means to access the original

dataset. Due to the nature of how NACR collects its data, there is a considerable number of missingness in the data. Although multiple imputation as a validated robust method of handling missingness in the data was adopted, it remains a computational approximation processes of replacing the missing value with a range of values that the true value could have taken. As a result, it is important to bear in mind the possible increased uncertainty and errors in any conclusions drawn. In addition, NACR data collection involves human operators keying in data which may occasionally introduce entry errors that can impact the quality of data and may affect the outcome result. However, the automated data auditing and cleaning techniques implemented in the NACR portal plus the manual data cleaning conducted by the researcher should help overcome this issue.

Another source of weakness in this thesis which could have affected the analyses was that the population investigated was a mix bag of all PCI types in which some intrinsic patient related clinical factors are different. However, PCI type was used as a predictor in the related analyses to minimise the effect of this issue.

8.4 Implications

The findings of this thesis have significant implications for the understanding of how to improve CR utilisation in the growing PCI cohort. The most obvious finding to emerge from this research:

- More emphasis should be placed on strategies to improve early CR engagement. Such strategies have the potential to benefit many more patients as they progress to their cardiology/rehab journey.
- CR utilisation is not a single patient decision but is also related to service level factors, over which healthcare systems have more direct control. Taken together, some of the determinants like age and gender are not modifiable and the only way to counter their influence is to understand how CR is offered and seek solutions around how to optimise throughput so that services tackle such inequalities. For example, future strategies to increase CR uptake in the PCI cohort should not consider age and gender as entirely independently determinants but should also consider age in the context of gender.

Approaches to increase CR uptake may therefore be differentiated by age and gender profile of the target population.

- Current CR programmes in England are not taking up by those who are socially deprived, diabetic, smokers and had previous cardiac event. These findings support the idea that CR programmes in England should be tailored to suite different patient groups and that one size CR programme doesn't fit all patients. In addition, CR commissioners should deploy tailored support to enable different patient groups to progress from the baseline assessment to completing the programme. Particularly, the results from this research suggest that there were no significant differences in adherence rates between home-based and group-based programmes either on patients' level or centre level.

8.5 Recommendations

The findings of this thesis suggest several courses of action for local CR programmes and CR stakeholders these include:

- First, early engagement with CR is a priority as it enables each local CR programme to maximise patient's throughput. This research has identified barriers and facilitators that programmes can learn from to aid engagement, uptake and adherence.
- Second, it was evident from this research that service level factors play a major role in CR utilisation. There is, therefore, a definite need for people who assure and regulate CR in the UK to intervene (Figure 1.3). NACR and BACPR have been working together to develop a certification system that ensures that CR programmes in the UK are meeting a pre-specified minimum standards. These minimum standards are designed to enable the assessment of any variation in the quality of service delivered to patients. Using the national audit data and the research generated through it, like the thesis, can inform how programmes meet the minimum standards in an objective and fair way. Based on this thesis new minimum standards such as the confirmed join date could be added to the national certification criteria.
- Third, continued efforts are needed to maintain and improve the quality of the NACR data. With the current ratio of missingness in the NACR dataset the quality and validity of research generated through it is compromised. Although some statistical techniques,

such as multiple imputation, have the potential to strengthen the validity of research outcomes, it comes with the expense of time and scarifying hybrid sophisticated statistical techniques like bootstrapping and multilevel modelling. Another aspect of improving the quality of the NACR data is through limiting data entry errors. Although NACR has tightened up on data quality procedures to align with NICE guidance and the emerging NHS commissioning and accountability frameworks, more work can be done by adding validations to the entry fields in the NACR portal system to prevent users from keying in extreme values accidentally.

8.6 Future research

This research has thrown up many questions in need of further investigation of CR utilisation determinants. These investigations might be conducted using different research methods and may include the following:

- There is a tendency in the CR literature to include mixed population when investigating CR utilisation. This is of a concern particularly with the presence of some intrinsic patient related clinical factors in each population. For example, the PCI cohort are different in terms of age, number of comorbidities and hospital length of stay than other patient groups such as CABG and heart failure. Future research should therefore concentrate on stratifying each group separately when conducting the analysis.
- The analysis of CR engagement undertaken in this thesis has revealed that service level factors play a major role at this critical stage of CR utilisation. This would be a fruitful area for further which will enhance our understanding of low CR utilisation rates.
- In the CR engagement study, the analysis revealed that patients who were given a firm date to attend the initial CR assessment were over 4 times more likely to engage in CR. A sub-analysis of patient groups who are most likely to benefit from this technique can be conducted.
- In the uptake study, it was found out that younger men and older women are less likely to start CR. Further qualitative research might explore why younger men and older women are less likely to uptake CR.

- With regards to CR adherence, the thesis analysis confirmed previously reported findings in the literature that there is no significant differences in adherence rates between home-based and group-based programmes either on patients' level or centre level. Further studies need to be done to investigate home-based CR in terms of availability, outcomes and possible methods of delivery such as web-based applications, home visits or telephone calls.
- This research has established a framework that can be utilised to develop an intervention with respect to identified barriers to promote CR utilisation in the PCI population.

Appendices

Appendix A.1 The five main search terms used to identify relevant literature.

1	CR Indication terms
Arteriosclerosis/ or Myocardial Infarction/ or Coronary Thrombosis/ or Acute Coronary Syndrome/ or Angina, Unstable/ or Angina Pectoris/ or Coronary Disease/ or Coronary Artery Disease/ or Coronary Artery Bypass/ or Arterial Occlusive Diseases/ or Angioplasty, Balloon/ or Angioplasty, Balloon, Coronary/ or Stents/ or Angioplasty/ or Postoperative Complications/ or Angioplasty, Balloon, Coronary/ or Coronary Angiography/ or Acute Coronary Syndrome/ or Percutaneous Coronary Intervention/ or Myocardial Reperfusion Injury/ or Coronary Disease/ or Myocardial Infarction/ or Coronary Circulation/ or Coronary Disease/ or Coronary Artery Bypass/rh [Rehabilitation]/ or Coronary Artery Disease/ or Coronary Disease/ or Myocardial Infarction/ or Coronary Angiography/ or Acute Coronary Syndrome/	
2	CR terms
Rehabilitation Research/ or Rehabilitation/ or Cardiac Rehabilitation/ or Psychiatric Rehabilitation/ or Rehabilitation Nursing/ or "Physical and Rehabilitation Medicine"/ or Rehabilitation Centers/	
3	Utilisation terms
(compliance or complie$ or comply$).ti,ab./ Or (take up or promot$ or utilisation or utilisation).ti,ab./ or (uptake or attend$ or accept or particip$).ti,ab./ or exp Patient Compliance/ or (non?compli$ or non?attend$).ti,ab./ or (nonparticipat$ or non-participat$).ti,ab./ or (nonattend$ or non-attend$).ti,ab./ or (non-utiliz$ or non-utilis$).ti,ab./ or (adher$ or non-adhere$).ti,ab./ or (compl$ or non-compl$).ti,ab.	
4	Determinants terms
exp Ethnic Groups/ or exp Refugees/ or exp Cultural characteristics/ or ((underserve$ or disadvantage$) adj6 (group$ or population$)).tw./ or ethnic$.tw./ or	

(migrant$ or immigrant$).tw./ or ((hard to reach or depriv$ or disadvantage$ or Under?represented or under-represented or under?served or underserved or low income or poor or low$ socio?economic? or low socio economic or low$ socio demographic$ or low socio?demographic or inequal$ or inequit$) adj3 (status or group? or population? or position or disparity or area or region or place?)).ti,ab./ or ((Gender adj difference) or (female adj patient?) or wom?n).ti,ab./ or ((Old or elder$ or homeless or traveler) adj patient?).tw./ or exp Aged/ or Sex factors/ or Age factors/ or Poverty/ or Minority Groups/ or Income/ or Social Class/ or (cormorbid$ or co-morbid$).ti,ab./ or exp Homeless Persons/	
5	Study design terms
randomized controlled trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]/ or controlled clinical trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]/ or randomized.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]/ or Cohort Studies/ or Follow-Up Studies/ or Longitudinal Studies/or Prospective Studies/ or Cohort Studies/ or Retrospective Studies/	

Appendix A.2 Medline (incl. PubMed): Search interface: PubMed – Date of search: Aug 16 2017.

#	Searches
1	Arteriosclerosis/ or Myocardial Infarction/ or Coronary Thrombosis/ or Acute Coronary Syndrome/ or Angina, Unstable/ or Angina Pectoris/ or Coronary Disease/ or Coronary Artery Disease/
2	Coronary Artery Bypass/
3	Arterial Occlusive Diseases/ or Angioplasty, Balloon/ or Angioplasty, Balloon, Coronary/ or Stents/ or Angioplasty/
4	Postoperative Complications/ or Angioplasty, Balloon, Coronary/ or Coronary Angiography/ or Acute Coronary Syndrome/ or Percutaneous Coronary Intervention/
5	Myocardial Reperfusion Injury/ or Coronary Disease/ or Myocardial Infarction/
6	Coronary Circulation/ or Coronary Disease/
7	Coronary Artery Bypass/rh [Rehabilitation]
8	Coronary Artery Disease/ or Coronary Disease/ or Myocardial Infarction/ or Coronary Angiography/ or Acute Coronary Syndrome/
9	Rehabilitation Research/ or Rehabilitation/ or Cardiac Rehabilitation/ or Psychiatric Rehabilitation/ or Rehabilitation Nursing/ or "Physical and Rehabilitation Medicine"/ or Rehabilitation Centers/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
11	randomized controlled trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	controlled clinical trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary

	concept word, rare disease supplementary concept word, unique identifier, synonyms]
13	randomized.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14	Cohort Studies/
15	Follow-Up Studies/
16	Longitudinal Studies/
17	Prospective Studies/
18	Cohort Studies/
19	Retrospective Studies/
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Ethnic Groups/
22	exp Refugees/
23	exp Cultural characteristics/
24	((underserve$ or disadvantage$) adj6 (group$ or population$)).tw.
25	ethnic$.tw.
26	(migrant$ or immigrant$).tw.
27	refugees.tw.
28	((hard to reach or depriv$ or disadvantage$ or Under?represented or under-represented or under?served or underserved or low income or poor or low$ socio?economic? or low socio economic or low$ socio demographic$ or low socio?demographic or inequal$ or inequit$) adj3 (status or group? or population? or position or disparity or area or region or place?)).ti,ab.
29	((Gender adj difference) or (female adj patient?) or wom?n).ti,ab.
30	((Old or elder$ or homeless or traveler) adj patient?).tw.

31	exp Aged/
32	Sex factors/
33	Age factors/
34	Poverty/
35	Minority Groups/
36	Income/
37	Social Class/
38	(cormorbid$ or co-morbid$).ti,ab.
39	exp Homeless Persons/
40	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	(compliance or complie$ or comply$).ti,ab.
42	(take up or promot$ or utilisation or utilisation).ti,ab.
43	(uptake or attend$ or accept or particip$).ti,ab.
44	exp Patient Compliance/
45	(non?compli$ or non?attend$).ti,ab.
46	(nonparticipat$ or non-participat$).ti,ab.
47	(nonattend$ or non-attend$).ti,ab.
48	(non-utiliz$ or non-utilis$).ti,ab.
49	(adher$ or non-adhere$).ti,ab.
50	(compl$ or non-compl$).ti,ab.
51	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	limit 51 to (english language and humans)
53	9 and 10 and 20 and 40 and 51 and 52

Appendix A.3 Extraction sheet for selected studies.

Study 1st author	Country of origin	Study design	Population diagnosis	Population treatment	Measured outcome	Sample size	Sample mean age	Female ratio
Gallagher 2003	Australia	Primary prospective	MI	CABG	uptake	196	67.1	100
Harlan 1995	US	Primary prospective	CAD	CABG	uptake	393	63	19
Shanmugasegaram 2013	Canada	Primary prospective	ACS	Mixed	uptake	1809	65.2	27
Brual 2010	Canada	Primary prospective	CAD	Mixed	uptake	1268	66.3	28.2

Mochari 2006	US	Primary prospective	CHD	Mixed	uptake	304	62.3	100
Dunlay2009	US	Primary prospective	MI	Mixed	uptake	179	64.8	34.1
Yohannes 2007	UK	Primary prospective	MI	Mixed	adherence	189	60	31.7
King 2001	Canada	Primary prospective	MI	mixed	uptake	304	N/A	24
Sanderson 2010	US	Primary prospective	mixed	Mixed	uptake	131	61	100
Reges 2013	Israel	Primary prospective	ACS	N/A	uptake	420	59.6	15.5

Molloy 2008	UK	Primary prospective	ACS	N/A	uptake	193	60.6	23
Missik 1999	US	Primary prospective	CHD	N/A	uptake	370	66.2	100
French 2005	UK	Primary prospective	MI	N/A	uptake	194	63.3	26.8
Cupples 2010	Northern Ireland	Primary prospective	MI	N/A	uptake	432	N/A	N/A
SooHoo 2016	Australia	Primary prospective	ACS	PCI	uptake	246	63.6	21
Gracea 2008	Canada	Primary prospective	CAD	Mixed	Engagement	1268	66	28

Hoffmanna 2013	Switzerland	Primary prospective	CAD	PCI/CABG	uptake	309	69.2	33.7
Lane 2001	UK	Primary prospective	MI	PCI/CABG	uptake	263	61.6	24
Grace 2010	Canada	Primary prospective	ACS	Mixed	Engagement	661	61.2	23.8
Allen 2004	US	Primary prospective	MI	PCI/CABG	uptake	253	66	100
Beckie2015	US	Primary prospective	mixed	Mixed	adherence	252	N/A	100
Grace 2011	Canada	Primary prospective	ACS	PCI/CABG	Engagement	2635	65	26.8

Sarrafzadegan 2007	Iran	Primary prospective	MI	PCI/CABG	adherence	1115	55	24
Worcester 2004	Australia	Primary prospective	MI	PCI/CABG	uptake/adherence	652	64.9	30
Harrison 2005	UK	Primary prospective	Mixed	PCI/CABG	uptake/adherence	313	67.3	31.4
Grace 2016	Canada	*	mixed	mixed	adherence	169	63.6	100
Beckie 2010	US	*	Mixed	Mixed	adherence	252	63.6	100
Banerjee 2007	Canada	Secondary retrospective	CAD	CABG	adherence	1200	57.5	78.5

Smith 2006	Canada	Secondary retrospective	CAD	CABG	Engagement/ uptake	3536	64	20.9
Doll 2015	US	Secondary retrospective	MI	Mixed	adherence	11862	73.5	37
Armstrong 2014	Canada	Secondary retrospective	MIxed	Mixed	adherence	8582	59.5	28
Turk-Adawi 2013	US	Secondary retrospective	mixed	MIxed	adherence	4412	65	30.4
Casey 2008	US	Secondary retrospective	mixed	Mixed	adherence	600	66.5	30.4
Suaya 2007	US	Secondary retrospective	MI	CABG	uptake	267427	N/A	44.1

McKee 2014	Ireland	Secondary retrospective	ACS	Mixed	uptake	1172	62.5	24.6
Lemstra 2013	Canada	Secondary retrospective	CHD	PCI/CABG	uptake/adherence	18980	N/A	N/A
Parashar 2012	US	Secondary retrospective	MI	mixed	uptake	2096	60.4	29
Dunlay 2014	US	Secondary retrospective	MI	Mixed	uptake	2991	67.3	40.6
Chamosa 2015	Spain	Secondary retrospective	mixed	Mixed	uptake	756	58.02	16.4
Turk-Adawi 2014	US	Secondary retrospective	mixed	Mixed	uptake	6874	N/A	30.7

Engen-Verheul 2012	Netherlands	Secondary retrospective	mixed	Mixed	uptake	35752	N/A	40.1
Evenson 1998	US	Secondary retrospective	MIxed	Mixed	uptake	3841	N/A	42
Melville 1999	UK	Secondary retrospective	MI	N/A	uptake	508	N/A	N/A
Nielsen K 2008	Denmark	Secondary retrospective	MI	PCI/CABG	uptake	206	59.8	24.5
Beauchamp 2013	Australia	Secondary retrospective	MI	PCI/CABG	uptake	281	62	48
Sundararajan 2004	Australia	Secondary retrospective	MI	PCI/CABG	uptake	12821	N/A	N/A

Appendix B.1 Predictor variables description for CR engagement.

Predictor variable	Description
Age	Patient's age calculated from date of birth to hospital admission in years
Sex	Male, female
Ethnicity	Patient's ethnic group as reported in primary data (White, Black, south Asian and other ethnicity)
Marital status	Patient's marital status during event (single, in partnership or previously partnered)
IMD rank	Index of Multiple Deprivation score grouped into 5 equal-sized groups according to score. Quintile 1 represents most-deprived patients and quintile 5 represents least-deprived patients.
High blood pressure, Diabetes, High blood cholesterol, Anxiety, Depression, Family history	Coded 'yes' if documented during hospital admission otherwise no
Total number of comorbidities	The sum of patient's total comorbidities reported in NACR dataset which includes (Angina, Arthritis, Cancer, Diabetes, Rheumatism, Stroke, Osteoporosis, Hypertension, Chronic bronchitis, Emphysema, Asthma, Claudication, Chronic Back Problems, Anxiety, Depression, Erectile Dysfunction, Dyslipidaemia and Other Comorbid Complaint).

Previous cardiac event	Coded 'yes' if patient has history of previous cardiac event such as MI, cardiac arrest, pacemaker, bypass surgery, congenital heart disease, PCI, heart failure…etc.
Referred to CR by	The healthcare professional who referred the patient to CR (consultant, cardiac nurse, general practitioner, primary care nurse or other).
Venue of source of referral to CR	The healthcare institution where referral was issued (national health service (NHS) trust, general practice (GB) or BMI/Private hospital.
Hospital stay length	A binary categorical variable that is coded into 1 if the PCI procedure was performed as 'day case' and 0 for overnight stay.
Received confirmed joining date	Coded 'yes' if patient's has received a firm start date for the core rehab phase.
PCI type	Type of PCI treatment delivered to patient during the cardiac event (primary, MI or elective).
Patient received early CR	Coded 'yes if the patient received early phase 1 CR

Appendix B.2 Explanation of the independent factors of CR uptake included in the analysis and their subcategories.

Predictor variable	Description
Age	Patient's age calculated from date of birth to hospital admission in two subcategories; young < 65 years and elderly > 65 years
Gender	Binary variable (Male, female)
Ethnicity	Patient's ethnic group (White, Black, south Asian or other)
High blood pressure, Diabetes, High blood cholesterol, Anxiety, Depression, Family history	Binary variable coded 'yes' if documented during baseline assessment otherwise no
Physical activity	Binary variable coded 'yes' if patients take regular physical activity of at least 150 minutes over 7 days
Being overweight	Binary variable coded 'yes' if patients body max index (BMI) > 30

Employment	Patients employment status during event (employed, unemployed or retired)
Marital status	Patient's marital status during event (single, partnered, or previous partnership)
Social support	Binary (yes/no) variable based on patient's own answer to the question 'During the past week was someone available to help you if you needed and wanted help?
Alcohol intake	Binary variable coded '1' if patient's alcohol intake > 21 units/week for men and > 14 units/week for women otherwise '0'
Smoking	Binary variable coded 'yes' if the patient was smoking during the event, no or unknown if otherwise
Physical fitness	Binary variable coded 'yes if the patient answered moderate, heavy or very heavy to the question 'during the past week what was the hardest physical activity you could do for at least 2 minutes?'
Comorbidities	Total number of comorbidities during the event

Referred to CR by	Who referred the patient to CR (hospital setting or primary setting)
Hospital stay length	Binary variable coded ‘1’ if PCI done as a day case procedure and ‘0’ if patient stayed overnight in hospital
Venue of source of referral	Where referral comes from (NHS trust, general practice or private hospital)
Time from event to Assessment	Waiting time from cardiac event to pre-CR assessment in weeks
Received confirmed joining date	Binary variable coded ‘1’ if patient received a confirmed date to start CR from CR centre otherwise ‘0’
PCI type	Type of PCI treatment received (primary PCI, MI PCI or elective PCI)
Previous cardiac event	Binary variable coded ‘yes’ if patient has a history of previous cardiac event such as PCI, MI, Angina… etc.

Received early CR	Binary variable coded ‘yes’ if patient received phase 1 CR during hospitalisation
Index of multiple deprivation (IMD)	IMD score was grouped into 5 equal-sized groups according to score where quintile 1 represents most-deprived patients and quintile 5 represents least-deprived patients.

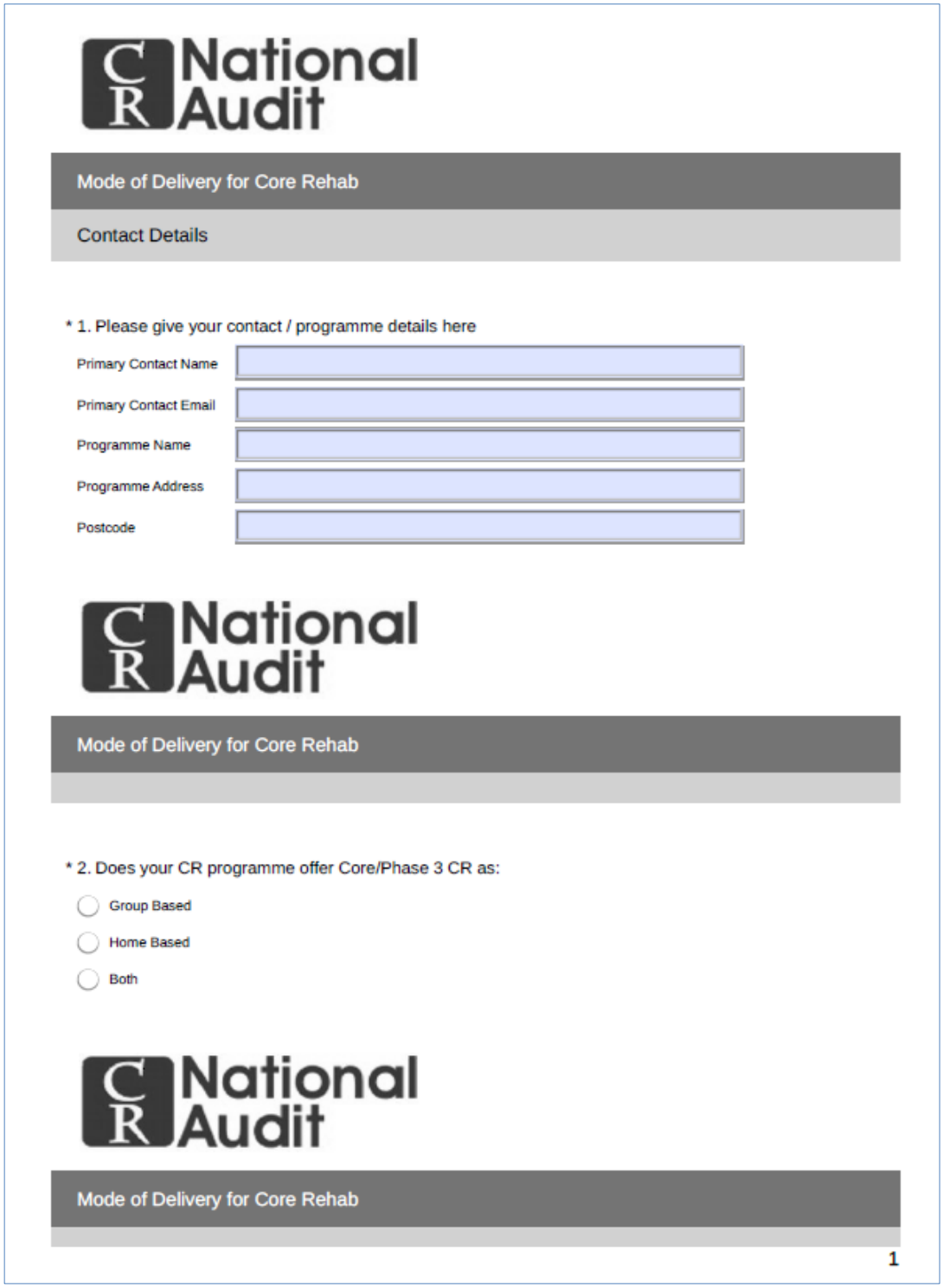
Appendix B.3 Explanation of the independent factors for CR adherence included in the analysis and their subcategories.

Predictor variable	Description
Age	Patient's age calculated from date of birth to hospital admission in two subcategories; young < 65 years and elderly > 65 years
Sex	Binary variable (Male, female)
Ethnicity	Patient's ethnic group (White, Black, south Asian or other)
Index of multiple deprivation (IMD)	IMD score was grouped into 5 equal-sized groups according to score where quintile 1 represents most-deprived patients and quintile 5 represents least-deprived patients.
Marital status	Patient's marital status during event (single, partnered, or previous partnership)
Social support	Binary (yes/no) variable based on patient's own answer to the question 'During the past week was someone available to help you if you needed and wanted help?
Employment	Patients employment status during event (employed either full time or part time, unemployed or retired)
High blood pressure, Diabetes, High blood cholesterol, Anxiety, Depression	Binary variable coded 'yes' if documented during baseline assessment otherwise no

Physical activity	Binary variable coded ‘yes’ if patients take regular physical activity of at least 150 minutes per week
Being overweight	Binary variable coded ‘yes’ if patients body max index (BMI) > 30
Alcohol intake	Binary variable coded ‘1’ if patient’s alcohol intake > 21 units/week for men and > 14 units/week for women otherwise ‘0’
Smoking	Binary variable coded ‘yes’ if the patient was smoking during the event, no or unknown if otherwise
Physical fitness	Binary variable coded ‘yes if the patient answered moderate, heavy or very heavy to the question ‘during the past week what was the hardest physical activity you could do for at least 2 minutes?’
Comorbidities	Total number of comorbidities during the event coded into 3 subcategories (0 comorbidity, ≤ 2 comorbidities and ≥ 3 comorbidities)
Previous cardiac event	Binary variable coded ‘yes’ if patient has a history of previous cardiac event such as PCI, MI, Angina… etc.
Family history	Binary variable coded ‘yes’ if patient has a family history of cardiac disease
Angina	Binary variable coded ‘yes’ if angina pectoris is documented during baseline assessment otherwise no

CR dose	Total number of sessions attended divided by programme duration in weeks (session/week)
Group/alone CR	Binary variable coded ‘1’ if the patient attended CR in a group based settings
Supervised/self-delivered	Binary variable coded ‘1’ if the programme was delivered under the supervision of the CR team either in group based or individually through home visits, telephone calls… etc.
MDT centre	The programme is delivered by a multidisciplinary team
BACPR certified programme	Binary variable coded ‘1’ if the programme is certified by the British Association for Cardiovascular Prevention and Rehabilitation
PCI type	Type of PCI treatment received (primary PCI, MI PCI or elective PCI)
Time from event to starting CR	Waiting time from the index cardiac event to the first session of the outpatient CR programme in days

Appendix C.1 CR mode of delivery survey.



CR National Audit

Mode of Delivery for Core Rehab

Contact Details

* 1. Please give your contact / programme details here

Primary Contact Name

Primary Contact Email

Programme Name

Programme Address

Postcode

CR National Audit

Mode of Delivery for Core Rehab

* 2. Does your CR programme offer Core/Phase 3 CR as:

- Group Based
- Home Based
- Both

CR National Audit

Mode of Delivery for Core Rehab

1

* 3. How is your Home Based Core/Phase 3 Rehab Delivered? (you can select more than one option)

- [ ] Heart Manual (facilitated by trained staff)
- [ ] Angina Plan (facilitated by trained staff)
- [ ] Individualised Patient Programme - Supervised
- [ ] Individualised Patient Programme - Not Supervised
- [ ] Other- please specify below, and say whether it is 'supervised' or 'not supervised'.

Mode of Delivery for Core Rehab

* 4. To the best of your knowledge, the information provided in question 3 and 4 is applicable for:

- ( ) The past 3 years
- ( ) The past 2 years
- ( ) This year only

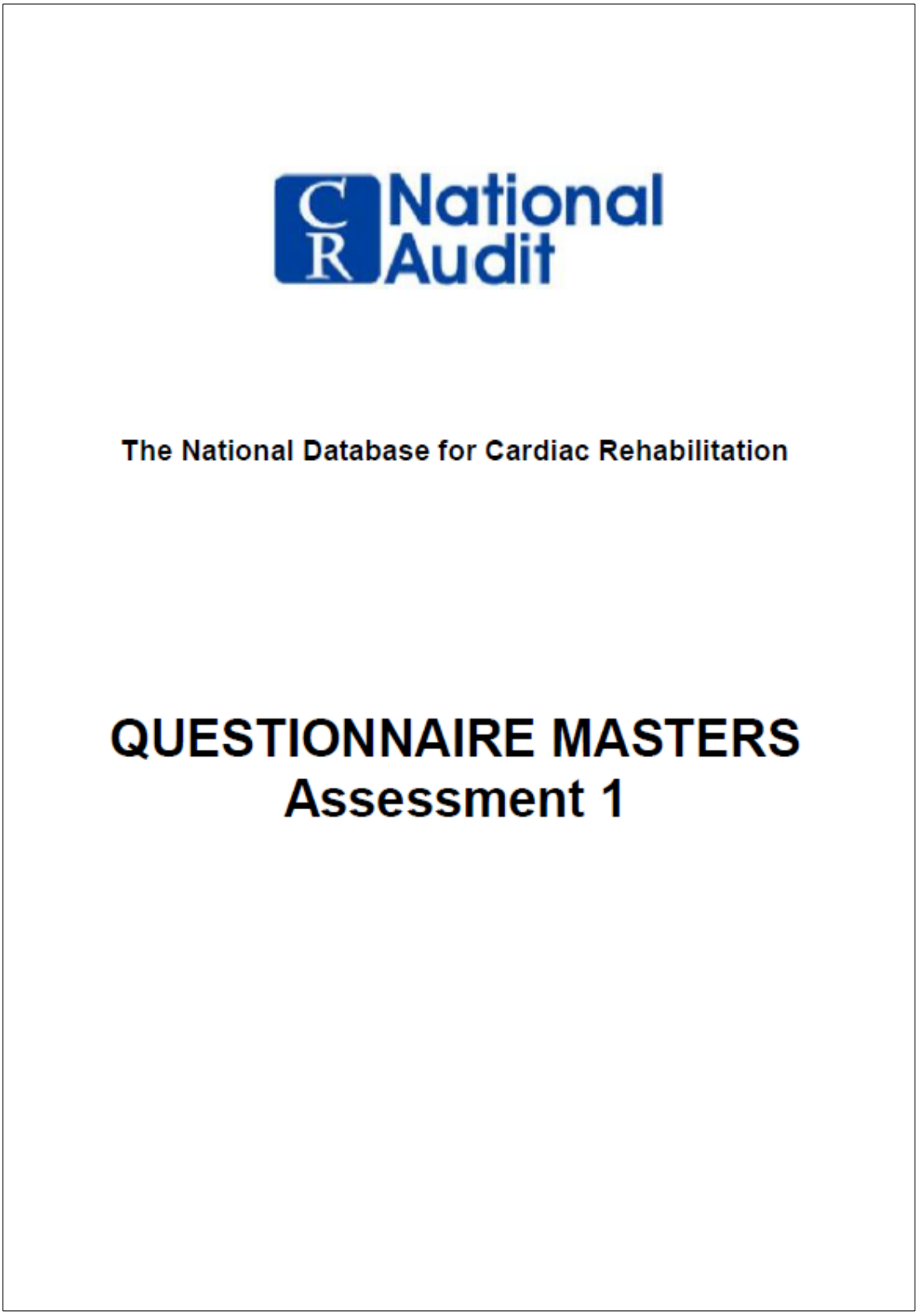
Mode of Delivery for Core Rehab

* 5. If you **DON'T** deliver Core CR as home based, please could you just help us understand why (you can pick more than one option):

- [ ] No Funding
- [ ] Provided elsewhere
- [ ] No appropriate staff
- [ ] No demand
- [ ] Other (please specify)

3

Appendix C.2 NACR self-reporting questionnaire.



CONTENTS

THE QUESTIONNAIRES AND THE NATIONAL AUDIT OF CARDIAC REHABILITATION

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

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

WHAT HAPPENS TO THE INFORMATION?

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

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

WHO SEES MY INFORMATION?

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

DO I HAVE TO TAKE PART

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

QUESTIONS?

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

THANK YOU FOR YOUR HELP

ABOUT YOU

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

Date: .....

Gender (please tick)

Male	☐1	Female	☐2

Marital Status (please tick)

Single	☐1	Married	☐2
Permanent partnership	☐3	Divorced	☐4
Widowed	☐5	Separated	☐6

Other heart problems you have had: (please tick all that apply)

Myocardial Infarction (Heart Attack)	☐	Acute Coronary Syndrome	☐
Bypass Surgery	☐	Angioplasty (Balloon in artery)	☐
Cardiac Arrest	☐	Angina	☐
Other Surgery	☐	Heart failure	☐
Pacemaker	☐	Implanted defibrillator (ICD)	☐
Heart transplant	☐	Congenital heart problem	☐
LV Assist Device	☐	Other	☐

ETHNIC CLASSIFICATION

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

What is your ethnic group?

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

3

OTHER ILLNESSES YOU HAVE BEEN TOLD YOU HAVE

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

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

Describe Other Complaint .....

PILLS, SMOKING AND WEIGHT/HEIGHT

4

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

1. Aspirin or other anticoagulant No ☐ Yes ☐

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

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

Examples include:

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

3. Beta Blocker No ☐ Yes ☐

Examples include:

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

4. Cholesterol pills (Statins) No ☐ Yes ☐

Examples include:

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

5. Omega 3 No ☐ Yes ☐

Examples include:

omacor

SMOKING

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

Weight (kg) and Height (m):

Weight ☐ kg or ☐ st ☐ lbs

Height ☐ m or ☐ ft ☐ inches

Waist Circumference ☐ cm or ☐ inches

5

HAD Scale

Name: Date:

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

Tick only one box in each section

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Do not write below this line

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PHYSICAL ACTIVITY

6

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

Number of times

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

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

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

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

Please tick only one box

A Often ☐

B Sometimes ☐

C Never/Rarely ☐

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

Please tick only one box

YES ☐ NO ☐

7

QUALITY OF LIFE

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

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

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

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

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

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

8

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

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

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

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

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

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

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

Excellent		1
Very good		2
Good		3
Fair		4
Poor		5

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

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

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

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

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

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

10

WORK AND EMPLOYMENT

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

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

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

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

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

Appendix D.1 Engagement study publication.

Original scientific paper

European Journal of Preventive Cardiology

European Journal of Preventive Cardiology 0(00) 1–7

DOI: 10.1177/2047487317717064
journals.sagepub.com/home/ejpc
SAGE

In the modern era of percutaneous coronary intervention: Is cardiac rehabilitation engagement purely a patient or a service level decision?

Abdulrahman Al Quait[1,2], Patrick Doherty[1], Nils Gutacker[3] and Joseph Mills[4]

Abstract

Aims: Despite the proven benefits of cardiac rehabilitation (CR), utilization rates remain below recommendation in the percutaneous coronary intervention cohort in most European countries. Although extensive research has been carried out on CR uptake, no previous study has investigated the factors that lead patients to attend the initial CR baseline assessment (CR engagement). This paper attempts to provide new insights into CR engagement in the growing percutaneous coronary intervention population.

Methods and results: In total, we analysed data on 59,807 patients who underwent percutaneous coronary intervention during 2013 to 2016 (mean age 65 years; 25% female). Twenty factors were hypothesized to have a direct impact on CR engagement and they were grouped into four main categories; namely socio-demographic factors, cardiac risk factors, medical status and service-level factors. A binary logistic regression model was constructed to examine the association between CR engagement and tested factors. All but one of the proposed factors had a statistically significant impact on CR engagement. Results showed that CR engagement decreases by 1.2% per year of age (odds ratio 0.98) and is approximately 7% lower (odds ratio 0.93) in female patients, while patients are 4.4 times more likely to engage if they receive a confirmed joining date (odds ratio 4.4). The final model achieved 86.6% sensitivity and 49.0% specificity with an area under the receiver operating characteristic curve of 0.755.

Conclusion: The present results highlight the important factors of the likelihood of CR engagement. This implies that future strategies should focus on factors that are associated with CR engagement.

Keywords

Cardiac rehabilitation, prevention, percutaneous coronary intervention, observational study

Received 27 March 2017; accepted 1 June 2017

Introduction

Cardiac rehabilitation (CR), which is defined as a structured multidisciplinary intervention for cardiovascular risk assessment and management, advice on structured exercise training, psychosocial support and the appropriate prescription and adherence to cardio-protective drugs, is the most investigated form of secondary prevention interventions.[1] CR has been established as the most clinically and cost-effective intervention in cardiovascular (CVD) disease management.[2] CR improves clinical outcomes by modifying cardiac risk factors and is cost saving through a reduction in unplanned re-admissions for cardiac problems.[3] Participation in a CR programme for patients hospitalized for an acute coronary event or revascularization is therefore recommended by European guidelines (class 1 level A).[4]

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[2]King Fahad Medical City, Riyadh, Saudi Arabia
[3]Centre for Health Economics, Faculty of Science, University of York, UK
[4]Liverpool Heart & Chest Hospital, UK

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Email: alaq500@york.ac.uk

Appendix D.2 Cardiac rehabilitation history publication.

Global Journal of Health Science

Overview of Cardiac Rehabilitation Evidence, Benefits and Utilisation

Abdulrahman Al Quait, Patrick Doherty

Abstract

Historically, the main objective of cardiac rehabilitation (CR) as an exercise-based programme was to restore or improve patients' regular physical activity after a cardiac event. Since then CR has evolved into a comprehensive secondary prevention programme, the objectives of CR, and indications and contraindications for its use have also developed in sophistication. Current CR programmes are designed to stabilise or even reverse the progression of heart disease by controlling all modifiable risk factors. They are also concerned with improving patients' quality of life by restoring their wellbeing. All this should be achieved with the maximum safety levels to patients. The first part of this review details on how CR evolved from a simple exercise programme to a comprehensive secondary prevention programme in the past few decades. The second part sets an example of modern CR provision, pathway and guidelines in a top leading country in this field, the UK.

Full Text:

PDF

DOI: https://doi.org/10.5539/gjhs.v10n2p38

Global Journal of Health Science ISSN 1916-9736(Print) ISSN 1916-9744(Online)

Email: gjhs@ccsenet.org

Appendix D.3 Impact of age and gender on CR uptake publication.

European Heart Journal

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Volume 38, Issue suppl_1
August 2017

Comments (0)

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5972

Impact of age and gender on cardiac rehabilitation uptake in percutaneous coronary intervention patients

A. Al Quait, P. Doherty

European Heart Journal, Volume 38, Issue suppl_1, 1 August 2017, ehx493.5972, https://doi.org/10.1093/eurheartj/ehx493.5972
Published: 29 August 2017

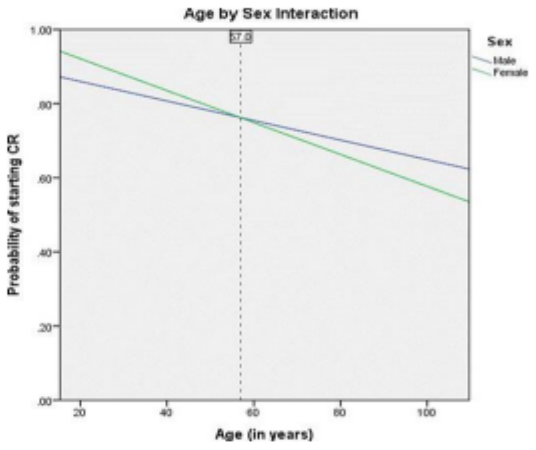
Views PDF Cite Permissions Share

Background: Cardiac rehabilitation (CR) uptake rates are still below recommendations in most European countries. Age and female gender have been identified in the literature as barriers against CR uptake.

Purpose: This study sought to evaluate the extent by which age and gender determine the likelihood of CR uptake among percutaneous coronary intervention (PCI) patients in England.

Methods: The UK National Audit of Cardiac Rehabilitation (NACR) database was used to obtain information on all PCI patients covering the period 01 April 2013 to 31 March 2016. A binary logistic regression model was constructed to assess the impact of age and gender on CR uptake while controlling for other variables; patient's demographics (marital status, employment status, ethnicity and social deprivation rank), Patient's wellbeing (comorbidities, previous cardiovascular events, social support and physical fitness and inactivity) and logistic factors (source of referral to CR, hospital length of stay, CR awareness and type of treatment received). Variables with missing values were handled by multiple imputation where 20 dataset were created and the pooled results reported.

Results: A total of 38,246 patients (64.2±11.7 years, 75.3% male) were analysed. Out of this cohort, 28,263 (73.9%) patients started CR (63.6±11.4 years, 76% male). In this analysis, the likelihood of starting CR is 1.2% less for every one year increase in population age (OR 0.98, 95% CI 0.98 to 0.995). Also there is a significant interaction term between age and gender, this interaction revealed that younger females (<57 years) are more likely to start CR compared to younger males (p=0.012, OR 1.6, 95% CI 1.1 to 2.2) while older female patients were found to be less likely to join compared to younger/middle age females or older male patients (>57 years old) (Figure).



Appendix E.1 SPSS syntax used to create analyses variables

```
* Encoding: UTF-8.

 *    type of treatment variable

DATASET ACTIVATE DataSet1.

RECODE survey_cat (2=1) (3=1) (6=1) (5=2) (15=2) (1=3) (4=3) (8=3) (ELSE=SYSMIS)
INTO

   Treatment_Type.

EXECUTE.



 *    Select MI and Young Age

USE ALL.

COMPUTE filter_$=(NVALID(MIonly) & NVALID(Age18to65)).

VARIABLE LABELS filter_$ 'NVALID(MIonly) & NVALID(Age18to65) (FILTER)'.

VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.

 * MT only variable
```

```
RECODE MT_Group (0=1) (ELSE=SYSMIS) INTO MT_Only.

EXECUTE.



 * Referred by split into cardiac source and primary source

RECODE ReferredBy (1=0) (2=0) (3=1) (4=1) (ELSE=SYSMIS) INTO ReferredBy2.

VARIABLE LABELS  ReferredBy2 'Cardiac Referral Vs Primary '.

EXECUTE.

 * Grouping By date Variable (for jan 2010 to dec 2015)

DATASET ACTIVATE DataSet1.

IF  (IEDate >= DATE.DMY(1,1,2010) & IEDate <= DATE.DMY(31,12,2010))
GroupingByDate=1.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,1,2011) & IEDate <= DATE.DMY(31,12,2011))
GroupingByDate=2.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,1,2012) & IEDate <= DATE.DMY(31,12,2012))
GroupingByDate=3.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,1,2013) & IEDate <= DATE.DMY(31,12,2013))
GroupingByDate=4.
```

```
EXECUTE.

IF  (IEDate >= DATE.DMY(1,1,2014) & IEDate <= DATE.DMY(31,12,2014))
GroupingByDate=5.

EXECUTE.



IF  (IEDate >= DATE.DMY(1,1,2015) & IEDate <= DATE.DMY(31,12,2015))
GroupingByDate=6.

EXECUTE.

 *  Grouping By date Variable (for july 2010 to june 2015)

DATASET ACTIVATE DataSet1.

IF  (IEDate >= DATE.DMY(1,7,2010) & IEDate <= DATE.DMY(30,6,2011))
GroupingByDate2015=1.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,7,2011) & IEDate <= DATE.DMY(30,6,2012))
GroupingByDate2015=2.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,7,2012) & IEDate <= DATE.DMY(30,6,2013))
GroupingByDate2015=3.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,7,2013) & IEDate <= DATE.DMY(30,6,2014))
GroupingByDate2015=4.
```

```
EXECUTE.

IF  (IEDate >= DATE.DMY(1,7,2014) & IEDate <= DATE.DMY(30,6,2015))
GroupingByDate2015=5.

EXECUTE.

 * Age Group Variable from 18 to 65 & >65

DATASET ACTIVATE DataSet1.

IF  (AgeAtInitiatingEvent  >= 66 & AgeAtInitiatingEvent <= 120) AgeGroup2=1.

EXECUTE.

IF  (AgeAtInitiatingEvent  >= 18 & AgeAtInitiatingEvent <= 65) AgeGroup2=0.

EXECUTE.

 * Reason for not joining core rehab splittied to medical and non medical reasons

RECODE ReasonForNotTakingPart.Core (3=1) (13=1) (14=1) (12=1) (10=1) (8=1) (20=1)
(21=1) (16=1)

    (1=2) (2=2) (4=2) (5=2) (6=2) (7=2) (9=2) (11=2) (15=2) (17=2) (18=2) (19=2) (22=3)
(99=3)
```

```
    (SYSMIS=SYSMIS) INTO ReasonsForNotStarting.

VARIABLE LABELS  ReasonsForNotStarting 'Medical Vs Non Medical Reasons'.

EXECUTE.



* Coding above variable into dichotomus (medical or non medical reasons)

RECODE ReasonsForNotStarting (1=0) (2=1) (ELSE=SYSMIS) INTO
Medical.NonMedical.Reasons.

EXECUTE.

 * Reasons for not completing core rehab into dichtomous variable



RECODE ReasonForNotCompleting.Core (5=0) (6=0) (7=0) (9=0) (1=1) (2=1) (3=1) (4=1)
(ELSE=SYSMIS)

    INTO Reasons.Not.Completing.

EXECUTE.



 * MAD for BMI.1

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=
```

```
  /BMI.1_median=MEDIAN(BMI.1).

Compute BMI_MED = -999.

if nvalid(BMI.1) = 1 BMI_MED = BMI.1 - BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).




IF  (BMI.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and BMI.1 >
BMI.1_median - (3*(BMI_MED_median*1.4826))) BMI1.NEW=BMI.1.

EXECUTE.



 * MAD for BMI.2
```

```
AGGREGATE
  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES
  /BREAK=
  /BMI.1_median=MEDIAN(BMI.2).
Compute BMI_MED = -999.
if nvalid(BMI.2) = 1 BMI_MED = BMI.2 - BMI.1_median.
RECODE BMI_MED (-999=SYSMIS).
EXECUTE.
COMPUTE BMI_MEDABS=ABS(BMI_MED).
EXECUTE.


AGGREGATE
  /OUTFILE=* MODE=ADDVARIABLES
  /BREAK=
  /BMI_MED_median=MEDIAN(BMI_MEDABS).
IF  (BMI.2 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and BMI.2 >
BMI.1_median - (3*(BMI_MED_median*1.4826))) BMI2.NEW=BMI.2.
```

```
EXECUTE.

 * BMI. Change variable

IF  (BMI1.NEW > 30 & BMI2.NEW > 30) BMI.Change=0.

EXECUTE.

IF  (BMI1.NEW > 30 & BMI2.NEW  < 30) BMI.Change=1.

EXECUTE.

 * Waist.1 MAD

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(waist.1).

Compute BMI_MED = -999.

if nvalid(waist.1) = 1 BMI_MED = waist.1 - BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.
```

```
AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).

IF  (waist.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and waist.1 >
BMI.1_median - (3*(BMI_MED_median*1.4826))) waist.1.NEW=waist.1.

EXECUTE.

 * Waist.2 MAD

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(waist.2).

Compute BMI_MED = -999.

if nvalid(waist.2) = 1 BMI_MED = waist.2 - BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.
```

```
AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).

IF  (waist.2 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and waist.2 >
BMI.1_median - (3*(BMI_MED_median*1.4826))) waist.2.NEW=waist.2.

EXECUTE.

* waist.1 for male

IF  (Sex=1 & NVALID(waist.1.NEW)) waist.1.male=waist.1.NEW.

EXECUTE.

 * waist.1 female

IF  (Sex=2 & NVALID(waist.1.NEW)) waist.1.Female=waist.1.NEW.

EXECUTE.

  * waist.2 for male

IF  (Sex=1 & NVALID(waist.2.NEW)) waist.2.male=waist.2.NEW.

EXECUTE.

 * waist.2 female

IF  (Sex=2 & NVALID(waist.2.NEW)) waist.2.Female=waist.2.NEW.
```

```
EXECUTE.

* WAIST Change variable

IF  (waist.1.male > 102 & waist.2.male > 102) Waist.Change.Male=0.

EXECUTE.

IF  (waist.1.male > 102 & waist.2.male  < 102) Waist.Change.Male=1.

EXECUTE.

 * Waist Change Female

IF  (waist.1.female > 88 & waist.2.female < 88) Waist.Change.Female=1.

EXECUTE.

IF  (waist.1.female > 88 & waist.2.female > 88) Waist.Change.Female=0.

EXECUTE.

 * Cholesterol Change Variable

DATASET ACTIVATE DataSet4.

IF  (CholesterolTotal.1 > 5 & CholesterolTotal.2 > 5) Cholesterol.Change=0.

EXECUTE.

IF  (CholesterolTotal.1 > 5 & CholesterolTotal.2  <= 5) Cholesterol.Change=1.

EXECUTE.
```

```
* MAD for BloodPressureSystolic.1

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(BloodPressureSystolic.1).

Compute BMI_MED = -999.

if nvalid(BloodPressureSystolic.1) = 1 BMI_MED = BloodPressureSystolic.1 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.



AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).
```

```
IF  (BloodPressureSystolic.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
BloodPressureSystolic.1 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
BloodPressureSystolic.1.NEW=BloodPressureSystolic.1.

EXECUTE.

* MAD for BloodPressureSystolic.2

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(BloodPressureSystolic.2).

Compute BMI_MED = -999.

if nvalid(BloodPressureSystolic.2) = 1 BMI_MED = BloodPressureSystolic.2 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=
```

```
 /BMI_MED_median=MEDIAN(BMI_MEDABS).

IF  (BloodPressureSystolic.2 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
BloodPressureSystolic.2 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
BloodPressureSystolic.2.NEW=BloodPressureSystolic.2.

EXECUTE.

 * BP Change variable

DATASET ACTIVATE DataSet4.

IF  (BloodPressureSystolic.1 > 140 & BloodPressureSystolic.2 > 140)
BloodPressureSystolic.Change=0.

EXECUTE.

IF  (BloodPressureSystolic.1 > 140 & BloodPressureSystolic.2  <= 140)
BloodPressureSystolic.Change=1.

EXECUTE.

 * Smoke Diff Variable

DATASET ACTIVATE DataSet6.

COMPUTE Smoke_Diff=Smoke1 - Smoke2.

EXECUTE.

 * Smoke Change Variable

RECODE Smoke_Diff (-1=0) (0=0) (1=1) (ELSE=SYSMIS) INTO Smoke.Change.

EXECUTE.
```

```
* MAD for ShuttleWalkTestMetres.1

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(ShuttleWalkTestMetres.1).

Compute BMI_MED = -999.

if nvalid(ShuttleWalkTestMetres.1) = 1 BMI_MED = ShuttleWalkTestMetres.1 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).
```

```
IF  (ShuttleWalkTestMetres.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
ShuttleWalkTestMetres.1 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
ShuttleWalkTestMetres.1.NEW=ShuttleWalkTestMetres.1.

EXECUTE.

* MAD for ShuttleWalkTestMetres.2

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(ShuttleWalkTestMetres.2).

Compute BMI_MED = -999.

if nvalid(ShuttleWalkTestMetres.2) = 1 BMI_MED = ShuttleWalkTestMetres.2 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=
```

```
  /BMI_MED_median=MEDIAN(BMI_MEDABS).




IF  (ShuttleWalkTestMetres.2 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
ShuttleWalkTestMetres.2 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
ShuttleWalkTestMetres.2.NEW=ShuttleWalkTestMetres.2.

EXECUTE.

 * ISWT_Diff Variable

IF  (NVALID(ShuttleWalkTestMetres.1.NEW) &
NVALID(ShuttleWalkTestMetres.2.NEW))

    ISWT_Diff=ShuttleWalkTestMetres.1.NEW - ShuttleWalkTestMetres.2.NEW.

EXECUTE.

 * ISWT. Change Variable

RECODE ISWT_Diff (SYSMIS=SYSMIS) (-900 thru -75=1) (-74 thru 1200=0) INTO
ISWT.Change.

EXECUTE.

* MAD for TAM2.1

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=
```

```
  /BMI.1_median=MEDIAN(TAM2.1).

Compute BMI_MED = -999.

if nvalid(TAM2.1) = 1 BMI_MED = TAM2.1 - BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).

IF  (TAM2.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and TAM2.1 >
BMI.1_median - (3*(BMI_MED_median*1.4826))) TAM2.1.NEW=TAM2.1.

EXECUTE.

* MAD for TAM2.2

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=
```

```
  /BMI.1_median=MEDIAN(TAM2.2).

Compute BMI_MED = -999.

if nvalid(TAM2.2) = 1 BMI_MED = TAM2.2 - BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.



AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=

  /BMI_MED_median=MEDIAN(BMI_MEDABS).



 * TAM2 Diff Variable

IF  (NVALID(TAM2.1.NEW) & NVALID(TAM2.2.NEW)) TAM2_Diff=TAM2.1.NEW -
TAM2.2.NEW.

EXECUTE.

 * TAM2 Change Variable
```

```
RECODE TAM2_Diff (SYSMIS=SYSMIS) (-10000 thru -1=1) (0 thru 20000=0) INTO
TAM2.Change.

EXECUTE.

 * HAD Anxiety difference variable

DATASET ACTIVATE DataSet1.

IF  (NVALID(HAD_Anx_1) & NVALID(HAD_Anx_2)) HAD_Anx_Dif=HAD_Anx_1 -
HAD_Anx_2.

EXECUTE.

 * HAD Anx change Variable

RECODE HAD_Anx_Dif (SYSMIS=SYSMIS) (-4 thru 0=0) (1 thru 4=1) INTO
HAD_Anx_Change.

EXECUTE.

* HAD Depression difference variable

DATASET ACTIVATE DataSet1.

IF  (NVALID(HAD_Dep_1) & NVALID(HAD_Dep_2)) HAD_Dep_Dif=HAD_Dep_1 -
HAD_Dep_2.

EXECUTE.

 * HAD Depression change Variable

RECODE HAD_Dep_Dif (SYSMIS=SYSMIS) (-4 thru 0=0) (1 thru 4=1) INTO
HAD_Dep_Change.
```

```
EXECUTE.

* MAD for SixMinuteWalkMetres.1

AGGREGATE

 /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

 /BREAK=

 /BMI.1_median=MEDIAN(SixMinuteWalkMetres.1).



Compute BMI_MED = -999.

if nvalid(SixMinuteWalkMetres.1) = 1 BMI_MED = SixMinuteWalkMetres.1 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

 /OUTFILE=* MODE=ADDVARIABLES

 /BREAK=

 /BMI_MED_median=MEDIAN(BMI_MEDABS).
```

```
IF  (SixMinuteWalkMetres.1 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
SixMinuteWalkMetres.1 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
SixMinuteWalkMetres.1.NEW=SixMinuteWalkMetres.1.

EXECUTE.

* MAD for SixMinuteWalkMetres.2

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES OVERWRITEVARS=YES

  /BREAK=

  /BMI.1_median=MEDIAN(SixMinuteWalkMetres.2).

Compute BMI_MED = -999.

if nvalid(SixMinuteWalkMetres.2) = 1 BMI_MED = SixMinuteWalkMetres.2 -
BMI.1_median.

RECODE BMI_MED (-999=SYSMIS).

EXECUTE.

COMPUTE BMI_MEDABS=ABS(BMI_MED).

EXECUTE.

AGGREGATE

  /OUTFILE=* MODE=ADDVARIABLES

  /BREAK=
```

```
  /BMI_MED_median=MEDIAN(BMI_MEDABS).

IF  (SixMinuteWalkMetres.2 < BMI.1_median + (3*(BMI_MED_median*1.4826)) and
SixMinuteWalkMetres.2 > BMI.1_median - (3*(BMI_MED_median*1.4826)))
SixMinuteWalkMetres.2.NEW=SixMinuteWalkMetres.2.

EXECUTE.

 * SixMinuteWalkMetres difference variable

DATASET ACTIVATE DataSet1.

IF  (NVALID(SixMinuteWalkMetres.1.NEW) & NVALID(SixMinuteWalkMetres.2.NEW))

    SixMinuteWalkMetres_Diff=SixMinuteWalkMetres.1.NEW -
SixMinuteWalkMetres.2.NEW.

EXECUTE.

 * SixMinuteWalkMetres change variable

RECODE SixMinuteWalkMetres_Diff (SYSMIS=SYSMIS) (-600 thru -1=1) (0 thru
1000=0) INTO

    SixMinuteWalkMetres_Change.

EXECUTE.

 * SixMinuteWalkMetres difference variable

DATASET ACTIVATE DataSet1.

IF  (NVALID(ThirtyMins5TimesAWeek.1.NEW) &
NVALID(ThirtyMins5TimesAWeek.2.NEW))
```

```
   ThirtyMins5TimesAWeek_Diff=ThirtyMins5TimesAWeek.1.NEW -
ThirtyMins5TimesAWeek.2.NEW.

EXECUTE.

 * SixMinuteWalkMetres change variable

RECODE ThirtyMins5TimesAWeek_Diff (SYSMIS=SYSMIS) (-600 thru -1=1) (0 thru
1000=0) INTO

   ThirtyMins5TimesAWeek_Change.

EXECUTE.

 * Exercise_50_A Diff Variable

DATASET ACTIVATE DataSet1.

COMPUTE Exercise_50_A_Diff=Exercise_50_A1 - Exercise_50_A2.

EXECUTE.

 * Exercise_50_A Change Variable

RECODE Exercise_50_A_Diff (-3 thru -1=1) (0 thru 3=0) (ELSE=SYSMIS) INTO
Exercise_50_A.Change.

EXECUTE.

 * 75 Vigrous Test Recoding to Dichtomous

DATASET ACTIVATE DataSet1.

RECODE SeventyFiveMinsOfVigorousExercise.1 SeventyFiveMinsOfVigorousExercise.2
('N'=0) ('Y'=1)
```

```
   (MISSING=SYSMIS) INTO SeventyFive.1 SeventyFive.2.

EXECUTE.

 * 75 Diff Variable



IF  (NVALID(SeventyFive.1) & NVALID(SeventyFive.2))
SeventyFive_Diff=SeventyFive.1 - SeventyFive.2.

EXECUTE.

 * 75 Change Varible

RECODE SeventyFive_Diff (-3 thru -1=1) (0 thru 3=0) (ELSE=SYSMIS) INTO
SeventyFive.Change.

EXECUTE.

 * IE Valid and not Referred Variable

DATASET ACTIVATE DataSet1.

IF  (AllCoreReferred = 0) IEventnotReferred=IEValid.

EXECUTE.

 * Referred but not Started Group

IF  (StartValid = 0 & AllCoreReferred = 1) ReferredNotStarted=StartValid.

EXECUTE.

 * Comorbidit total variable
```

```
COMPUTE
Comorbidity_Sum=SUM(Angina1,Arthritis2,Cancer3,Diabetes4,Rheumatism5,Stroke6,Oste
oporosis7,


Hypertension8,Chronic9,Emphysema10,Asthma11,Claudication12,Chronic13,Anxiety14,De
pression15,

   Family16,Erectile17,Hyper18,Other99).

EXECUTE.

 * Comorbidity by 2 variabel

IF  (Comorbidity_Sum > 2) ComorbidBy2=1.

EXECUTE.

IF  (Comorbidity_Sum  <= 2) ComorbidBy2=0.

EXECUTE.

 * New Ethnic Groups Variable

RECODE EthnicGroup ('A'=1) ('B'=2) ('C'=3) ('H'=4) ('J'=4) ('K'=4) ('D'=5) ('E'=5) ('F'=5)
('G'=5)

   ('L'=5) ('M'=5) ('N'=5) ('P'=5) ('R'=5) ('S'=5) (ELSE=SYSMIS) INTO
New_Ethnic_Groups.

EXECUTE.

 * New employment Variable
```

```
RECODE CurrentEmploymentStatus.1 (1=1) (3=1) (2=2) (4=2) (8=3) (6=4) (11=4) (5=4)
(7=4) (9=4)

    (10=4) (12=4) (ELSE=SYSMIS) INTO New_Employment.

EXECUTE.

 * New marital status variable

DATASET ACTIVATE DataSet1.

RECODE MaritalStatus (1=1) (2=2) (3=2) (4=3) (5=3) (6=3) (ELSE=SYSMIS) INTO
New_Marital.

EXECUTE.



 * currently smoking variabel

DATASET ACTIVATE DataSet1.

RECODE Smoked.1 Smoked.2 (4=1) (1=0) (2=0) (3=0) (SYSMIS=SYSMIS)
(ELSE=SYSMIS) INTO

    CurrentlySmoking.1 CurrentlySmoking.2.

EXECUTE.

 * Baseline for males waist above 102cm

DATASET ACTIVATE DataSet1.

RECODE waist.1.male (SYSMIS=SYSMIS) (102 thru 1000=1) (1 thru 101=0) INTO
WaistBaselineRatioMale.
```

```
EXECUTE.

 * BAseline female waist 88c

DATASET ACTIVATE DataSet1.

RECODE waist.1.female (SYSMIS=SYSMIS) (88 thru 1000=1) (1 thru 87=0) INTO
WaistBaselineRatioFemale.

EXECUTE.

 * BMI above 30 at baseline

RECODE BMI1.NEW (SYSMIS=SYSMIS) (0 thru 30=0) (31 thru 1000=1) INTO
BMIabove30atBaseline.

EXECUTE.

 * BMI above 25 at baeline



RECODE BMI1.NEW (SYSMIS=SYSMIS) (0 thru 25=0) (26 thru 1000=1) INTO
BMIabove25atBaseline.

EXECUTE.

 * Grouping By date Variable (for April 2011 to March 2016)

DATASET ACTIVATE DataSet1.

IF  (IEDate >= DATE.DMY(1,4,2011) & IEDate <= DATE.DMY(31,3,2012))
GroupingByDate=1.

EXECUTE.
```

```
IF  (IEDate >= DATE.DMY(1,4,2012) & IEDate <= DATE.DMY(31,3,2013))
GroupingByDate=2.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,4,2013) & IEDate <= DATE.DMY(31,3,2014))
GroupingByDate=3.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,4,2014) & IEDate <= DATE.DMY(31,3,2015))
GroupingByDate=4.

EXECUTE.

IF  (IEDate >= DATE.DMY(1,4,2015) & IEDate <= DATE.DMY(31,3,2016))
GroupingByDate=5.

EXECUTE.
```

Abbreviations

AACVPR	*Association of Cardiovascular Pulmonary Rehabilitation*
ACCF	*American College of Cardiology Foundation*
ACE	*Angiotensin-Converting Enzyme*
ACS	*Acute Coronary Syndrome*
AHA	*American Heart Association*
BACPR	*British Association for Cardiovascular Prevention and Rehabilitation*
BCIS	*British Cardiovascular Intervention Society*
BHF	*British Heart Foundation*
BMI	*Body Mass Index*
CABG	*Coronary Artery Bypass Grafts*
CAD	*Coronary Artery Disease*
CEBR	*Centre for Economics and Business Research*
CHD	*Coronary Heart Disease*
CI	*Confidence Interval*
CPRP	*Cardiovascular Prevention And Rehabilitation Programme*
CR	*Cardiac Rehabilitation*
CVD	*Cardiovascular Diseases*

ECG	*Electrocardiogram*
ESC	*European Society of Cardiology*
HF	*Heart Failure*
HRQL	*Health Related Quality of Life*
IMD	*Index of Multiple Deprivation*
MI	*Myocardial Infarction*
MLHFQ	*Minnesota Living with Heart Failure Questionnaire*
NACR	*National Audit of Cardiac Rehabilitation*
NHS	*National Health Service*
NICE	*National Institute For Health and Care Excellence*
PCI	*Percutaneous Coronary Intervention*
RCT	*Randomised Control Trial*
STEMI	*ST Elevation Myocardial Infarction*
WHF	*World Health Federation*
WHO	*World Health Organisation*

References

Adèr, H.J. & Mellenbergh, G.J., 2008. *Advising on Research Methods: a consultant's companion*, Johannes van Kessel Pub. Available at: http://books.google.co.nz/books?id=LCnOj4ZFyjkC [Accessed August 1, 2017].

Aggarwal, C.C., 2013. Outlier analysis. In *Outlier Analysis*. Cham: Springer International Publishing, pp. 1–446. Available at: http://link.springer.com/10.1007/978-3-319-14142-8_8 [Accessed August 7, 2017].

Ago, L. & Realized, E., 1979. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation*, 59(3), pp.607–609.

Allen, J.K. et al., 2004. Disparities in women's referral to and enrollment in outpatient cardiac rehabilitation. *Journal of General Internal Medicine*, 19(7), pp.747–753.

Anderson, L. et al., 2016. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease. *Journal of the American College of Cardiology*, 67(1), pp.1–12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26764059.

Anderson, L. et al., 2017a. Home-based versus centre-based cardiac rehabilitation. In R. S. Taylor, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd. Available at: http://doi.wiley.com/10.1002/14651858.CD007130.pub4 [Accessed August 15, 2017].

Anderson, L. et al., 2017b. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database of Systematic Reviews*. Available at: http://doi.wiley.com/10.1002/14651858.CD007130.pub4 [Accessed October 19, 2017].

Andy, F., 2013. *Discovering Statistics Using IBM SPSS Statistics*, SAGE Publications.

Anglemyer, A., Horvath, H.T. & Bero, L., 2014. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *The Cochrane database of systematic reviews*, 4(4), p.MR000034.

Arena, R. et al., 2012. Increasing referral and participation rates to outpatient cardiac rehabilitation: The valuable role of healthcare professionals in the inpatient and home health settings: A science advisory from the american heart association. *Circulation*, 125(10), pp.1321–1329.

Armstrong, M.J. et al., 2014. Patients with diabetes in cardiac rehabilitation: Attendance and exercise capacity. *Medicine and Science in Sports and Exercise*, 46(5), pp.845–850. Available at: http://journals.lww.com/acsm-msse/Fulltext/2014/05000/Patients_with_Diabetes_in_Cardiac_Rehabilitation__.1.aspx.

Astin, F. et al., 2008. The information needs of patients treated with primary angioplasty for heart attack: An exploratory study. *Patient Education and Counseling*, 73, pp.325–332.

Austin, P.C., 2011. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research*, 46(3), pp.399–424. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3144483&tool=pmcentrez&rendertype=abstract [Accessed August 12, 2017].

BACPR, 2017. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation, 3rd ed. , p.28. Available at: http://www.bacpr.com/resources/AC6_BACPRStandards&CoreComponents2017.pdf [Accessed June 29, 2017].

BACPR, 2012. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation 2012. *Components*. Available at: http://www.bacpr.com/resources/46C_BACPR_Standards_and_Core_Components_2012.pdf.

Balady, G.J. et al., 2011. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: A presidential advisory from the american heart association. *Circulation*, 124, pp.2951–2960.

Banerjee, A.T., Gupta, M. & Singh, N., 2007. Patient characteristics, compliance, and exercise outcomes of South Asians enrolled in cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation & Prevention*, 27(4), pp.212–218. Available at: http://ovidsp.tx.ovid.com/sp-3.26.1a/ovidweb.cgi?WebLinkFrameset=1&S=EPEAFPGJNJDDHGCKNCGKCFIBCDKGAA00&returnUrl=ovidweb.cgi%3F%26Full%2BText%3DL%257cS.sh.49.50%257c0%257c01273116-200707000-00005%26S%3DEPEAFPGJNJDDHGCKNCGKCFIBCDKGAA00&directlink=http%3A%2F.

Banerjee, A.T., Gupta, M. & Singh, N., 2007. Patient Characteristics, Compliance, and Exercise Outcomes of South Asians Enrolled in Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 27(4), pp.212–218.

Beauchamp, A. et al., 2013. Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart*, 99(9), pp.620–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23213175.

Beckie, T.M. et al., 2015. Biopsychosocial Health Disparities Among Young Women Enrolled in Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 35(2), pp.103–113. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01273116-201503000-00003.

Beckie, T.M. & Beckstead, J.W., 2010. Predicting Cardiac Rehabilitation Attendance in a Gender-Tailored Randomized Clinical Trial. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 30(3), pp.147–156.

Berkwits, M. & Inui, T.S., 1998. Making use of qualitative research techniques. *Journal of general internal medicine*, 13(3), pp.195–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9541377 [Accessed October 18, 2017].

Bethell, H. et al., 2000. The BACR database of cardiac rehabilitation units in the UK. *Coronary Health Care*, 4(2), pp.92–95. Available at: http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=107141747&site=ehost-live [Accessed July 13, 2017].

Bhaskaran, K. & Smeeth, L., 2014. What is the difference between missing completely at random and missing at random? *International Journal of Epidemiology*, 43(4), pp.1336–1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24706730 [Accessed August 7, 2017].

Bhatnagar, P. et al., 2015. The epidemiology of cardiovascular disease in the UK 2014. *Heart*, 101(15), pp.1182–1189. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2015-307516.

Bjarnason-Wehrens, B. et al., 2010. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, 17(4), pp.410–418.

Bolooki, H.M. & Askari, A., 2010. Acute Myocardial Infarction. Available at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/acute-myocardial-infarction/ [Accessed December 22, 2015].

Brual, J. et al., 2010. Drive time to cardiac rehabilitation: at what point does it affect utilization?. *International journal of health geographics*, 9, p.27. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=20525345.

Carlson, M.D.A. & Morrison, R.S., 2009. Study design, precision, and validity in observational studies. *Journal of palliative medicine*, 12(1), pp.77–82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19284267 [Accessed October 9, 2017].

Casey, E. et al., 2008. Depression predicts failure to complete phase-II cardiac rehabilitation. *Journal of Behavioral Medicine*, 31(5), pp.421–431.

CEBR, 2014. The Rising Cost of CVD | Centre for Economics and Business Research. Available at: http://www.cebr.com/reports/the-rising-cost-of-cvd/ [Accessed July 4, 2017].

Centre for Reviews and Dissemination, 2009. *Systematic reviews: CRD's guidance for undertaking reviews in health care*, CRD, University of York. Available at: https://gate2.library.lse.ac.uk/login?url=http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2524.2003.00433.x/abstract%5Cnhttp://zw4gk5cr3l.search.serialssolutions.com?sid=CentralSearch:null&genre=article&atitle=Scoping+the+field&volume=11&issue=4&titl

e=H [Accessed August 10, 2017].

Chamosa, S. et al., 2015. Predictors of Enrollment in Cardiac Rehabilitation Programs in Spain. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 35(4), pp.255–262.

Cheng, H.G. & Phillips, M.R., 2014. Secondary analysis of existing data: opportunities and implementation. *Shanghai archives of psychiatry*, 26(6), pp.371–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25642115%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4311114 [Accessed August 1, 2017].

Clark, A.M. et al., 2012. A qualitative systematic review of influences on attendance at cardiac rehabilitation programs after referral. *American Heart Journal*, 164(6), p.835–845.e2. Available at: http://dx.doi.org/10.1016/j.ahj.2012.08.020.

Collet, J.P., 2000. Limitations of clinical trials. *La Revue du praticien*, 50(8), pp.833–837. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10874859 [Accessed July 24, 2017].

Collins, G.S. et al., 2014. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC medical research methodology*, 14(1), p.40. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3999945&tool=pmcentrez&rendertype=abstract [Accessed August 5, 2017].

Cook, D.G. et al., 1990. Consultation rates among middle aged men in general practice over three years. *British Medical Journal*, 301(October), pp.647–650.

Cupples, M.E. et al., 2010. Cardiac rehabilitation uptake following myocardial infarction: Cross-sectional study in primary care. *British Journal of General Practice*, 60(575), pp.431–435.

Dalal, H.M., Doherty, P. & Taylor, R.S., 2015. Cardiac rehabilitation. *BMJ (Clinical research ed.)*, 351(sep29_11), p.h5000. Available at: http://www.bmj.com/content/351/bmj.h5000.full.pdf+html [Accessed November 14, 2015].

David Hosmer, Stanely Lemeshow, R.S., 2013. *Applied Logistic Regression* 3rd ed., New Jersey: John Wiley & Sons, Inc.

Davis, J.W., 2008. *Medical Statistics: A Textbook for the Health Sciences*, Wiley.

DCLG, 2015. The English Index of Multiple Deprivation 2015: Guidance. , (Imd), pp.1–7. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [Accessed January 13, 2017].

Deeks, A. et al., 2009. The effects of gender and age on health related behaviors. *BMC Public Health*, 9(1), p.213. Available at: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-9-213.

Deeks, J.J. et al., 2003. Evaluating non-randomised intervention studies. *Health Technology Assessment*, 7(27), p.iii–x, 1-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14499048 [Accessed August 12, 2017].

DH Cardiovascular Disease Team, 2013. *Cardiovascular Disease Outcomes Strategy; Improving outcomes for people at risk or with cardiovascular disease*, Available at: https://www.gov.uk/government/publications/cardiovascular-disease-outcomes-strategy-improving-outcomes-for-people-with-or-at-risk-of-cardiovascular-disease.

Dictionary, M., 2014. Revascularization. , 187(May 2004), pp.4–5.

Didier, J. et al., 2010. *Rethinking Physical and Rehabilitation Medicine*, Springer. Available at: http://link.springer.com/content/pdf/10.1007/978-2-8178-0034-9.pdf [Accessed June 30, 2017].

Diletti, R. et al., 2014. Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study. *European Heart Journal*, 35(12), pp.777–786. Available at: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/eht546 [Accessed November 6, 2017].

Doherty, P. & Lewin, R., 2012. The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart*, 98(8), pp.605–606. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2012-301728 [Accessed July 12, 2017].

Doll, J.A. et al., 2015. Effectiveness of cardiac rehabilitation among older patients after acute myocardial infarction. *American Heart Journal*, 170(5), pp.855–864.

Dressler, C. et al., 2012. Interventions to increase the uptake of cardiac rehabilitation: Systematic review. *British Journal of Cardiac Nursing*, 7(7), pp.338–346. Available at: http://www.magonlinelibrary.com/doi/abs/10.12968/bjca.2012.7.7.338 [Accessed August 9, 2017].

Dunlay, S.M. et al., 2009. Barriers to participation in cardiac rehabilitation. *American Heart Journal*, 158(5), pp.852–859. Available at: http://dx.doi.org/10.1016/j.ahj.2009.08.010.

Dunlay, S.M. et al., 2014. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. *The American journal of medicine*, 127(6), pp.538–46. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4035431&tool=pmcentrez&rendertype=abstract.

Dupont, W.D., 2011. B IOSTATISTICS II Statistical Modeling for Biomedical Researchers.

van Engen-Verheul, M. et al., 2013. Cardiac rehabilitation uptake and its determinants in the Netherlands. *European journal of preventive cardiology*, 20(2), pp.349–56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22345699.

England, P. & Guideline, C., 2014. *Factsheet : Increase uptake of cardiac rehabilitation for*

people with coronary artery disease and following acute heart failure, Available at: https://www.england.nhs.uk/wp-content/uploads/2014/02/pm-fs-3-10.pdf.

Evenson, K., Rosamond, W. & Luepker, R., 1998. Predictors of outpatient cardiac rehabilitation utilization: the Minnesota Heart Surgery Registry. *Journal of cardiopulmonary rehabilitation*, 18(3), pp.192–8. Available at: http://journals.lww.com/jcrjournal/Abstract/1998/05000/Predictors_of_Outpatient_Cardiac_Rehabilitation.2.aspx%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/9632320.

Few, S., 2004. EENIE , MEENIE , MINIE , MOE : Selecting the Right Graph for Your Message. *Intelligent Enterprise*, 7(14), p.35. Available at: http://www.perceptualedge.com/articles/ie/the_right_graph.pdf [Accessed August 1, 2017].

Field, A., 2013. *Discovering statistics using IBM SPSS Statistics: and sex and drugs and rock 'n' roll (fourth edition)*, Available at: https://books.google.co.uk/books?id=srb0a9fmMEoC&printsec=frontcover&dq=discovering+statistics+using+spss&hl=en&sa=X&ved=0ahUKEwj37-65jLTVAhXLhrQKHWK5AREQ6AEIMTAB#v=onepage&q=discovering statistics using spss&f=false [Accessed July 31, 2017].

Freedman, D., 2005. *Statistical models : theory and practice*, Cambridge University Press. Available at: http://www.cambridge.org/gb/academic/subjects/statistics-probability/statistical-theory-and-methods/statistical-models-theory-and-practice-2nd-edition?format=HB&isbn=9780521743853#URshgdGp9eu1akgb.97 [Accessed August 4, 2017].

French, D.P. et al., 2005. Do illness perceptions predict attendance at cardiac rehabilitation and quality of life following myocardial infarction? *Journal of Psychosomatic Research*, 59(5), pp.315–322.

Galdas, P.M., Cheater, F. & Marshall, P., 2005. Men and health help-seeking behaviour: Literature review. *Journal of Advanced Nursing*, 49(6), pp.616–623.

Gallagher, R., McKinley, S. & Dracup, K., 2003. Predictors of women's attendance at cardiac rehabilitation programs. *Progress in cardiovascular nursing*, 18(3), pp.121–126. Available at: http://ezproxy.lib.ucalgary.ca:2048/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=2003132140&site=ehost-live.

Giuliano, C. et al., 2017. Cardiac Rehabilitation for Patients With Coronary Artery Disease: A Practical Guide to Enhance Patient Outcomes Through Continuity of Care. *Clinical Medicine Insights. Cardiology*, 11, p.1179546817710028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28638244%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5470863 [Accessed November 14, 2017].

Goff, D.C. et al., 2014. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation*, 129.

Grace, S. et al., 2016. Cardiac rehabilitation delivery model for low-resource settings. *Heart*, 102(18), pp.1449–1455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27181874 [Accessed December 30, 2017].

Grace, S.L. et al., 2010. A prospective comparison of cardiac rehabilitation enrolment following automatic versus usual referral. *Journal of Rehabilitation*, 39(3), pp.239–245. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2935486/.

Grace, S.L. et al., 2009. Barriers to cardiac rehabilitation: DOES AGE MAKE A DIFFERENCE? *Journal of cardiopulmonary rehabilitation and prevention*, 29(3), pp.183–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19471138 [Accessed September 8, 2016].

Grace, S.L. et al., 2016. Cardiac Rehabilitation Program Adherence and Functional Capacity Among Women: A Randomized Controlled Trial. *Mayo Clinic Proceedings*, 91(2), pp.140–148. Available at: http://dx.doi.org/10.1016/j.mayocp.2015.10.021.

Grace, S.L. et al., 2008. Contribution of patient and physician factors to cardiac rehabilitation referral: a prospective multilevel study. *Nature clinical practice. Cardiovascular medicine*, 5(10), pp.653–662.

Grace, S.L. et al., 2008. Contribution of Patient and Physician Factors to Cardiac Rehabilitation Rehabilitation Enrollment: A Prospective Multi-Level Study. *Eur J Cardiovasc Prev Rehabil*, 15(5), pp.548–556. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3266303&tool=pmcentrez&rendertype=abstract.

Grace, S.L. et al., 2011. Effect of Cardiac Rehabilitation Referral Strategies on Utilization Rates A. S. A. D. B. S. G. S. G. M. H. P. J. M. K. R. O. P. P. C. P. J. R. R. R. E. R. J. S. DE Williamson K, ed. *Archives of Internal Medicine*, 171(3), pp.235–242. Available at: http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/416448.

Graham, I. et al., 2007. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Atherosclerosis*, 194(1), pp.1–45.

Gravely-Witte, S. et al., 2010. Effects of cardiac rehabilitation referral strategies on referral and enrollment rates. *Nature reviews. Cardiology*, 7(2), pp.87–96. Available at: http://dx.doi.org/10.1038/nrcardio.2009.223.

Groden, B.M., Semple, T. & Shaw, G.B., 1971. Cardiac rehabilitation in Britain (1970). *British heart journal*, 33(5), pp.756–8. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=487247&tool=pmcentrez&rendertype=abstract [Accessed July 13, 2017].

Gutacker, N., Bloor, K. & Cookson, R., 2015. Comparing the performance of the Charlson/Deyo and Elixhauser comorbidity measures across five European countries and three conditions. *European journal of public health*, 25, pp.15–20.

Hajian-Tilaki, K., 2013. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. *Caspian Journal of Internal Medicine*, 4(2), pp.627–635.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/24009950 [Accessed January 2, 2017].

Hannan, E.L., 2008. Randomized Clinical Trials and Observational Studies. Guidelines for Assessing Respective Strengths and Limitations. *JACC: Cardiovascular Interventions*, 1(3), pp.211–217. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1936879808001702 [Accessed July 22, 2017].

Harlan, W.R. et al., 1995. Importance of Baseline Functional and Socioeconomic Factors for Participation in Cardiac Rehabilitation. *American Journal of Cardiology*, 76(1–2), pp.36–39.

Harrell, F.E.J., 2015. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, 2nd ed.* 2nd ed., Available at: https://books.google.co.uk/books?hl=en&lr=&id=94RgCgAAQBAJ&oi=fnd&pg=PR7&dq=logistic+regression+model+validation&ots=ZAl5Nm8RZi&sig=PEGY4Ijcwf-fe1hWNR8CrCrfZl8#v=onepage&q=logistic regression model validation&f=false [Accessed August 5, 2017].

Harrison, W.N. & Wardle, S.A., 2005a. Factors affecting the uptake of cardiac rehabilitation services in a rural locality. *Public Health*, 119(11), pp.1016–1027. Available at: http://www.sciencedirect.com/science/article/pii/S0033350605000867?via%3Dihub#!

Harrison, W.N. & Wardle, S.A., 2005b. Factors affecting the uptake of cardiac rehabilitation services in a rural locality. *Public Health*, 119(11), pp.1016–1027.

Hartwell, D. (Debbie L.. et al., 2005. Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction : systematic review and economic evaluation. *Health Technology Assessment*. Available at: http://wrap.warwick.ac.uk/52138/2/WRAP_waugh10_Coversheet_FinalVersion.pdf [Accessed December 24, 2015].

Hellerstein, J.M., 2008. Quantitative Data Cleaning for Large Databases. *United Nations Economic Commission for Europe*, p.42. Available at: http://db.cs.berkeley.edu/jmh/cleaning-unece.pdf%5Cnpapers2://publication/uuid/DC7173AB-6B26-4B8B-AEC3-4C7E65CEEFED.

Hernández-Orallo, J., 2013. ROC curves for regression. *Pattern Recognition*, 46(12), pp.3395–3411. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0031320313002665 [Accessed August 5, 2017].

Higgins et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, 343, p.d5928. Available at: http://www.bmj.com/content/343/bmj.d5928.long [Accessed August 12, 2017].

Higgins, J. & Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *The Cochrane Collaboration, 2011*. Available at: www.cochrane-

handbook.org. [Accessed January 28, 2016].

Hippisley-Cox, J. et al., 2007. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ (Clinical research ed.)*, 335(7611), p.136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17615182%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1925200 [Accessed August 8, 2017].

Hoffmann, A. et al., 2013. Rehabilitation enrollment after cardiac procedures. *Kardiovaskulare Medizin*, 16(7–8), pp.203–207. Available at: https://cardiovascmed.ch/resource/jf/journal/file/view/article/cvm.2013.00169/cvm-00169.pdf/.

Hosmer, D.W. & Lemeshow, S., 2013. *Applied logistic regression*, Available at: http://www.amazon.com/dp/0471356328 [Accessed August 5, 2017].

Humphrey, R., Guazzi, M. & Niebauer, J., 2014. Cardiac rehabilitation in Europe. *Progress in Cardiovascular Diseases*, 56(5), pp.551–556. Available at: http://dx.doi.org/10.1016/j.pcad.2013.08.004.

Javaid, A. et al., 2007. Outcomes of Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention With Drug-Eluting Stents for Patients With Multivessel Coronary Artery Disease. *Circulation*, 116(11_suppl), p.I-200-I-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17846304 [Accessed December 30, 2017].

Judd, C.M. & McClelland, G.H., 1989. *Data analysis : a model-comparison approach*, Harcourt Brace Jovanovich. Available at: https://books.google.co.uk/books/about/Data_analysis.html?id=MaEZAQAAIAAJ [Accessed August 1, 2017].

Karmali, K. et al., 2014. Promoting patient uptake and adherence in cardiac rehabilitation. *Cochrane Database of Systematic Reviews*, (2).

Karmali, K.N. et al., 2014. Promoting patient uptake and adherence in cardiac rehabilitation. *The Cochrane database of systematic reviews*, 6(2), p.CD007131.

King, K.M. et al., 2001. Psychosocial components of cardiac recovery and rehabilitation attendance. *Heart (British Cardiac Society)*, 85(3), pp.290–294. Available at: http://heart.bmj.com/content/85/3/290.

Kwak, S.K. & Kim, J.H., 2017. Statistical data preparation: management of missing values and outliers. *Korean journal of anesthesiology*, 70(4), pp.407–411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28794835 [Accessed October 9, 2017].

Lane, D. et al., 2001. Predictors of attendance at cardiac rehabilitation after myocardial infarction. *Journal of Psychosomatic Research*, 51(3), pp.497–501.

Langkamp, D.L., Lehman, A. & Lemeshow, S., 2010. Techniques for handling missing data in secondary analyses of large surveys. *Academic pediatrics*, 10(3), pp.205–10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20338836 [Accessed October 9,

2017].

Lapierre, H., Chan, V. & Ruel, M., 2006. Off-pump coronary surgery through mini-incisions: is it reasonable? *Current Opinion in Cardiology*, 21(6), pp.578–583. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001573-200611000-00006 [Accessed December 30, 2017].

Lavie, C.J. & Milani, R. V, 2006. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. *Archives of internal medicine*, 166(17), pp.1878–1883.

Lawler, P.R., Filion, K.B. & Eisenberg, M.J., 2011. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. *American Heart Journal*, 162(4), p.571–584.e2. Available at: http://dx.doi.org/10.1016/j.ahj.2011.07.017.

Lear, S.A. & Ignaszewski, A., 2001. Cardiac rehabilitation: a comprehensive review. *Current controlled trials in cardiovascular medicine*, 2(5), pp.221–232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11806801 [Accessed July 4, 2017].

Lemstra, M.E. et al., 2013. Neighbourhood income and cardiac rehabilitation access as determinants of nonattendance and noncompletion. *Canadian Journal of Cardiology*, 29(12), pp.1599–1603. Available at: http://dx.doi.org/10.1016/j.cjca.2013.08.011.

Ligthelm, R.J. et al., 2007. Importance of Observational Studies in Clinical Practice. *Clinical Therapeutics*, 29(6 PART 1), pp.1284–1292. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0149291807001841 [Accessed July 24, 2017].

Linden, W., Stossel, C. & Maurice, J., 1996. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. *Archives of internal medicine*, 156(7), pp.745–52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8615707 [Accessed July 13, 2017].

Little, R.J.A., Rubin, D.B., 1987. *Statistical Analysis With Missing Data*, Wiley. Available at: https://books.google.co.uk/books?id=AyVeBAAAQBAJ&printsec=frontcover&dq=statistical+analysis+with+missing+data&hl=en&sa=X&ved=0ahUKEwi96p3hi7TVAhVEb1AKHcq1DTsQ6AEIKTAA#v=onepage&q=statistical analysis with missing data&f=false [Accessed July 31, 2017].

Long-Sutehall, T., Sque, M. & Addington-Hall, J., 2011. Secondary analysis of qualitative data: a valuable method for exploring sensitive issues with an elusive population? *Journal of Research in Nursing*, 16(4), pp.335–344. Available at: http://eprints.soton.ac.uk/193035/1/Sec_analysis_paper_[final]_03.06.10.doc [Accessed July 25, 2017].

Lund, M., Lund, A., 2015. Binomial logistic regression in SPSS Statistics _ Laerd Statistics Premium. Available at: https://statistics.laerd.com/premium/spss/blr/binomial-logistic-

regression-in-spss-13.php [Accessed August 4, 2017].

Mampuya, W.M., 2012. Cardiac rehabilitation past, present and future: an overview. *Cardiovascular diagnosis and therapy*, 2(1), pp.38–49. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3839175&tool=pmcentrez&rendertype=abstract.

McGavock, J.M. et al., 2009. A forty-year follow-up of the Dallas Bed Rest and Training Study: The effect of age on the cardiovascular response to exercise in men. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 64(2), pp.293–298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19196908 [Accessed July 4, 2017].

McKee, G. et al., 2014. Cardiac rehabilitation after myocardial infarction: What influences patients' intentions to attend? *European Journal of Cardiovascular Nursing*, 13(4), pp.329–337.

Melville, M.R. et al., 1999. Cardiac rehabilitation: socially deprived patients are less likely to attend but patients ineligible for thrombolysis are less likely to be invited. *Heart (British Cardiac Society)*, 82(3), pp.373–7. Available at: http://heart.bmj.com/content/82/3/373#T1.

Menard, S., 2010. *Logistic Regression: From Introductory to Advanced Concepts and Applications: From Introductory to Advanced Concepts and Applications*, 2455 Teller Road, Thousand Oaks California 91320 United States : SAGE Publications, Inc. Available at: http://methods.sagepub.com/book/logistic-regression-from-introductory-to-advanced-concepts-and-applications [Accessed August 4, 2017].

Menezes, A.R. et al., 2014. Cardiac Rehabilitation in the Elderly. *Progress in Cardiovascular Diseases*, 57(2), pp.152–159. Available at: http://dx.doi.org/10.1016/j.pcad.2014.01.002.

Milani, R. V. et al., 2011. Impact of exercise training and depression on survival in heart failure due to coronary heart disease. *American Journal of Cardiology*, 107(1), pp.64–68. Available at: http://dx.doi.org/10.1016/j.amjcard.2010.08.047.

Miller, G., Hughes-Cromwick, P. & Roehrig, C., 2011. National spending on cardiovascular disease, 19962008. *Journal of the American College of Cardiology*, 58(19), pp.2017–2019.

Miller, M.E., Hui, S.L. & Tierney, W.M., 1991. Validation techniques for logistic regression models. *Statistics in Medicine*, 10(8), pp.1213–1226. Available at: http://doi.wiley.com/10.1002/sim.4780100805 [Accessed August 5, 2017].

Missik, E., 1999. Personal perceptions and women's participation in cardiac rehabilitation. *Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses*, 24(4), pp.158–165. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=10754904.

Mochari, H. et al., 2006. Ethnic differences in barriers and referral to cardiac rehabilitation

among women hospitalized with coronary heart disease. *Preventive cardiology*, 9(1), pp.8–13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16407697.

Molenberghs, G, K.M., 2007. *Missing Data in Clinical Studies*, Wiley. Available at: https://books.google.co.uk/books?id=SuPJkcfdn1YC&printsec=frontcover&dq=missing+data+in+clinical+studies&hl=en&sa=X&ved=0ahUKEwiv1b3_i7TVAhXFY1AKHbmSCd0Q6AEIKTAA#v=onepage&q=missing data in clinical studies&f=false [Accessed July 31, 2017].

Molloy, G.J. et al., 2008. Social networks and partner stress as predictors of adherence to medication, rehabilitation attendance, and quality of life following acute coronary syndrome. *Health Psychology*, 27(1), pp.52–58.

Montalescot, G. et al., 2013. 2013 ESC guidelines on the management of stable coronary artery disease. *European Heart Journal*, 34(38), pp.2949–3003. Available at: https://oup.silverchair-cdn.com/oup/backfile/Content_public/Journal/eurheartj/34/38/10.1093_eurheartj_eht296/1/eht296.pdf?Expires=1499509124&Signature=G-iBRjxV6ccfIkQzJst4fWW7weDowZ5dS6PtkVIjC23ZDm68Fg~gNRSliHvKqAkPaGfUv0K8EyNgxGjKIo64L7mDZlr9TwAJ6ft6TTga [Accessed July 7, 2017].

Morgan, D.L., 1998. Practical Strategies for Combining Qualitative and Quantitative Methods: Applications to Health Research. *Qualitative Health Research*, 8(3), pp.362–376. Available at: http://journals.sagepub.com/doi/10.1177/104973239800800307 [Accessed October 18, 2017].

MORRIS, J.N. & HEADY, J.A., 1953. Mortality in relation to the physical activity of work: a preliminary note on experience in middle age. *British journal of industrial medicine*, 10(4), pp.245–54. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1037497&tool=pmcentrez&rendertype=abstract [Accessed July 3, 2017].

Mozaffarian, D. et al., 2015. *Heart Disease and Stroke Statistics--2015 Update: A Report From the American Heart Association*, Available at: http://circ.ahajournals.org/cgi/doi/10.1161/CIR.0000000000000152.

Murray, J. et al., 2012. A systematic review of patient reported factors associated with uptake and completion of cardiovascular lifestyle behaviour change. *BMC cardiovascular disorders*, 12(1), p.120. Available at: http://www.biomedcentral.com/1471-2261/12/120.

NACR, 2014. *The National Audit of Cardiac Rehabilitation- Annual statistical report 2014*, York. Available at: http://www.cardiacrehabilitation.org.uk/docs/2007.pdf.

NACR, 2015. *The National Audit of Cardiac Rehabilitation- Annual statistical report 2014*, Available at: http://www.cardiacrehabilitation.org.uk/docs/2007.pdf.

NACR, 2007. *The National Audit of Cardiac Rehabilitation Annual Statistical Report 2007*, York. Available at: http://www.cardiacrehabilitation.org.uk/docs/2007.pdf.

NACR, 2016. the National Audit of Cardiac Rehabilitation Annual Statistical Report 2016. Available at: http://www.cardiacrehabilitation.org.uk/docs/BHF_NACR_Report_2016.pdf.

National Institute for Health and Care Excellence, 2013. *Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease*, Available at: https://www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-cardiac-rehabilitation-and-prevention-of-further-cardiovascular-disease-35109748874437.

Newman, 2000. *Logistic Regression*, 2455 Teller Road, Thousand Oaks California 91320 United States of America : SAGE Publications, Inc. Available at: http://methods.sagepub.com/book/logistic-regression [Accessed August 4, 2017].

NHS, 2015. Physical activity guidelines for adults - Live Well - NHS Choices. Available at: http://www.nhs.uk/Livewell/fitness/Pages/physical-activity-guidelines-for-adults.aspx [Accessed January 2, 2017].

NICE, 2015. [Secondary prevention after a myocardial infarction]. *Secondary prevention after a myocardial infarction (QS99)*, 61(5–6), pp.380–385. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16910265.

NICE, 2013. MI – secondary prevention care for patients following a myocardial. *NICE Guidelines*, (November). Available at: https://www.nice.org.uk/guidance/cg172/resources/myocardial-infarction-cardiac-rehabilitation-and-prevention-of-further-cardiovascular-disease-pdf-35109748874437 [Accessed June 29, 2017].

NICE commissioning guides, 2013. Cardiac rehabilitation services | Guidance and guidelines | NICE. Available at: https://www.nice.org.uk/guidance/cmg40#ftn.footnote_1 [Accessed January 22, 2016].

Nichols, M. et al., 2014. Cardiovascular disease in Europe 2014: Epidemiological update. *European Heart Journal*, 35, pp.2950–2959. Available at: http://eurheartj.oxfordjournals.org/content/35/42/2950.long.

Nielsen, K.M. et al., 2008. Cardiac rehabilitation: Health characteristics and socio-economic status among those who do not attend. *European Journal of Public Health*, 18(5), pp.479–483. Available at: https://academic.oup.com/eurpub/article-lookup/doi/10.1093/eurpub/ckn060.

Noordzij, M. et al., 2009. Study designs in clinical research. *Nephron - Clinical Practice*, 113(3), pp.c218-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19690439 [Accessed July 23, 2017].

Osborne, J.W., 2015. *Best Practices in Data Cleaning: A Complete Guide to Everything You Need to Do Before and After Collecting Your Data*, SAGE. Available at: https://books.google.com/books?id=bzkXBAAAQBAJ&pgis=1 [Accessed August 7, 2017].

Parashar, S. et al., 2012. Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction. *Circulation*, 126(13), pp.1587–1595.

Pavy, B. et al., 2006. Safety of exercise training for cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Archives of internal medicine*, 166(21), pp.2329–34. Available at: http://archinte.jamanetwork.com/article.aspx?articleid=411298 [Accessed January 16, 2016].

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., et al., 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *European Journal of Preventive Cardiology*, 23(11), p.NP1-NP96. Available at: http://journals.sagepub.com/doi/10.1177/2047487316653709 [Accessed May 8, 2017].

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., et al., 2016. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*, 37(29), pp.2315–2381.

Piepoli, M.F. et al., 2016. Challenges in secondary prevention after acute myocardial infarction: A call for action. *European Journal of Preventive Cardiology*, 23(18).

Piepoli, M.F. et al., 2015. Challenges in secondary prevention of cardiovascular diseases: A review of the current practice. *International journal of cardiology*, 180C, pp.114–119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25438230.

Piepoli, M.F.M.F. et al., 2016. Challenges in secondary prevention after acute myocardial infarction: A call for action. *European Journal of Preventive Cardiology*, 23(18), pp.1994–2006. Available at: http://journals.sagepub.com/doi/10.1177/2047487316663873 [Accessed June 27, 2017].

Polgar, S. & Thomas, S.A., 2013. *Introduction To Research In The Health Sciences*,

Polit, D.F. & Beck, C.T., 2012. *Nursing Research: Generating and Assessing Evidence for Nursing Practice*, Wolters Kluwer Health/Lippincott Williams & Wilkins. Available at: http://books.google.com/books?hl=en&lr=&id=Ej3wstotgkQC&pgis=1 [Accessed August 7, 2017].

Al Quait, A. et al., 2017. In the modern era of percutaneous coronary intervention: Is cardiac rehabilitation engagement purely a patient or a service level decision? *European Journal of Preventive Cardiology*, p.204748731771706. Available at: http://journals.sagepub.com/doi/10.1177/2047487317717064.

Al Quait, A. & Doherty, P., 2016. Does cardiac rehabilitation favour the young over the old? *Open Heart*, 3(2), p.e000450. Available at: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2016-000450.

Randolph, J.J., 2009. A Guide to Writing the Dissertation Literature Review. *Practical Assessment, Research & Evaluation*, 14(13), pp.1–13. Available at:

http://lemass.net/capstone/files/A Guide to Writing the Dissertation Literature Review.pdf [Accessed August 16, 2017].

Rauch, B. et al., 2016. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). *European Journal of Preventive Cardiology*, 23(18), pp.1914–1939. Available at: http://eprints.whiterose.ac.uk/106630/ [Accessed July 29, 2017].

Rcr, B. & Project, H., 2008. *Responsible Conduct of Research Toolkit*, Oxford University Press. Available at: https://books.google.co.uk/books?hl=en&lr=&id=dP7oKntCUUUC&oi=fnd&pg=PR9&dq=Shamoo,+A.E.,+Resnik,+B.R.+(2003).+Responsible+Conduct+of+Research.+Oxford+University+Press.&ots=PF-ZO5Jxiu&sig=v3KovhS3QXPjQ_b9wD6U7K0W5Os#v=onepage&q&f=false [Accessed July 31, 2017].

Reges, O. et al., 2013a. Arab-Jewish differences in attending cardiac rehabilitation programs following acute coronary syndrome. *Int J Cardiol*, 163(2), pp.218–219. Available at: https://www.researchgate.net/profile/Noa_Vilchinsky2/publication/229159697_Arab-Jewish_differences_in_attending_cardiac_rehabilitation_programs_following_acute_coronary_syndrome/links/5471a68a0cf2d67fc0345277.pdf.

Reges, O. et al., 2013b. Systemic determinants as barriers to participation in cardiac prevention and rehabilitation services after Acute Coronary Syndrome. *International Journal of Cardiology*, 168(5), pp.4865–4867. Available at: http://dx.doi.org/10.1016/j.ijcard.2013.07.056.

Riley, R.D. et al., 2016. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *Bmj*, 353(mar31_1), p.i3140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27334381%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4916924%5Cnhttp://www.bmj.com/lookup/doi/10.1136/bmj.i3140 [Accessed August 5, 2017].

Rogers, W.H., 1993. Regression standard errors in clustered samples. *Stata Technical Bulletin*, 13(July), pp.19–23. Available at: http://www.stata.com/support/faqs/statistics/stb13_rogers.pdf [Accessed October 18, 2017].

Rosenbaum, P., 2002. *Observational Studies* 2nd ed., Springer. Available at: http://dx.doi.org/10.1007/978-1-4757-3692-2_1 [Accessed July 23, 2017].

Ruano-Ravina, A. et al., 2016. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International Journal of Cardiology*, 223, pp.436–443.

Sagar, V.A. et al., 2015. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart*, 2(1), p.e000163. Available at: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2014-000163.

Saito, M. et al., 2014. Safety of Exercise-Based Cardiac Rehabilitation and Exercise Testing for Cardiac Patients in Japan. *Circulation Journal*, 78 (7), The Japanese Circulation Society., pp.1646–1653. [Online]. Available at: doi:10.1253/circj.CJ-13-1590 [Accessed 11 July 2017].

Sanchis-Gomar, F. et al., 2016. Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of Translational Medicine*, 4(13), pp.256–256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27500157 [Accessed July 29, 2017].

Sanderson, B.K., Shewchuk, R.M. & Bittner, V., 2010. Cardiac Rehabilitation and Women. *Journal of cardiopulmonary rehabilitation and prevention*, pp.12–21.

Sandywell, B., 2011. *Dictionary of Visual Discourse: A Dialectical Lexicon of Terms*, Ashgate. Available at: https://books.google.co.uk/books?id=ZXJ7BgAAQBAJ&printsec=frontcover&dq=Dictionary+of+Visual+Discourse&hl=en&sa=X&redir_esc=y#v=onepage&q=Dictionary of Visual Discourse&f=false.

Sarrafzadegan, N. et al., 2007. Drop-out predictors in cardiac rehabilitation programmes and the impact of sex differences among coronary heart disease patients in an Iranian sample: a cohort study. *Clinical Rehabilitation*, 21(4), pp.362–372. Available at: http://journals.sagepub.com/doi/10.1177/0269215507072193.

Schulz, K.F. et al., 1995. Empirical Evidence of Bias . *JAMA*, 273(5), p.408. Available at: http://xa.yimg.com/kq/groups/20758258/1080166292/name/Evidence+of+Bias_Schulz.pdf [Accessed August 10, 2017].

Schutt, R. & O´neil, C., 2014. *Doing Data Science straight talk*, Available at: https://books.google.co.uk/books?id=vcVKAQAAQBAJ&printsec=frontcover&dq=Doing+Data+Science&hl=en&sa=X&ved=0ahUKEwi_kt6UpbbVAhUFL1AKHa9jD6sQ6AEIKTAA#v=onepage&q=Doing Data Science&f=false [Accessed August 1, 2017].

Seaman, S. et al., 2013. What Is Meant by ‘Missing at Random’? *Statistical Science*, 28(2), pp.257–268. Available at: http://projecteuclid.org/euclid.ss/1369147915 [Accessed August 7, 2017].

Sign 150, 2017. *SIGN 150*, Available at: http://www.sign.ac.uk/assets/sign150.pdf [Accessed December 30, 2017].

Silverman, S.L., 2009. From Randomized Controlled Trials to Observational Studies. *American Journal of Medicine*, 122(2), pp.114–120. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0002934308009522 [Accessed July 24, 2017].

Smith, E., Smith, J. & Jr., 2008. *Using Secondary Data in Educational and Social Research*, McGraw-Hill Education (UK). Available at: https://books.google.com/books?hl=en&lr=&id=qudEBgAAQBAJ&pgis=1 [Accessed December 28, 2015].

Smith, K.M., Harkness, K. & Arthur, H.M., 2006. Predicting cardiac rehabilitation enrollment: the role of automatic physician referral. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, 13(1), pp.60–66. Available at: http://journals.sagepub.com/doi/abs/10.1097/01.hjr.0000186626.06229.7f.

Soo Hoo, S.Y., Gallagher, R. & Elliott, D., 2016. Predictors of cardiac rehabilitation attendance following primary percutaneous coronary intervention for ST-elevation myocardial infarction in Australia. *Nursing & health sciences*, (May 2015), pp.230–237.

Stampfer, M.J. et al., 2000. Primary prevention of coronary heart disease in women through diet and lifestyle. *N.Engl.J.Med.*, 343(1), pp.16–22. Available at: http://www.nejm.org/doi/abs/10.1056/NEJM200007063430103 [Accessed July 5, 2017].

Stang, A., 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, 25(9), pp.603–605. Available at: https://link.springer.com/content/pdf/10.1007/s10654-010-9491-z.pdf [Accessed August 10, 2017].

Sterne, J.A.C. et al., 2016. pitfalls Multiple imputation for missing data in epidemiological and clinical research : potential and pitfalls. *BMJ*, 339(7713), pp.157–160. Available at: http://www.bmj.com/content/338/bmj.b2393 [Accessed August 7, 2017].

Steyerberg, E.W. et al., 2001. Internal validation of predictive models: Efficiency of some procedures for logistic regression analysis. *Journal of Clinical Epidemiology*, 54(8), pp.774–781. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0895435601003419 [Accessed August 5, 2017].

Suaya, J.A. et al., 2007. Use of Cardiac Rehabilitation by Medicare Beneficiaries After Myocardial Infarction or Coronary Bypass Surgery. *Circulation*, 116(15), pp.1653–1662.

Sumner, J., Grace, S.L. & Doherty, P., 2016. Predictors of cardiac rehabilitation utilization in England: Results from the national audit. *Journal of the American Heart Association*, 5(10).

Sumner, J., Harrison, A. & Doherty, P., 2017. The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. *PLoS ONE*, 12(5). Available at: http://eprints.whiterose.ac.uk/116754/ [Accessed July 29, 2017].

Sundararajan, V. et al., 2004. Attendance rates and outcomes of cardiac rehabilitation in Victoria, 1998. *Medical Journal of Australia*, 180(6), pp.268–271. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=38372230.

Tabachnick, B. & Linda Fidell, 2007. Multiple regression. In *Using multivariate statistics*. Boston: Pearson/Allyn & Bacon, pp. 148–167.

Tashakkori, A., 2010. *SAGE Handbook of Mixed Methods in Social & Behavioral Research*, SAGE Publications. Available at: http://methods.sagepub.com/book/sage-handbook-of-mixed-methods-social-behavioral-research-2e [Accessed August 9, 2017].

Thomas, R.J. et al., 2010. AACVPR/ACCF/AHA 2010 update: Performance measures on cardiac rehabilitation for referral to cardiac rehabilitation/secondary prevention services. *Journal of the American College of Cardiology*, 56(14), pp.1159–1167.

Thomas, R.J. et al., 2014. National Survey on Gender Differences in Cardiac Rehabilitation Programs. Patient characteristics and enrollment patterns. *Journal of cardiopulmonary rehabilitation*, 16(6), pp.402–12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8985799.

Thompson, A.E. et al., 2016. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. *BMC Family Practice*, 17(1), p.38. Available at: http://bmcfampract.biomedcentral.com/articles/10.1186/s12875-016-0440-0.

Thompson, D.R. et al., 1996. Cardiac rehabilitation in the United Kingdom: guidelines and audit standards. National Institute for Nursing, the British Cardiac Society and the Royal College of Physicians of London. *Heart*, 75(1), pp.89–93. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=8624882%5Cnhttp://imp-primo.hosted.exlibrisgroup.com/openurl/44IMP/44IMP_services_page?sid=OVID&isbn=&issn=1355-6037&volume=75&issue=1&date=1996&title=Heart&atitle=Cardiac+rehabi [Accessed July 14, 2017].

Thompson, D.R., 1998. The development of a programme of research in cardiac rehabilitation. *International Journal of Nursing Studies*, 35((199X) 72-78), pp.72–78. Available at: http://ac.els-cdn.com/S0020748998000042/1-s2.0-S0020748998000042-main.pdf?_tid=2041d07c-6873-11e7-8c14-00000aab0f01&acdnat=1500023113_11276990451435a173be5849c2b6c698.

Thompson, P.D. et al., 2007. Exercise and acute cardiovascular events: Placing the risks into perspective a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*, 115(17), pp.2358–2368. Available at: http://scholarcommons.sc.edu/ [Accessed July 11, 2017].

Thygesen, K. et al., 2012. How to use high-sensitivity cardiac troponins in acute cardiac care. *European Heart Journal*, 33(18), pp.2252–2257. Available at: http://eurheartj.oxfordjournals.org/cgi/doi/10.1093/eurheartj/ehs154.

Thygesen, K. & Searle, J., 2013. Update on the Universal Definition of Acute Myocardial Infarction in the Light of New Data. *Conference Papers in Medicine*, 2013, pp.1–5. Available at: http://www.hindawi.com/cpis/medicine/2013/479352/.

Timmis, A., 2015. Beta blockers - British Heart Foundation. Available at: https://www.bhf.org.uk/heart-matters-magazine/medical/drug-cabinet/beta-blockers [Accessed December 22, 2015].

Townsend, N. et al., 2015. *Cardiovascular Disease Statistics 2014*, London.

Tukey, J.W., 1962. The Future of Data Analysis. *The Annals of Mathematical Statistics*, 33(1), pp.1–67. Available at: http://www.jstor.org/stable/2237638 [Accessed August 1, 2017].

Turk-Adawi, K.I. et al., 2014. Cardiac Rehabilitation Enrollment Among Referred Patients. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 34(2), pp.114–122.

Turk-Adawi, K.I. et al., 2013a. Cardiac rehabilitation patient and organizational factors: What keeps patients in programs? *Journal of the American Heart Association*, 2(5).

Turk-Adawi, K.I. et al., 2013b. Cardiac rehabilitation patient and organizational factors: What keeps patients in programs? *Journal of the American Heart Association*, 2(5), pp.1–9.

Turk-Adawi, K.I. et al., 2013c. Cardiac rehabilitation patient and organizational factors: What keeps patients in programs? *Journal of the American Heart Association*, 2(5). Available at: http://jaha.ahajournals.org/content/2/5/e000418.

Varenne, O. & Hemery, Y., 2008. Cardiologie interventionnelle. *La Revue du praticien*, 58(14), pp.1549–1557. Available at: http://cat.inist.fr/?aModele=afficheN&cpsidt=20667905 [Accessed July 16, 2015].

Vartanian, T.P., 2011. *Secondary data analysis*, Oxford University Press. Available at: https://books.google.co.uk/books?hl=en&lr=&id=KKh1Q_OuKqIC&oi=fnd&pg=PR7&dq=+Secondary+Data+Analysis&ots=sneHMew4JR&sig=Pa1mr6ckN8Mf8Ohx-vDhWijCKTc#v=onepage&q=Secondary Data Analysis&f=false [Accessed October 9, 2017].

Verhagen, A.P. et al., 2001. The art of quality assessment of RCTs included in systematic reviews. *Journal of Clinical Epidemiology*, 54(7), pp.651–654. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0895435600003607 [Accessed August 10, 2017].

Wells, G. et al., 2013. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. *Research Synthesis Methods*, 4(1), pp.1–11. Available at: http://doi.wiley.com/10.1002/jrsm.1068.

Wells, G.A. et al., 2013. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Research Synthesis Methods*, 4(1), pp.63–77.

Wenger, N.K., 2008. Current Status of Cardiac Rehabilitation. *Journal of the American College of Cardiology*, 51(17), pp.1619–1631.

West, R.R., Jones, D.A. & Henderson, A.H., 2012. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart*, 98(8), pp.637–644. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2011-300302 [Accessed July 12, 2017].

Whitehurst et al., 2006. Treatment of hypertension. Available at: https://www.google.com/patents/US7155284 [Accessed December 22, 2015].

Whiting, P. et al., 2003. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 3(1), p.25. Available at: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-3-25 [Accessed August 10, 2017].

WHO, 2011. WHO _ Cardiovascular diseases (CVDs). *Cardiovascular diseases (CVDs)*. Available at: www.who.int/mediacenter/factsheets/fs317en/. [Accessed July 16, 2017].

WHO, 2015. WHO | Cardiovascular diseases (CVDs). Available at: http://www.who.int/mediacentre/factsheets/fs317/en/ [Accessed December 23, 2015].

WHO, 2014. WHO | Risk factors. *Who*. Available at: http://www.who.int/topics/risk_factors/en/ [Accessed July 7, 2017].

Wilkins, E. et al., 2017. European Cardiovascular Disease Statistics 2017 edition. *European Heart Network, Brussels*, p.192.

Williams, R.L., 2000. A Note on Robust Variance Estimation for Cluster-Correlated Data. *Biometrics*, 56(2), pp.645–646. Available at: http://doi.wiley.com/10.1111/j.0006-341X.2000.00645.x [Accessed October 18, 2017].

Windecker, S. et al., 2014. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) * Developed with the special contributio. *European Heart Journal*, 35, pp.2541–2619. Available at: http://eurheartj.oxfordjournals.org/cgi/doi/10.1093/eurheartj/ehu278.

Wood, A.M., White, I.R. & Thompson, S.G., 2004. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals_Read **. *Clinical Trials*, 1(4), pp.368–376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16279275 [Accessed August 7, 2017].

Worcester, M.U.C. et al., 2004. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, 11, pp.328–335.

Yohannes AM, Yalfani A, Doherty P, B.C., 2007. Predictors of drop-out from an outpatient

cardiac rehabilitation programme. *Clin Rehabil.*, 21(3), pp.222–9.