Depression in Cardiac Rehabilitation

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Abstract

Aim: History of comorbid depression (HCD) and new onset depressive symptoms following cardiac event are associated with adverse cardiac events and increased mortality. The purpose of this thesis is to investigate the factors associated with depressive symptoms in patients with HCD and patients with new onset depressive symptoms at baseline cardiac rehabilitation (CR) assessment. In addition, it is also aimed to examine which baseline characteristics determine improvement in depression levels following CR in depressed patients with and without a HCD.

Methods: Observational studies using routine clinical data from National Audit of Cardiac Rehabilitation were conducted following a critical review of the literature that identify the known determinants of depression in patients with cardiovascular disease. Logistic regression models were constructed to identify determinants of depressive symptoms measured by hospital anxiety and depression scale (HADS). A survey of CR centres also investigated the extent of psychosocial support offered to CR patients.

Results: Around 45% of patients with HCD experienced high levels of depressive symptoms at the start of CR whereas this percentage was around 20% in patients with new onset depression. In patients with HCD, the determinants of reduced likelihood of improvement in depression levels following CR were; smoking, physical inactivity, higher total number of comorbidities, male gender and HADS anxiety score, aligned with the findings of critical review. For those patients with new onset depression the key determinants were; comorbidities of emphysema, stroke, angina, diabetes, higher total number of comorbidities, HADS anxiety score, physical inactivity, and smoking.

Conclusion: The baseline characteristics of the patients determining depression outcome following CR has been identified in patients with HCD and patients with new onset depressive symptoms. In order to optimise outcome these patient groups need to be assessed adeptly accounting for their complex multimorbid condition and psychosocial risk factors.

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Author's Declaration

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

- **The articles published from this thesis**

1. Sever, S., Golder, S. and Doherty, P. (2018). Factors associated with acute depressive symptoms in patients with comorbid depression attending cardiac rehabilitation. BMC Cardiovascular Disorders, 18 (230), pp.1–8.
2. Sever, S. et al. (2019). Determinants of depression in patients with comorbid depression following cardiac rehabilitation. Open Heart, 6 (e000973).
3. Sever, S. et al. (2019). To what extent is multi-morbidity associated with new onset depression in patients attending cardiac rehabilitation? BMC Cardiovascular Disorders, 19 (256), pp.1–9.

- **Congress presentations**

1. Sever, S. et al. (2019). P302 Determinants of depression in patients with comorbid depression following cardiac rehabilitation. In: ESC Preventive Cardiology (Formerly EuroPrevent). 2019. Lisbon.
2. Sever, S. et al. (2019). Do comorbidities determine the improvement in depression in patients with new onset depressive symptoms following cardiac rehabilitation? In: BACPR Annual Conference. 2019. Nottingham. (Oral presentation, new investigator award received).
3. Sever, S. et al. (2020). What are the baseline patient characteristics that determine improvement in depression following CR in patients with new onset depressive symptoms? In: ACRA online ASM. 2020. (abstract has been accepted for an oral presentation).

Chapter 1: Introduction

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is an overarching term applied to all heart and circulation related diseases, including coronary heart disease (CHD), myocardial infarction (MI), angina, heart valve disease, cardiomyopathy, heart failure (HF), congenital heart disease and stroke (BHF, 2020; Timmis et al., 2020).

CVD is one of the non-communicable diseases with the highest mortality rate. WHO figures recorded around 17.9 million deaths worldwide in 2016 from CVD (WHO, 2017b). Moreover, in Europe, CVD is responsible for over 3.9 million deaths a year, accounting for 45% of all deaths (Wilkins et al., 2017). In the UK, it was the cause of 167,116 deaths in 2018, equating to 27% of all deaths that year (BHF, 2020). In addition, the most recent European Society of Cardiology (ESC) cardiovascular statistics report states that 108.7 million people are living with CVD in its 54 member countries (Timmis et al., 2020).

Globally, CVD demands a huge proportion of national healthcare budgets (Timmis et al., 2020; Benjamin et al., 2019; BHF, 2020; Wilkins et al., 2017). According to recent data in the European Society of Cardiology (ESC) report, the total annual cost of CVD to the EU economy is estimated to be €210 billion a year (Timmis et al., 2020; Wilkins et al., 2017). In the USA, the direct and indirect cost of CVD between 2014 and 2015 was $351.2 billion (Benjamin et al., 2019). In addition, the economic burden of CVD in the UK is estimated to be £9 billion each year, and this number rises to £19 billion if premature deaths and disabilities are included (BHF, 2020). All the statistics given above elucidate the significance of CVD and other associated medical diagnoses.

As mentioned earlier, CVD refers to all heart and circulation related diseases (BHF, 2020). The most common CVD is coronary heart disease (CHD) which is also referred to as coronary artery disease (CAD) or ischemic heart disease (IHD). It often occurs due to insufficient blood supply as a consequence of atherosclerosis (a build-up of fatty

plaque on the inner wall of the coronary artery) (BHF, 2020). Myocardial infarction (MI) (heart attack) is the most common presentation of CHD. During MI, coronary fatty plaque ruptures leading to a blood clot, which blocks the arterial blood flow with the result that the myocardium (heart muscle) lacks oxygen, eventually causing cell and tissue death in the myocardium (ischemia) (Lu et al., 2015).

Patients who have narrowed coronary arteries (stenosis) may require revascularisation to remove blockages or bypass them. Many patients undergo surgical procedures for revascularisation in the form of percutaneous coronary intervention (PCI) (angioplasty and stenting) or coronary artery bypass graft (CABG) (Neumann et al., 2019). PCI involves insertion of a catheter thorough the circulatory system; when it reaches the blockage at the effected site, either a balloon is inflated or a stent inserted into the artery to prevent plaque reforming or arterial collapse (Lu et al., 2015). CABG is another revascularisation procedure that requires grafting of an alternative blood vessel (often taken from the patient's leg or another part of their body) onto the coronary artery, thereby re-routing the blood flow and bypassing the blocked area (Alexander and Smith, 2016).

In the current thesis, CVD will be used as a general term to describe cardiac patients. However, when reporting information from other papers, the original author(s)' choice of definition will be respected and used **(Appendix -1)**.

1.1.1 CVD risk factors

A risk factor is a characteristic which increases the possibility of contracting a disease. The risk factors for CVD are: high blood pressure, smoking, diabetes, high blood cholesterol, inactivity, obesity, depression, ethnicity, gender, age, and a family history of heart disease (Timmis et al., 2020; Benjamin et al., 2019; Timmis et al., 2017; Mozaffarian et al., 2016; Rapsomaniki et al., 2014). These risk factors are categorised as either modifiable or non-modifiable. Modifiable risk factors are those that can be changed or controlled if positive improvements are, whereas non-modifiable risk factors

cannot be changed (Bath et al., 2009). Modifiable risk factors for CVD are; smoking, high cholesterol, obesity, high blood pressure, excess alcohol intake, physical inactivity and diabetes (Timmis et al., 2020; Benjamin et al., 2019). On the other hand, non-modifiable risk factors are; age, gender, ethnicity and family history (Bath et al., 2009). In addition to other modifiable risk factors, depression is recognised as a modifiable risk factor for CVD in recent European guidelines and its treatment is emphasized (Piepoli et al., 2016). Therefore, depression is particularly important and a subject of interest in the following thesis, as a means to modify and reduce the risk of further adverse cardiac incidents.

1.2 Depression and CVD

CVD and depression have a significant impact on service utilisation and medical costs (Baumeister et al., 2015). World Health Organisation (WHO, 2020) describes depression as a serious depressed mood accompanied by an inability to continue routine daily activities which continues for two or more weeks. According to the National Institute for Heath and Care Excellence (NICE, 2009) depression guideline, depression symptoms are reported to be low mood, loss of pleasure in activities, fatigue, changes in appetite, distorted concentration and sleep disturbance.

Depression is an extremely common condition, affecting 322 million people worldwide, having increased 18.4% between 2005 and 2015 (WHO, 2017a). The proportion of the general population with depression was estimated to be 4.4% in 2015 across the world (WHO, 2017a). Moreover, depression accounts for 40.5% of disability adjusted life years caused by mental health problems during a lifetime (Whiteford et al., 2013).

According to a systematic review the reported prevalence of depression in the cardiac population varies according to the assessment methods used; for instance, clinical assessments have revealed MI patients who meet DSM-IV criteria (this was updated to DSM-V by the American psychiatric association in 2013) for major depression was 15% to 20%, and this proportion rises when considering elevated depression symptoms as

is assessed by self-administered questionnaires (Thombs et al., 2006). Although depression is common among CVD patients, there is a bidirectional relationship in which either CVD leads to depression or depression leads to CVD (Teismann et al., 2014). Furthermore, a recent study has confirmed the bidirectional association of depression and CVD (Wium-Andersen et al., 2019).

Depression has been the focus of most studies as a psychosocial risk factor for CVD which is also emphasized in several literature reviews (Bradley and Rumsfeld, 2015; Elderon and Whooley, 2013; Kent and Shapiro, 2009). Recent prognostic studies reveal depression to be associated with increased risk of adverse cardiac outcomes (Hawkins et al. 2014; Huang et al. 2013; Brown et al. 2011), and mortality among different cardiac populations (Kozela et al., 2016; Frasure-Smith et al., 2009; Sherwood et al., 2007).

The evidence suggests depression is one of the most common psychosocial problems, and it is an independent risk factor for recurrence of cardiac events, cardiac-related mortality (Lichtman et al., 2014; Meijer et al., 2011), and all-cause mortality (Sokoreli et al., 2016; Stenman, Holzmann and Sartipy, 2016; Meijer et al., 2013, 2011). Another systematic review of observational studies has demonstrated that increased rates of depression worsen the CVD prognosis (Nicholson, Kuper and Hemingway, 2006). A similar association has been reported in other studies in HF patients (Rutledge et al., 2006) and in CHD patients (De Miranda Azevedo et al., 2014).

Some meta-analyses has shown that patients with depression were nearly twice as likely to have repeat cardiac events after 1-2 years (Nicholson, Kuper and Hemingway, 2006; Rutledge et al., 2006; Barth, Schumacher and Herrmann-Lingen, 2004; van Melle et al., 2004). However, although the more recent meta-analysis have supported this association, the risk could be smaller than previously suggested (Gan et al., 2014). Nevertheless, as can be seen from a variety of studies, the risk of depression on cardiac events is evident (Stenman, Holzmann and Sartipy, 2016; Lichtman et al.,

2014; Meijer et al., 2013, 2011). Therefore, depression is one of the most important indicators of psychosocial health that need to be treated in reference to CVD (BACPR, 2017; SIGN, 2017; Piepoli et al., 2016).

1.2.1 Assessment of depression

Commonly used tools for the clinical diagnosis of depression are; Diagnostic and Statistical Manual of Mental Disorders five (DSM-V) (APA, 2013), which is commonly used by the USA and International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1992) around the world. ICD-10 classifies depression symptoms as poor appetite, problems in sleeping, disturbance in concentration, low mood or sadness, fatigue, suicidal thoughts, reduced activity and decreased self-esteem (WHO, 1992).

Although ICD-10 and DSM-V are used for the diagnosis of depression by clinical psychologists and physicians through clinical interview, alternative validated and standardized self-administered questionnaires can be used for the assessment of depressive symptoms in CVD patients such as Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), Patients Health Questionnaire (PHQ-9) (Gilbody et al., 2007), and Becks Depression Inventory (BDI) (Lahlou-Laforêt et al., 2015; Beck, Steer and Carbin, 1988). Rather than being diagnostic tools, these questionnaires assess the level of depressive symptoms as reported by patients (Davidson, Rieckmann and Rapp, 2005). The specificity and validity of HADS and PHQ-9 assessment tools has been found to be good and similar among CHD patients (Stafford, Berk and Jackson, 2007). Therefore, HADS will be the assessment tool focused to identify depression symptoms in the following thesis. It has been widely used by several cardiac rehabilitation (CR) programmes across the UK for several years, and is referenced in the recent National Audit of Cardiac Rehabilitation (NACR) (NACR, 2019). Furthermore, HADS was also employed in the most recent clinical trial of CR and depression, namely the PATHWAY trial (Wells et al., 2018). HADS is a validated tool for screening depression symptoms among cardiac patients in various

countries (Wang, Lopez and Martin, 2006; Spinhoven et al., 1997; Zigmond and Snaith, 1983).

1.2.2 Management of depression

Although depression is associated with CVD, the possible mechanisms linking depression with poorer outcomes remains uncertain in the literature (Vaccarino et al., 2019). Nevertheless, depression and related cardiac outcomes should be recognized and managed in CVD patients to prevent further events and improve quality of life (Vaccarino et al., 2019; Lichtman et al., 2014). Depression is a modifiable risk factor which may benefit from cardiac management (Vaccarino et al., 2019; Piepoli et al., 2016; Lichtman et al., 2014). Therefore, depressed CVD patients are managed with CR programmes, psychological therapies such as cognitive behavioural therapy (CBT), behavioural activation (BA), pharmacological treatment (antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) for CVD patients), and exercise (Richards et al., 2017; Whalley, Thompson and Taylor, 2014; Hare et al., 2014).

The ENRICHD (the Enhancing Recovery in Coronary Heart Disease Patients) trial is one of the largest behavioural trials to date, and included 2481 MI patients (1238 patients were assigned to treatment arm and 1243 in control arm) (Berkman et al., 2003). It investigated the effectiveness of CBT for improving depression, cardiac morbidity and mortality outcomes. Although the intervention improved depressive symptoms, there was no improvement in recurrent MI, cardiac mortality and all-cause mortality when compared to usual care (Berkman et al., 2003).

Although psychological therapies and antidepressants reduce the symptoms of depression, uncertainty remains in terms of their association with cardiac mortality, recurrent cardiac events and all-cause mortality (Richards et al., 2017; Rutledge et al., 2013; Baumeister, Hutter and Bengel, 2011). Besides, psychotropic medications may not be useful for all patients, as they have unfavourable side effects (Coupland et al., 2011). Furthermore, the most recent Cochrane Review, conducted by Richards et al.

(2017), questioned the efficacy of psychological interventions. Similarly, another systematic review has shown publication bias might inflate the efficacy of psychological treatments for major depression (Driessen et al., 2015). Therefore, alternative treatment approaches to depression are required. The literature has demonstrated that CR and exercise could comprise a viable alternative approach (Zheng et al., 2019; Schuch et al., 2016; Rutledge et al., 2013).

CR programmes and general aerobic exercise do increase cardiovascular fitness and reduce depression (Zheng et al., 2019; Schuch et al., 2016; Rutledge et al., 2013). One possible explanation for this could be that structured exercise is the main component in CR programmes, therefore reductions in depression symptoms might relate to this. Indeed, exercise in the general population has been found to be reduce depressive symptoms in some meta-analyses (Schuch et al., 2016; Josefsson, Lindwall and Archer, 2014; Danielsson et al., 2013). In the following section, CR programmes and their association to depression management will be further explained.

1.3 Cardiac rehabilitation

The definition of CR in the most recent British Association for Cardiovascular Prevention and Rehabilitation (BACPR) guideline is:

“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).

CR programmes in the UK are mainly group-based multicomponent programmes which include structured exercise training as one of the main components, and are considered an evidence-based treatment able to prevent further cardiac events and improve patients’ quality of life (Salzwedel et al., 2020; BACPR, 2017; SIGN, 2017; Piepoli et al., 2016; Anderson et al., 2016; Rauch et al., 2016) . CR programmes are

also cost effective (Shields et al., 2018). CR programmes aim to recruit patients with CVD following a heart event (BACPR, 2017; SIGN, 2017; Piepoli et al., 2014), and are crucial for providing secondary prevention to them (Lavie, Arena and Franklin, 2016; Dalal, Doherty and Taylor, 2015; Menezes et al., 2014). They combine several interventions, as required and tailored to the needs of individuals. These interventions have been reported in several position statements and guidelines for secondary prevention in the UK, Europe, Australia and the USA as: risk factor management (hypertension, obesity, diabetes mellitus, smoking, and high cholesterol), exercise training, nutritional counselling and psychosocial status management (BACPR, 2017; SIGN, 2017; Woodruffe et al., 2015; Piepoli et al., 2014; Hamm et al., 2011; Piepoli et al., 2010).

Patients recovering from an acute cardiac illness need support and knowledge to maintain their health, recover from the physical and psychosocial effects of cardiac event and reduce risk of further events which could be achieved participating CR (BACPR, 2017; SIGN, 2017; Woodruffe et al., 2015; Piepoli et al., 2014; Hamm et al., 2011; Piepoli et al., 2010). In addition to the traditional component of exercise, health education, risk factor modification and the management of psychosocial status are incorporated into modern CR programmes. Moreover, education programmes aim to support patients and improve their knowledge of cardiac risk factors and their appropriate management strategies (Dalal, Doherty and Taylor, 2015). Accordingly, CR programmes often serve as a starting point for encouraging patients to adhere to healthy lifestyles for life.

The effectiveness of CR has been widely debated throughout the last decade, especially in terms of all-cause mortality. Systematic reviews by Heran et al. (2011) and Lawler et al. (2011) revealed that CR has been effective at reducing recurrent cardiac events, cardiac mortality and all-cause mortality. Nevertheless, there was a much broader debate after the RAMIT trial was published in 2012 which recruited patients between 1997 and 2001 (West, Jones and Henderson, 2012). Researchers

have argued that advancing medical treatments meant that there were no differences in the overall-mortality rates of the patients who received CR and control groups. They concluded that CR is not effective in terms of not only for overall mortality, but also for cardiac morbidity, psychosocial state, risk factors and health related quality of life (HRQoL) (West, Jones and Henderson, 2012). The RAMIT trial has been widely criticised in terms of its methodology and recruitment problems, and for not having a CONSORT diagram, among other limitations (Lewin and Doherty, 2013; Doherty and Lewin, 2012). However, the findings from the most recent Cochrane review undertaken on exercise-based CR have shown that CR is effective, despite the findings included in the analysis of RAMIT RCT (Anderson et al., 2016). Anderson et al. (2016) included 63 RCTs with nearly 14,500 participants and 12-month median follow up. The results showed that CR is effective for reducing cardiac mortality, hospital admissions and improving HRQoL. However, there was no significant effect on overall mortality reported (Anderson et al., 2016). Possibly, the inclusion of the RAMIT trial in this systematic review could have impacted overall mortality. Similar results were seen in HF patients in another systematic review (Sagar et al., 2015).

Meanwhile, a recent systematic review of Rauch et al. (2016), cardiac rehabilitation outcome study (CROS-I), designed to investigate the effectiveness of CR in the modern era included not only RCTs, but also controlled cohort studies providing real life data. The inclusion criteria was set to encompass the modern era, including studies dated after 1995 only, after acute revascularisation and statin therapy had been established, and only multicomponent CR programmes with more than one component at least. 24 controlled cohort studies and 1 RCT were included with nearly 200.000 participants. The only RCT included was the RAMIT trial. Despite including this, the overall results of the review found CR is associated with reduced all-cause mortality (Rauch et al., 2016). Furthermore, recent cohort studies from the Netherlands, Germany and the USA have also shown an association between CR and reduced all-cause mortality (De Vries et al., 2015; Rauch et al., 2014; Pack et al., 2013).

A recent systematic review by Powell et al. (2018) aimed to investigate the effectiveness of exercise based CR on hospital admission, cardiovascular mortality, and all-cause mortality. 22 RCTs published after the year 2000, involving 4834 participants (mean age 59.5, 78.4% male) were included in their analysis. The results revealed no difference between exercise-based CR and no exercise for all-cause mortality and cardiovascular mortality. However, there was a small reduction in hospital admissions. This study has been criticised in terms of its quality by leading authorities including the Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR), the British Association for Cardiovascular Prevention and Rehabilitation (BACPR), and the International Council of Cardiovascular Prevention and Rehabilitation (Grace, Ghisi and Chessex, 2018; Cowie et al., 2018; Buckley et al., 2018). Firstly, judging the effectiveness of CR based on mortality alone may not be appropriate. Secondly, in this systematic review there was a lack of analysis measuring patient's compliance with exercise, which may have impacted on fitness and thereby morbidity and mortality. Thirdly, in developing countries the value of CR and lifestyle interventions has been questioned as programmes may not have well structured, to include modern medical approaches to prevent CVD (Grace, Ghisi and Chessex, 2018; Cowie et al., 2018; Buckley et al., 2018). Moreover, in Powell et al.'s (2018) study, there were generally short follow up periods, which may explain the apparent lack of effect on mortality. Taylor et al. (2017) found that long-term participation (above 36 months) in a supervised CR within a community-based maintenance programme is associated with improved survival rates. Although this might explain the mortality result, drawing a definitive conclusion that CR is not effective only based on mortality would be misleading.

The most recently published systematic review of CROS-II study (update of CROS-I), on the other hand, investigated the effectiveness of comprehensive CR and found significantly reduced total mortality after CR participation, which was the primary end point (Salzwedel et al., 2020). A total of 31 studies (19 retrospective controlled cohort

studies, nine prospective controlled cohort studies and three randomised controlled trials (RCTs), with follow-up periods ranging from 9 months to 14 year) and 228,337 patients were included in this meta-analysis. Although the effectiveness of CR in routine clinical practice was confirmed, emphasis was placed on the pressing need to define international standards for programme delivery (Salzwedel et al., 2020). Furthermore, the inclusion of registry based studies with the strictly applied aforementioned CROS criteria might be deemed more useful for clinical decision-making in the modern era.

In summary, CR is effective at reducing the risk of morbidity, mortality, and modifying cardiac risk factors. In addition, it has further benefits overall for improving patients' quality of life. In accordance, the European Society of Cardiology guideline recommends that cardiac patients participate in CR programmes to improve patient outcomes (Class 1 level A recommendation) (Piepoli et al., 2016).

A meta-analysis has shown CR reduces depression and recurrent cardiac events similar to psychological treatments (Rutledge et al., 2013). However total mortality reduction has only been observed with CR. Thus, CR appears to be ideal option for the management of depression in CVD patients. This study is particularly significant for this thesis, because its focus is on depression in CR. Another meta-analysis of Gellis & Kang-Yi (2012) investigated the effectiveness of CR on depression symptoms in 64 years old and older population. 18 RCTs were included in this study, with approximately 1900 participants in each treatment and control arm. The results have shown that CR, delivered in both home based settings and outpatient clinics, significantly reduced the depression symptoms in old CVD patients. However, caution is required here, as the majority of the trials included home based CR and only three trials were conducted in outpatient clinics and another three combined both outpatient clinic and home based interventions (Gellis & Kang-Yi, 2012). On the other hand, a recent observational study has shown that mode of delivery does not appear to determine depression outcomes when comparing supervised and self-delivered CR

(Harrison and Doherty, 2018). Therefore, we may consider self-delivered CR programmes to have a positive impact on depression outcomes as well as supervised CR programmes.

A British cohort study by Yohannes et al. (2010) examined the long-term impact of a six-week CR programme on depression. They found that CR was beneficial for improving depression and quality of life outcomes, and this even continued to be the case 12 months later. The findings of another American cohort study was in line with this (Silberman et al., 2010). The study investigated the impact of CR programmes by recruiting nearly 3000 individuals from 24 socioeconomically diverse locations. Measurements were taken at baseline, 12 weeks and a year after. The findings revealed significant improvements with regard to depression at 12 weeks and after 1 year (Silberman et al., 2010). Another study retrospectively assessed the impact of CR on depression and long term mortality (1296$\pm$551 mean follow up) (Milani and Lavie, 2007). In total, 701 CHD patients included 522 patients in the study, all of whom completed cardiac rehabilitation were compared to a non-random sample of 179 patients who dropped out within 2 weeks (attending < 5 sessions of CR). Two thirds of the patients with initial depression symptoms no longer had these symptoms at the end of the CR period (reduced from 17% on entry to 6% following CR). The patients with depressive symptoms who completed the CR programme had a significantly lower mortality rate (73%) than the patients who dropped out (8% compared to 30%). Therefore, recommendations have been made to assure that depressed CVD patients are referred and attend CR (Milani and Lavie, 2007).

CR programmes are multicomponent which means they are more than just exercise therapy, the importance of which was shown earlier (Salzwedel et al., 2020; BACPR, 2017; SIGN, 2017; Piepoli et al., 2016; Anderson et al., 2016; Rauch et al., 2016). For instance, the education component within CR may contribute to patients' psychological state and alter their perspective with regard to CVD by explaining misconceptions (Woodruffe et al., 2015; Piepoli et al., 2014; Hamm et al., 2011). This may also improve

patients' ability to cope with illness, as well as their psychosocial recovery, thereby empowering them (Pogosova et al., 2015). Moreover, a group based approach is largely applied in CR programmes (NACR, 2019) and may contribute to attendants' socialisation with other patients and improve upon their depression state (Pogosova et al., 2015).

Although CR is effective at reducing depressive symptoms (Zheng et al., 2019; Rutledge et al., 2013; Gellis and Kang-Yi, 2012), some patients remain depressed after CR. According to Lavie et al. (2007), the mortality rates of patients who continued to suffer from depression after receiving CR was four times higher than in participants who did not present with any depressive symptoms after the programme. Therefore, patients who are unlikely to show improvements in depression outcomes following CR must be carefully observed and managed. An emerging hypothesis for the presented thesis is that patients with comorbidity depression could comprise part of this patient group. Some studies have found that a comorbid history of depression is a risk factor for CVD patients to experience persistent depression post-hospitalisation (Lesperance, Frasure-Smith and Talajic, 1996). Investigation of this particular group seems to be vital to uncovering the factors associated with persistent depression among patients with a comorbid history of depression undergoing CR.

The present thesis aimed to focus on the role of patient and CR service characteristics in determining depression severity, prior to and following CR among patients with a comorbid history of depression and in patients who present with new onset depressive symptoms. This new knowledge could assist clinical teams to better tailor CR to those patient groups with the potential to improve depression outcomes in these populations. The CR literature showed the value of CR programmes for reducing depression symptoms and mortality (Anderson et al., 2016; Rauch et al., 2016; Rutledge et al., 2013; Gellis and Kang-Yi, 2012). However, few studies have ever considered comorbid history of depression and new onset depressive symptoms.

1.4 Comorbidities in CVD

The expansion of the ageing population in recent years has resulted in an increased number of comorbidities prevalent in people with CVD, with a concomitant need for addressing the impact of comorbidities in cardiac patients (Uhlig et al., 2014). According to NACR data, CR programmes managed 17,753 patients with comorbidities in 2006 (NACR, 2007), rising to nearly 46,000 with 2 or more comorbidities in 2019 (NACR, 2019). The most common comorbidities in CVD patients have been shown to be hypertension, hyperlipidaemia, diabetes mellitus, arthritis, anaemia and depression (Arnett et al., 2014). Although depression is in the lower sequence compared to these comorbidities, its prevalence is significantly increasing every year (WHO, 2017a). Therefore, the management of comorbidity depression becomes important in the CR context. Furthermore, patients with comorbid depression are reportedly less physically fit at baseline CR according to a recent NACR study (Doherty, Harrison and Hossain, 2019).

The management of patients with multiple comorbidities is more difficult than that of patients with single disease which increases the complexity for health care professionals to not only assess clinical outcomes in these individuals, but also manage their health condition (Arnett et al., 2014). Therefore, risk factors and clinical outcome management are becoming increasingly significant for patients with comorbid conditions (Uhlig et al., 2014). In addition, a recent Slovenian study has shown that comorbidities were one of the most important factors associated with quality of life in CHD patients (Tušek-Bunc and Petek, 2016). More studies are needed to enlighten the health care providers about the impact of comorbidities to assist clinicians; however, this is not easily achieved by the tendency of clinical trials to exclude patients with comorbidities (Cherubini et al., 2011). Therefore, in the current thesis observational studies will be conducted to investigate patients with multi-comorbidities.

The importance of including patients with multiple comorbidities has also been emphasised by other researchers in the context of CR (Listerman et al., 2011). Brown et al. (2009) examined the predictors of CR referral in CHD patients. American Heart Association's data has been used for the analysis. The study included approximately 73,000 patients from 156 hospitals. The findings showed that increased comorbidities were associated with reduced CR referral. However, a cohort study by Listerman et al. (2011) demonstrated that aged CHD patients with multiple comorbidities benefited from CR. Therefore, recommendations have been made that aged populations with multiple comorbidities be included in CR programmes. Similarly, another study has shown that CR attenders were more likely to be men, younger and with fewer comorbidities (Witt et al., 2004). Thus, there is a necessity to deliberately recruit patients with multi-comorbidities and females for CR. It is an aim of the present thesis to include more multi-comorbid and female population compared to other studies.

More specifically, there is no previous study that has examined patients with a comorbid history of depression or patients with new onset depressive symptoms in CR setting. Therefore, the present thesis will be unique, as it will be the first to investigate the baseline characteristics and determinants of depression in patients with a comorbid history of depression, and in patients with new onset depressive symptoms in CR programmes. Therefore, the results of the planned studies, within this thesis, are relevant to present day clinical challenges, and have the potential to inform clinical practice significantly.

1.4.1 Comorbid depression

Comorbid depression could have implications which affect the prognosis of CVD patients (Albert et al., 2009; Nicholson, Kuper and Hemingway, 2006). In addition, it is highly possible that a prior episode of depression may also influence post heart event depression levels (Lesperance, Frasure-Smith and Talajic, 1996), and perhaps depression levels after CR. Despite clear implications, the management of depression symptoms through CR, the comorbid history of depression and its potential role in

recovery has not been studied in CVD patients in a CR setting. Although comorbid depression is more frequently investigated in psychology literature, there is very limited evidence pertaining to the comorbid history of depression in the CVD population and perhaps none in a CR setting. Therefore, the present study will provide an original contribution to the literature by enlightening the baseline characteristics of patients with a comorbid history of depression, and that in patients with new onset post heart event depressive symptoms in the CR population and the determinants of depression outcomes in these populations.

A previous study highlighted the significance of identifying CVD patients with comorbid depression. Lesperance et al. (1996) was first to examine the prognostic impact of previous depression among 222 MI patients. The findings of this study revealed that a comorbid history of depression increases the risk of depression in the hospital and after discharge. Patients were assessed with a Diagnostic Interview Schedule and Beck Depression Inventory at 1 week, 6 months and 12 months after MI. Additionally, patients with recurrent depression have been found to be at increased risk of mortality at 18 months, compared to patients experiencing their first episode of depression. The findings of this study emphasized the need for treating MI patients with depression comorbidity.

Albert et al. (2009) examined comorbidity depression and clinical outcomes in heart failure patients in hospital settings. A total of 48612 individuals from nearly 260 different hospitals were included in the study, and comorbid depression was present in 10.6% of the population. The results showed that patients with comorbid depression were less likely to be referred to outpatient management programmes, and the duration of their hospital stays was longer. In addition, their post-discharge mortality rates at 60 to 90 days were also higher (Albert et al., 2009). The study was conducted in a hospital setting, so exploring comorbid depression in a CR setting, focusing on what determines depression outcome in patients with a comorbid history of depression remains important.

Denus et al. (2004) observed that a comorbid history of depression was associated with poor in-hospital outcomes and higher mortality rates for heart failure patients. However, this observational, single-centred study focused only on heart failure patients in a hospital setting. Due to the small sample size (34 patients with comorbidity depression), the researchers recommended carrying out further studies to confirm the results with a larger, multi-centred population (Denus et al., 2004). It is unsurprising that their study had a very wide confidence interval (1.01-10.6), considering the sample size. Additionally, to fully evaluate comorbidity other variables such as age, smoking, anxiety, physical activity, and marital status need to be included (Ernstsen et al., 2016; Stafford, Berk and Jackson, 2013; Murphy et al., 2012). Unlike the study conducted by Denus et al. (2004), which focused on mortality outcomes, the current investigation focuses on baseline the characteristics of depression among patients with a comorbid history of depression, and patients with new onset depressive symptoms and determinants of depression levels following CR.

To the best of the author's knowledge, this is the first study to explore the factors associated with depressive symptoms at the start of CR in patients with a comorbid history of depression, and the determinants of depression outcome in patients with comorbid depression following CR across the UK. Additionally, this is again the first study differentiating patients with new onset post heart event depressive symptoms and analysing factors associated with new onset depressive symptoms at the start of CR and the determinants of their depression levels following CR. The reason for this is that factors associated with depressive symptoms in patients with a comorbid history of depression might differ from patients with new onset post heart event depressive symptoms, as well as determinants of depression outcomes following CR in these populations.

Many patients experience a prior history of comorbid depression, although other patients have new onset post heart event depressive symptoms. The time of onset of depressive symptoms has been the focus point in recent studies in terms of cardiac

morbidity and mortality (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016; Dickens et al., 2008; de Jonge et al., 2006). Patients with a comorbid history of depression prior to the a cardiac event experience worse cardiac prognosis and mortality in some studies (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016). On the other hand, patients with new onset depressive symptoms after a cardiac event were found to be more likely to have adverse cardiac events and a higher mortality in other studies (Dickens et al., 2008; de Jonge et al., 2006). Yet, both patient groups seem to be at risk of mortality and experience adverse cardiac events. Therefore, depression is widely recommended to be assessed and managed according to recent guidelines of clinical practice (BACPR, 2017; SIGN, 2017; Piepoli et al., 2016; Lichtman et al., 2014). Thus, further research is needed to understand the determinants of depressive symptoms in patients with a comorbid history of depression, and in patients with new onset post heart event depressive symptoms.

1.5 Research questions

Research questions for exploration in this thesis are:

- What are the factors associated with depressive symptoms in patients with comorbid depression attending CR, at baseline?
- Which baseline characteristics determine depression in patients with comorbid depression, following CR?
- What are the factors associated with new onset depressive symptoms in patients attending CR, at baseline?
- What are the baseline patient characteristics that determine improvement in depression in patients with new onset depressive symptoms, following CR?

1.6 Research aims and thesis structure

This study aims to explore whether patients with comorbid depression, and those with high levels of depressive symptoms at the start of CR differ by characteristics at baseline compared to patients with low levels of depressive symptoms. This study is novel, as there is no research in existing literature examining determinants of depression in patients with comorbid depression in CR. The same applies for patients with new onset depressive symptoms, whereby the association between new onset depressive symptoms and baseline characteristics at the start of CR and determinants of change in their depression levels following CR will be explored.

The results of this thesis may affect clinical practice significantly. Knowing the determinants of depression in patients with a comorbid history of depression and patients with new onset depressive symptoms may require CR programmes to be tailored to the individual needs of these specific patients.

The studies presented in this thesis will further explore the impact of a comorbid history of depression. The factors associated with depressive symptoms at baseline, and determinants of change in depression levels following CR may differ in patients with a comorbid history of depression, and in patients with new onset depressive symptoms. Therefore, investigating patients with a comorbid history of depression and patients with new onset depressive symptoms would enable us to test these hypotheses.

The aims of the presented thesis are to explore whether comorbidity depression influences the baseline characteristics and outcomes of CR. This will be done by examining two different populations:

Firstly, patients with a comorbidity history of depression will comprise the study population in the first study. The association between depression and baseline characteristics among patients with comorbidity depression will be explored. Then, the determinants of depression in patients with comorbid depression for CR outcomes will be investigated.

Secondly, patients with new onset depressive symptoms will be targeted as the population in the second study. The factors associated with new onset depressive symptoms at the start of CR will be explored. Then, the baseline characteristics that determine depression levels in patients with new onset depressive symptoms following CR will be examined.

The current thesis aims to critically review and identify the determinants of depressive symptoms in CVD patients in chapter 2; investigate the sociodemographic and clinical factors associated with depressive symptoms in patients with a comorbid history of depression at the start of CR, in addition, to identifying the factors that determine the change in depressive symptoms in patients with a comorbid history of depression following CR in chapter 4. In chapter 5 part 1, the purpose is to identify patient characteristics associated with new onset depressive symptoms at the start of CR. In chapter 5 part 2, the aim was aimed to examine the baseline patient characteristics that determine improvements in depression in patients with new onset depressive symptoms following CR. Patient characteristics that determine depression levels following CR might be expected differ in patients with a history of depression and in patients with new onset depressive symptoms. It is important to identify which characteristics determine better improvement in these populations to understand their characteristics and provide tailored approaches to these specific populations within the CR programmes, to enable them to benefit in the same way as other patients from CR. Furthermore, understanding what patient characteristics determine changes in depression levels following CR is crucial. In chapter 6, a synthesis has been provided to deepen understanding of those factors determining depressive symptoms in CR patients with a comorbid history of depression and new onset depressive symptoms, as well as to evaluate the findings more successfully across all the chapters. Chapter 7 provides the concluding remarks for the thesis.

Thesis structure will be as follows:

Chapter 1 – Introduction

Chapter 2 – Critical review of the literature

Chapter 3 – Research methodology

Chapter 4 – Determinants of depression in patients with comorbid depression in CR

- Factors associated with depressive symptoms in patients with comorbid depression at baseline
- Determinants of depression outcome following CR in patients with comorbid history of depression

Chapter 5 – Determinants of depression in patients with new onset depressive symptoms in CR

- Part - 1) Factors associated with new onset depressive symptoms at that start of CR
- Part - 2) Determinants of CR depression outcome in patients with new onset depressive symptoms

Chapter 6 – Synthesis chapter

Chapter 7 – Conclusion

Chapter 2: Critical review of the studies examining the determinants of depression in cardiovascular disease patients

2.1 Abstract

Aim

To critically review studies that examine the determinants of depressive symptoms among cardiovascular disease (CVD) patients. Standardized critical appraisal tools were used to critically evaluate the studies included so that the determinants of depressive symptoms could be identified from the analysis.

Method

The literature search was conducted systematically using Medline, PsycINFO, EMBASE, Cochrane Library, and CINAHL Complete. The inclusion criteria for the studies selected were: (1) recruiting patients over the age of >18 (adults); (2) including patients with cardiovascular disease (CVD); (3) reporting factors, predictors, determinants, patient characteristics that have an impact on depressive symptoms; (4) being written in English; and (5) including a multivariate analysis which is conducted to better demonstrate the independent association between potential determinants and depressive symptoms.

Results

Fifteen studies were included in the analysis. Fourteen were observational studies and one was a randomised controlled trial (RCT). The identified determinants of depressive symptoms were physical inactivity, smoking, anxiety, BMI, age, gender, diabetes, and diet.

Conclusion

The current review found some variation in the included studies, particularly in terms of the determinants identified in each. The characteristics that are highly likely to

determine depressive symptoms are physical inactivity, smoking, anxiety, BMI, age, gender, diabetes, and diet. However, definitive conclusions cannot be drawn due to inconsistencies in the included studies, such as adjusting for different covariates, population characteristics and sample size. In addition, the reporting of the studies needs to be improved in publications as well as study designs in order to allow performance of more robust critical reviews and systematic reviews.

2.2 Background

2.2.1 Objective

To critically review the studies investigating the determinants of depressive symptoms in patients with CVD by applying standardised critical appraisal tools, to highlight the study limitations of the included papers and to reach a conclusion regarding the characteristics determining depressive symptoms.

2.3 Method

2.3.1 Critical review

The primary aim of a critical review is to present a thorough understanding of relevant research and critique each studies quality, prior to drawing conclusions about the determinants of depression. A critical review extends beyond the mere description of identified papers, it intended as a conceptual analysis and synthesis of diverse materials. The key element of this review type is its 'critical' component which provides an opportunity to understand what is of value based on previous bodies of work (Grant and Booth, 2009). Systematic reviews are often conducted to address questions regarding the effectiveness of an intervention (Clarke, 2011). However, in the current review the aim was to identify the potential determinants of depressive symptoms. Therefore, to liaise this aim and to address the strength and weaknesses of the included studies, and critique their quality, a critical review of relevant studies was conducted.

A critical review aims to critically evaluate the current state of the subject of knowledge in specific areas, to reveal strengths and weaknesses, controversies, inconsistencies, bias and other important factors regarding hypotheses, research methods and results, and how research fits into the wider context (Lau and Kuziemsky (Eds), 2016). This is done by assessing the credibility of previous research, and by employing appraisal instruments or critical interpretive methods. By doing so, other scholars are informed of the weaknesses and strengths of prior studies, and thus, the development of

knowledge is empowered by providing focus and direction to studies to support future improvements (Lau and Kuziemsky (Eds), 2016). Therefore, previous studies were critically appraised and the direction of improvements for future studies have been provided in the current review.

2.3.2 Search strategy

A literature search was conducted on the 22/12/2017 in Medline (OVID), PsycINFO (OVID), EMBASE (OVID), Cochrane Library (Wiley), CINAHL Complete (EBSCO) and later updated on the 27/02/2020. Search terms combined the following concepts: depression, cardiovascular disease, cardiac rehabilitation intervention, and determinant terms. The literature search was performed using the terms shown in the following table **(Table 2.1)**. The search strategy was translated as being appropriate for each database in line with the interface and specific syntax and keywords employed for each interface. The detailed search results for each database are given in **appendix - 2,** and the updated search results can be seen in **appendix - 3.**

Table 2.1: Search syntax for MEDLINE

PICO heading	Syntax set
Population	exp Myocardial Ischemia OR exp Coronary Artery Bypass/ OR ((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. OR CORONARY.ti,ab. OR exp Coronary Disease/ OR Coronary disease*.tw. OR exp Myocardial Revascularization/ OR exp Myocardial Infarction/ OR (HEART adj4 INFARCT$5).tw. OR exp Cardiovascular diseases/ OR exp Heart diseases/ OR (cardiovascular adj4 (disorder*1 or disease*1)).tw. OR (heart adj4 (disorder*1 or disease*1)).ti,ab. OR (HEART adj4 INFARCT$5).tw. OR exp Heart Failure/ OR (HEART adj6 Failure).tw. OR (Heart adj4

	disease$2).tw. OR MYOCARD$5.tw. OR CARDIAC$2.tw. OR CABG.tw. OR (STENT$4 and HEART).tw.
Intervention	exp exercise therapy/ OR rehabilitat*.tw. OR (physical* adj5 (fit* or train* or therap* or activit*)).tw. OR exp exercise/ OR (train* adj5 (strength* or aerobic* or exercise*)).tw. OR ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. OR exp rehabilitation/ OR exp cardiac rehabilitation/
Outcome	Depression/ OR Depress$.ti,ab. OR exp Depressive Disorder/
Other terms	Predict*.tw. OR Determin*.tw. OR Characteristic*.tw. OR Social determinants of health/ OR Risk factors/ OR Risk factor*.tw. OR risk/ OR risk$.tw. OR related.tw. OR relationship.tw. OR rates.tw. OR difference$.tw. OR associated factors.tw.

2.3.3 Inclusion and exclusion criteria

The inclusion criteria set for the studies to be selected were:

1) Recruiting adult patients (age >18),

2) Involving CVD patients, including patients with myocardial infarction (MI) and heart failure (HF) and those who receive treatment of percutaneous coronary intervention

(PCI) and coronary artery bypass graft (CABG), as recommended in the clinical guidelines (NICE, 2018, 2013),

3) Reporting factors, predictors, determinants, and patient characteristics that have an impact on depressive symptoms,

4) Being written in English,

5) Including multivariate analysis, which is conducted to better demonstrate the independent association between potential determinants and depressive symptoms.

2.3.4 Data extraction

The data extracted from the fifteen studies included in the current review explored the following items: title, authors, publication year, country of study, type of study, the population, sample size, mean age, percentage of females, screening tools employed for identifying depressive symptoms, significant determinants, and covariates included in the multivariate analysis. The data extraction was conducted by the author of the current thesis.

2.3.5 Quality assessment of included studies

Two types of quality assessment tool were employed in this review in accordance with the included study designs. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies employed for critical appraisal of individual observational studies and developed jointly by the experts from National Heart and Lung Institute (NHLBI) and the Research Triangle Institute International. This standardised tool utilises quality assessment methods and other tools established by methodologists and researchers from different institutions including the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centres, the National Health Service Centre for Reviews and Dissemination, the Scottish Intercollegiate Guidelines Network, and Cochrane, with necessary adaptations applied by NHLBI staff.

This tool was designed in order to support reviewers wishing to critically appraise studies and enable them to focus on key concepts for the internal validity of those studies examined. This tool does not provide any numerical value to the list of items included for quality assessment. Instead, the reviewers can select the options "yes," "no," or "cannot determine/not reported/not applicable" for each of the items included in the tool. The reviewers should consider a risk of bias, where a "no" option was selected for an item related to a flaw in the study's implementation or design. "Cannot determine" and "not reported" options could also reveal potential flaws. There are fourteen items included in the tool evaluating factors in relation to study methods, confounding, sources of bias such as selection, performance, attrition and detection, study power, and the strength of causality. The studies are rated as good, fair or poor, where "good" represents a low risk of bias, "poor" represents a risk of bias, and "fair" may indicate some bias.

One RCT was included in this study (Van Melle et al., 2006) and the Cochrane risk of bias (RoB) tool was employed to examine that study's quality (Sterne et al., 2019). This tool assesses the quality of an RCT by examining studies in terms of risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The criteria for judgement options are "low risk", "high risk" and "unclear risk". The study is assessed as "fair quality" when one of these criterions is not met; for instance, one domain might be rated as conveying a high risk of bias, or two criteria might be rated as having unclear risk of bias, and there is no limitation could invalidate the findings. A study is rated as "poor quality" when one of the criteria has a high risk of bias or two criteria are present with an unclear risk of bias, or two criteria have a high risk of bias and there are important limitations that might negatively impact study validity. A study can be referred as "good quality" when all the criteria assessed carry a low risk of bias.

2.4 Results

An initial search of the five databases, identified 20,485 articles (including duplicates). EndNote reference manager software was used to merge the search results. Once the find duplicates command had been applied in EndNote and duplicates removed 15,882 papers remained. After title and abstract screenings, 225 studies remained for full text screening and 210 were excluded with reasons for exclusions as shown in **figure 2.1.** (In this **figure 2.1**, the updated search results, conducted in 27/02/2020, were given after the '+' sign. Total search numbers are given in the text to avoid confusion). Finally, fifteen studies meeting the inclusion criteria were included. Fourteen were observational studies and one was an RCT. The included studies were published between 2005 and 2019 and included a total of 22,930 patients with CVD and related risk factors. The sample sizes ranged from 114 to 8580 in the studies included in this review. The studies were conducted in different countries, including China (1 study), Oman(1), Norway (1), Canada (2), Australia (3), The USA (2), Israel (1), Finland (1), the Netherlands (1), France (1) and one of the studies included data from 22 European countries. **Table 2.2** demonstrates the study characteristics.

The RCT included in this review originally investigated the effect of antidepressant treatment (sertraline) versus care-as-usual for post-MI depression on cardiac prognosis. However, the paper used in this review was a sub-study of a large, multicentre trial in The Netherlands: the Myocardial INfarction and Depression–Intervention Trial (MIND-IT) (Van Melle et al., 2006).

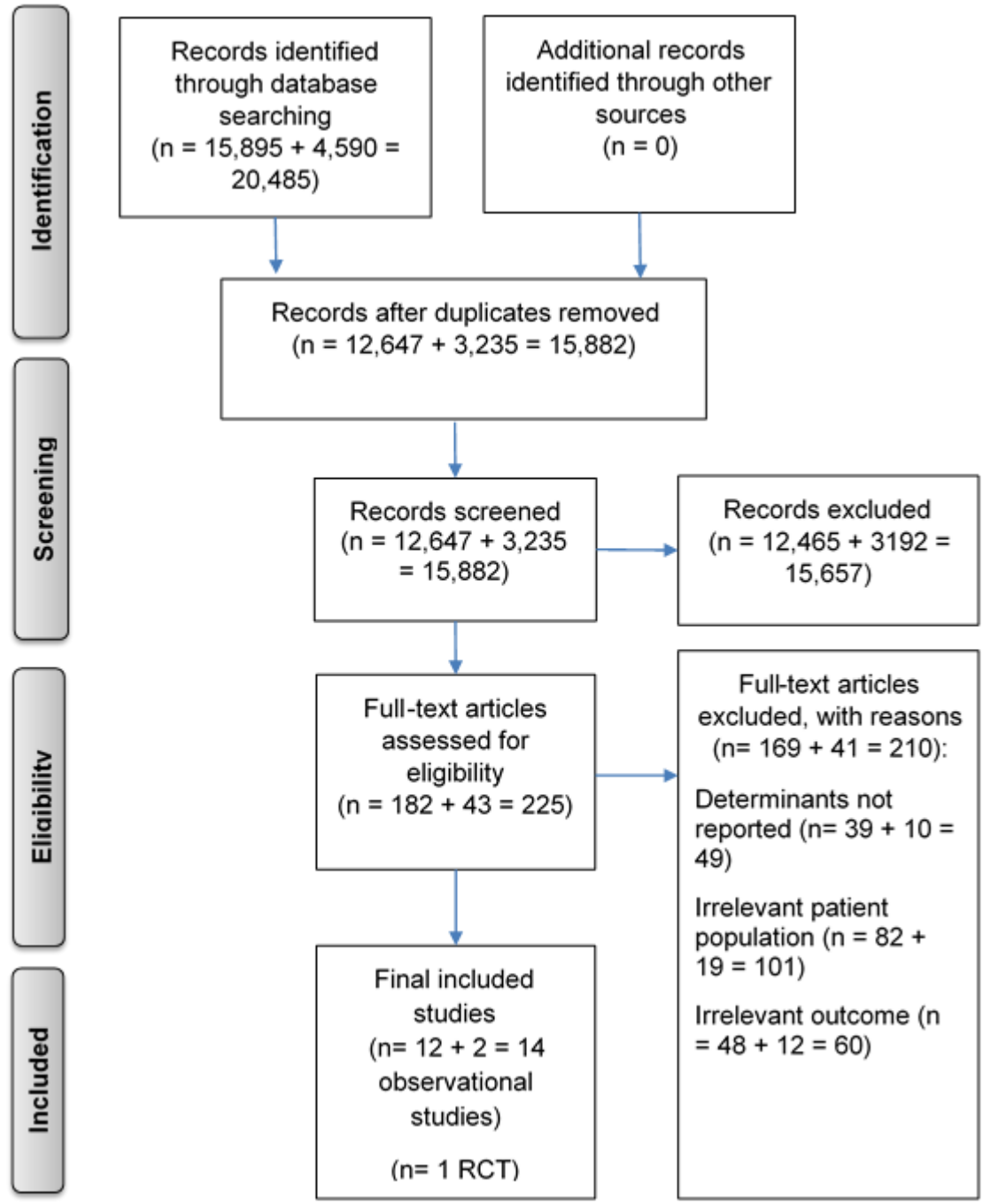

Figure 2.1: Flow diagram for the process of study identification

Table 2.2: Characteristics of included studies

Author/Study design	Country	Participants	Age/Gender	Measurement Tool	Determinants	Not Significant/ Adjusted for but results not reported
Almamari, Muliira and Lazarus, 2019 Cross-sectional	Oman	180 MI patients	Mean age, 62±11.3 Female: 31.7%	PHQ-9	Physical inactivity	**Not significant:** BMI, smoking, age, gender, education level
Zhu et al., 2019 Cross-sectional	China	4043 MI/UA patients	Mean age, 61±10 Female: 37%	PHQ-9	Physical inactivity, poor sleep quality	**Not significant:** Smoking, unhealthy drinking, BMI **Adjusted for:** Age, gender, marital status, education level
Ernstsen et al., 2016 Prospective	Norway	189 MI patients	Mean age, Stable inactive group: 61.1±7.2 Stable active group: 62.3±7.4 Female: 24%	HADS	Physical inactivity	**Adjusted for:** Age, gender, BMI, systolic blood pressure, comorbidity

Horne et al., 2013 Prospective	Canada	436 CABG patients	Mean age, Naïve group: 65 (57-71 range) At risk group: 67 (58-77) Depressed group: 64 (58-72) Female: 32.4%	PHQ-9	Physical inactivity, stressful event, preoperative depressive symptoms	Not reported
Stafford, Berk and Jackson, 2013 Prospective	Australia	193 MI/PCI/CABG patients	Mean age, 64.14±10.37 Female: 19%	MINI and HADS	Smoking, anxiety, neuroticism	**Not significant:** Gender, marital status, BMI, income, diabetes, history of depression, CABG, LVEF, excessive alcohol
Eastwood et al., 2012 Retrospective	The USA	N= 622 HF patients	Mean age, 61±13 Female: 30%	PHQ-9	Perceived attitude control, anxiety (both men and women)	**Not significant:** Age, ethnicity, marital status, financial status, smoking, BMI, Charlson comorbidity index scores, NYHA class, functional capacity, health perception

Murphy et al., 2012 Cross-sectional	Australia	N= 275 MI/PCI/CABG patients	Mean age, 59±9.1 Female: 14%	HADS	Physical inactivity Dietary fat intake Social support score	**Not significant:** Smoking, gender, education, Marital status, insurance status
Myers et al., 2012 Prospective	Israel	632 MI patients	Mean age, 52±8.6 Female: 14%	BDI	Physical inactivity, smoking	**Adjusted for:** Age, gender
Pajak et al., 2012 Cross-sectional	22 European countries	8580 MI/PCI/CABG patients	Mean age, Men: 62.3 ±9.5 Women: 65.9 ±8.9 Female: 25%	HADS	Physical inactivity, smoking, BMI, waist circumference, self-reported diabetes	**Adjusted for:** Age, country, diagnostic category, education
Koivula, Halme and Åstedt-Kurki, 2010 Cross-sectional	Finland	114 CABG patients	Mean age, 69.7±8.9 Female: 17%	Zung Self-Rating Depression Scale	Perceived health, cardiac ischemic symptoms at rest, and emotional support of spouse	**Adjusted for:** Gender
Gravely-Witte et al., 2009 Cross-sectional	Canada	1489 CHD patients	Mean age, 66.99±11.42 Female: 28.6%	BDI	Smoking, age, marital status, weight	**Not significant:** Gender, work status, comorbid condition
Naqvi et al., 2007 Cross-sectional	The USA	944 MI/UA patients	Mean age, Men: 67±13 Women: 71±12 Female: 24.1%	Zung Self-Rating Depression Scale	Being female, smoking, stroke, prior MI	**Not significant:** Age, hypertension, peripheral vascular disease

Van Melle et al., 2006 RCT	The Netherlands	2177 MI/HF patients	Mean age, 63±11.9 Female: 23%	BDI and ICD-10	Age, left ventricular ejection fraction (LVEF) <30	**Not significant:** Hypercholesterolemia, calcium channel blockers
Schrader et al., 2006 Prospective	Australia	1444 MI/PCI/CABG/HF/ UA/Arrhythmia patients	Mean age, 62.2±12.4 Female: 32%	CES-D	Past experience of emotional health (e.g. depression, anxiety), smoking	**Adjusted for:** Age, gender
Bonnet et al., 2005 Cross-sectional	France	1612 patients who possessed at least one cardiovascular risk factor	Mean age, Men: 49.2±10.6 Women: 50.8±12.8 Female: 39%	HADS	Smoking, physical inactivity, diet	**Adjusted for:** Age, socioeconomic status, marital status, BMI, presence of hypertension, dyslipidemia, diabetes

Hospital Anxiety and Depression Scale (HADS); Beck Depression Inventory (BDI); The Patient Health Questionairre-9 (PHQ-9); Centre for Epidemiologic Studies Depression Scale (CES-D); International Classification of Diseases 10th revision (ICD-10); Mini International Neuropsychiatric Interview Version 5 (MINI).

2.4.1 Quality assessment

There are fourteen observational studies quality assessed as shown in the **table 2.3** based on fourteen criteria/questions included in The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, as explained in detail in **table 2.3**. On completion of study quality assessment, only one of the included studies was rated as good quality (Pajak et al., 2012), eight studies were rated as fair quality (Zhu et al., 2019; Ernstsen et al., 2016; Horne et al., 2013; Stafford, Berk and Jackson, 2013; Myers et al., 2012; Gravely-Witte et al., 2009; Naqvi et al., 2007; Schrader et al., 2006), and five studies were rated as poor (Almamari, Muliira and Lazarus, 2019; Eastwood et al., 2012; Murphy et al., 2012; Koivula, Halme and Åstedt-Kurki, 2010; Bonnet et al., 2005). The research objectives were clearly stated and the study population were well defined in all included studies. The participation rate of eligible participants was at least 50% in nine of the included studies and in five studies it was below 50% of eligible participants. The study subjects were recruited from the same population and over the same time period in all the included studies with the exception of one (Eastwood et al., 2012) which did not report the time period for the enrolment of participants. All of the studies reported their sample size, however, only two were able to meet the fifth criterion requiring sample size justification or power description (Koivula, Halme and Åstedt-Kurki, 2010; Naqvi et al., 2007). Considering the 6th criterion, which is questioning whether exposures of interest were assessed before the outcomes were measured, only five studies met this criteria, eight studies did not. This was mainly attributable to the cross sectional design of these studies, and one study failed to report this criteria in their methods. The time frame for the association between independent variables and outcomes was sufficient in five of the included studies, whereas it was not sufficient in nine studies due to their cross sectional design in general. All the included studies reported the different levels of exposure as categories or continuous variables where appropriate. The independent variables were clearly defined and implemented consistently across the study participants in thirteen studies. However, in one study, exposure measures were not clearly reported (Koivula, Halme and Åstedt-

Kurki, 2010). Only two of the included studies met the tenth criteria, assessing the exposure variable more than once overtime (Ernstsen et al., 2016; Horne et al., 2013). The outcome measure was clearly defined, reliable, valid, and consistently implemented across the study participants in thirteen studies, whereas this was not the case in one remaining study (Bonnet et al., 2005). In Bonnet et al.'s (2005) study, the unhealthy behaviour scoring system seemed arbitrary and may not be validated, and has not been reported and justified well in accordance with the literature. The blinding of the outcome assessors with regard to the participants' exposure status was not reported in any of the observational studies included. The loss to follow up after baseline was 20% or lower in the four studies (Horne et al., 2013; Stafford, Berk and Jackson, 2013; Gravely-Witte et al., 2009; Schrader et al., 2006). However, in one study this was more than 20% (Ernstsen et al., 2016), and in the remainder of the studies this was either not reported nor applicable, because they were cross-sectional studies. The final criterion required the measurement and adjustment of key potential confounders in the analysis. Eight of the included studies met this criterion. Adjusting for the higher number of potential confounders in the analysis is one of the important indicators of good quality studies, along with the rest of the thirteen criterions. However, there was a great variation in the variables included in the multivariate analyses in these studies, which might have influenced their findings.

The only trial included in this review was quality assessed employing the Cochrane risk of bias assessment tool, which can be seen in **figure 2.2** (Van Melle et al., 2006). This RCT rated as poor quality according to the tool, because two criterion constituted a high risk of bias and two had an unclear risk of bias **(figure 2.2)**.

Table 2.3: Quality assessment of the included studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality
Almamari, Muliira and Lazarus, 2019	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NR	NA	N	Poor
Zhu et al., 2019	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NR	NA	Y	Fair
Ernstsen et al., 2016	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	NR	N	N	Fair
Horne et al., 2013	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	Y	N	Fair
Stafford, Berk and Jackson, 2013	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	Fair
Eastwood et al., 2012	Y	Y	N	NR	N	NR	N	Y	Y	NR	Y	NR	NR	Y	Poor
Murphy et al., 2012	Y	Y	N	Y	N	N	N	Y	Y	N	Y	NR	NA	Y	Poor

Myers et al., 2012	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	NR	NR	N	Fair
Pajak et al., 2012	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NR	NA	Y	Good
Koivula, Halme and Åstedt-Kurki, 2010	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	NR	NA	N	Poor
Gravely-Witte et al., 2009	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NR	Y	Y	Fair
Naqvi et al., 2007	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	NR	NA	Y	Fair
Schrader et al., 2006	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	Fair
Bonnet et al., 2005	Y	Y	Y	Y	N	N	N	Y	Y	N	N	NR	NA	Y	Poor

The quality of the included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Question/Criterion 1 (Q1). Was the research

question or objective clearly stated? Q2- Was the study population clearly specified and defined? Q3- Was the participation rate of eligible persons at least 50%? Q4- Were all the subjects selected or recruited from the same or similar populations (including over the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants? Q5- Was a sample size justification, power description, or variance and effect estimates provided? Q6- For the analyses in this paper, were the exposure(s) of interest assessed prior to the outcome(s) being measured? Q7- Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Q8- For exposures that can vary in amount or level, did the study examine different levels of exposure as related to outcome (e.g., categories of exposure, or exposure measured as continuous variable)? Q9- Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all the study participants? Q10- Was the exposure(s) assessed more than once over time? Q11- Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q12- Were the outcome assessors blinded to the exposure status of participants? Q13- Was loss to follow-up after baseline 20% or less? Q14- Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? Q, question; CD, cannot be determined; NA, not applicable; NR, not reported; N, no; Y, yes.

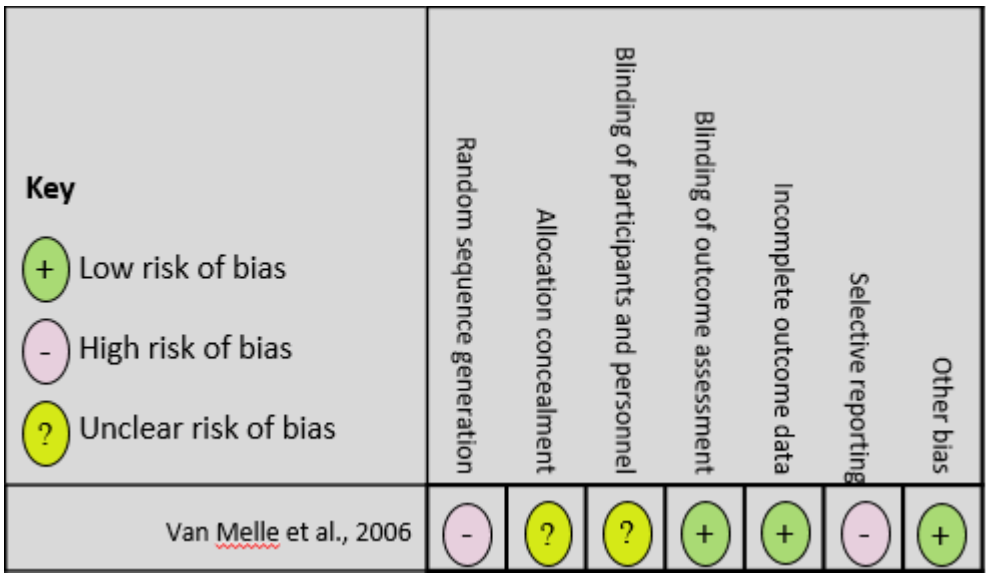

Figure 2.2: Cochrane risk of bias assessment for the included RCT

2.4.2 Outcome

The presence and extent of depression is routinely captured by diagnostic assessment tools such as ICD-10 and MINI and a variety of self-reported assessments tools including HADS, PHQ-9, BDI, Zung Depression Scale and CES-D were employed for the assessment of depressive symptoms. Only one study used ICD-10 (Van Melle et al., 2006) and one used MINI (Stafford, Berk and Jackson, 2013). The most commonly used measurement for the assessment of depressive symptoms was HADS which was employed in five of the included studies (Ernstsen et al., 2016; Stafford, Berk and Jackson, 2013; Murphy et al., 2012; Pajak et al., 2012; Bonnet et al., 2005). The PHQ-9 was the second most commonly employed measure and was used in four studies (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Horne et al., 2013; Eastwood et al., 2012). This is followed by the BDI which was used in three studies (Myers et al., 2012; Gravely-Witte et al., 2009; Van Melle et al., 2006). The Zung depression scale was employed in two studies (Koivula, Halme and Åstedt-Kurki, 2010; Naqvi et al., 2007), whereas CESD was only used in one (Schrader et al., 2006).

HADS has been categorised using a clinical cut off point of 8, by means of ≥ 8 indicating depressive symptoms, and <8 below a cut off point in three of five studies

employing HADS measurements (Ernstsen et al., 2016; Stafford, Berk and Jackson, 2013; Murphy et al., 2012). The two other remaining studies used cut off points of ≤7 to indicate absence of depression, 8-10 mild to moderate depression, and >10 as moderate to severe depression (Pajak et al., 2012; Bonnet et al., 2005).

Two of the three studies that employed BDI to assess depressive symptoms categorised the patients as ≥10 having depressive symptoms and <10 as below the cut off (Myers et al., 2012; Van Melle et al., 2006), and one study used >14 for the cut off point for having depressive symptoms (Gravely-Witte et al., 2009). Of the four studies that measured depressive symptoms with a PHQ-9 assessment tool, two categorised the patients as having depressive symptoms ≥10, and no depressive symptoms <10 (Zhu et al., 2019; Eastwood et al., 2012); in addition, one study used as continues outcome (Almamari, Muliira and Lazarus, 2019), and another study categorised 0-4 as naive, 5-9 as at risk, and 10-27 as depressed (Horne et al., 2013).

Turning to the Zung Depression Scale, one study used a cut off ≥45 for depression (Koivula, Halme and Åstedt-Kurki, 2010), whereas another considered >50 the cut off for depressive symptoms (Naqvi et al., 2007). The only study employing CES-D scores categorised the patients according to <16 not depressed, 16-26 mild depression, >26 moderate to severe depression.

2.4.3 Determinants

When analysing the fifteen studies included there were 37 exposure variables in total. Of these variables, 28 (76%) were only reported in two or fewer studies. 22 of the 37 variables were found to be significantly associated with depressive symptoms in CVD patients. Moreover, 13 of these variables were found to be significant in just one study. Crucially, no single variable was statistically significant in all the studies included.

Age and gender were the two most commonly reported variables in the included studies. Age was reported in 11 out of the 15 studies, and gender was also reported in 11 out of 15. In terms of age, two studies showed that younger age associated with

depressive symptoms, whereas three studies found no statistical significance, and in six studies age was adjusted for but the results not reported. Turning to gender, females were found to be statistically significantly and more likely to possess depressive symptoms in one study. However, in four out of the eleven studies reporting gender, no significant association emerged. In the remaining six studies, gender was adjusted for in the analysis, but the results not reported. Potential determinants and direction of association are summarised below in **figure 2.3**.

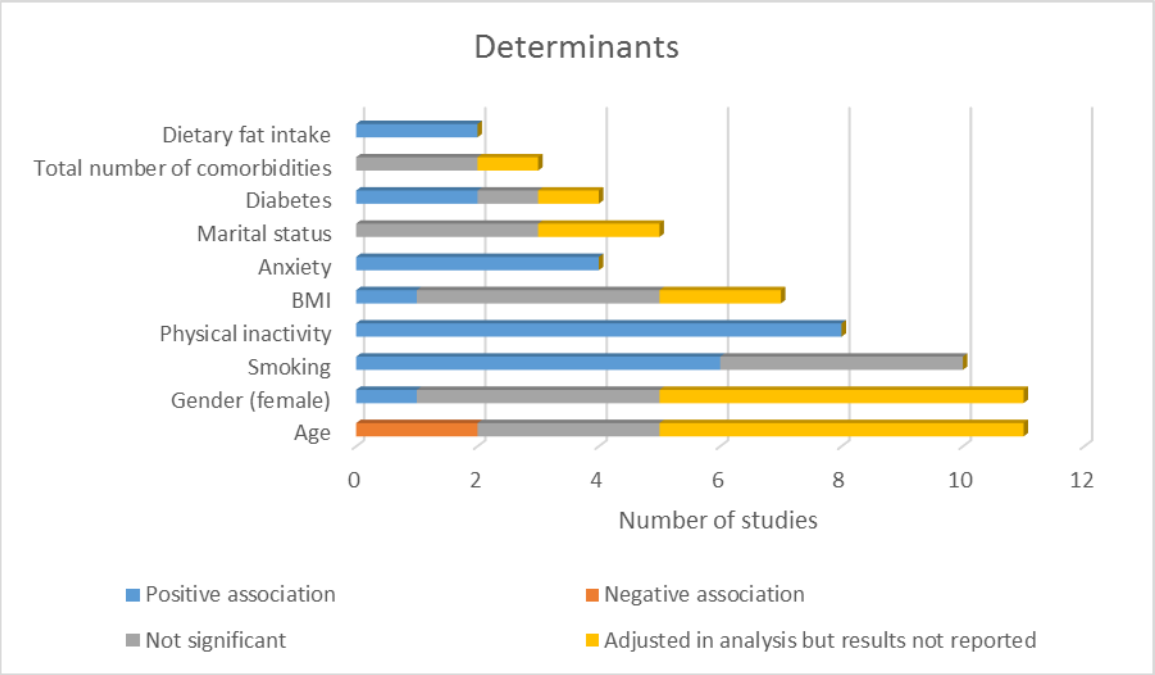

Figure 2.3: Potential determinants and direction of association

Smoking was reported in 10 out of 15 of the included studies. It was found to be one of the most common significant determinants in the multivariate analyses of 6 studies reporting this variable. Patients who smoked were more likely to suffer depressive symptoms. However, four studies showed no significant association between smoking and depression. Physical inactivity was another common significant determinant in the analysis in 8 out of 15 studies. All 8 studies identified a statistically significant association demonstrating that patients who are physically inactive are more likely to experience depressive symptoms.

Of the 15 included studies, 7 reported BMI. One in 7 studies revealed positive association between BMI and depression. Four of the studies of the were unable to show a significant association in a multivariate analysis, and the remaining two studies adjusted for BMI but did not report the results.

Anxiety was reported in 4 out of 15 studies, and all of these studies found that anxiety was a significant determinant of depressive symptoms and there was a positive association showing increase in anxiety was associated with increased depressive symptoms. Marital status was also reported in 5 out of 15 studies. According to the results of three studies, this variable did not significantly determine depressive symptoms. The other two studies referred to adjustments having been made for marital status, however results were not reported. Diabetes was reported in four of the studies. Two found a significant positive association between diabetes and depressive symptoms in a multivariate analysis. One study found no significant association, and in one study it was reportedly adjusted in their analysis, but no results were given related to diabetes. Total number of comorbidity scores was reported in three studies, in two of these studies it was unable to be a significant determinant, and one study adjusted for it without reporting the result.

Health perception, dietary fat intake, left ventricular ejection fraction (LVEF), dyslipidaemia and education variables were also reported in two studies. Only dietary fat intake was identified as a significant determinant in two studies. Reduced LVEF and poor sleep quality were significant in one study, with the remainder of the variables either not significant, or adjusted in the analysis without presenting the results.

2.5 Discussion

The current study aimed to critically review previous studies designed to determine variables that correlate with depressive symptoms in patients with CVD. The review found great variation and inconsistency in the included studies in terms of the determinants reported to be statistically significant. One of the reasons for this was the

differences in sample sizes in each study, as the studies ranged from 114 patients (insufficient for the analysis of multiple variables) to 8580 patients as well as the variation in variables included as potential determinants in multivariate analyses.

The quality of the included studies assessed in this review was highly variable, with six studies rated as low quality (Almamari, Muliira and Lazarus, 2019; Eastwood et al., 2012; Murphy et al., 2012; Koivula, Halme and Åstedt-Kurki, 2010; Van Melle et al., 2006; Bonnet et al., 2005). Eight studies were rated as of fair quality (Zhu et al., 2019; Ernstsen et al., 2016; Horne et al., 2013; Stafford, Berk and Jackson, 2013; Myers et al., 2012; Gravely-Witte et al., 2009; Naqvi et al., 2007; Schrader et al., 2006), and only one was rated as good quality (Pajak et al., 2012).

2.5.1 Determinants

2.5.1.1 Smoking

Smoking was found to be the one of the most common significant correlates of depressive symptoms which was reported in six studies (Stafford, Berk and Jackson, 2013; Myers et al., 2012; Pajak et al., 2012; Gravely-Witte et al., 2009; Naqvi et al., 2007; Bonnet et al., 2005).

Stafford, Berk and Jackson, (2013) aimed to investigate the association between smoking and depression in patients with coronary heart disease. This prospective cohort study recruited 193 patients (mean age: 64.14±10.37, female: 19%) and assessed their depressive symptoms at 3, 6 and 9 months post-discharge from hospital related to heart event. Depression is assessed via clinical interview at three months and depressive symptoms are assessed with HADS at six and nine months. In addition, smoking was assessed by self-report during hospitalisation and patients were categorised as either smokers or non-smokers. Smoking, at the time of a heart event was found to be associated with a higher likelihood of being diagnosed with major depression at three months, OR: 4.30 (95% CI, 1.12-16.46; $p < .05$), adjusting for anxiety, neuroticism, gender, marital status, BMI, income, diabetes, history of

depression, CABG, LVEF, and excessive alcohol in a multivariate analysis; however, it was unable to predict depressive symptoms at 6 and 9 months. In addition, gender, marital status, BMI, income, diabetes, history of depression, CABG, LVEF, and excessive alcohol were not significant determinants. One limitation of this study was due to having a relatively small sample size compared to the other included studies, it had very wide confidence intervals, which negatively influenced the precision of the estimate of effect size.

Myers et al. (2012) was another prospective observational study conducted in Israel. 632 patients who had been admitted for their first-ever MI (mean age: 52±8.6, Female: 14%) were followed up for a median of 13 years. At time of hospitalisation, depressive symptoms were assessed employing the BDI measurement. The results showed patients with depressive symptoms were less likely to stop smoking (OR, 0.75, CI, 0.60–0.94), and less likely to be physically active (OR, 0.80, CI, 0.69–0.94) during the follow up stage; age and gender were adjusted for in the multivariate analysis. From an initial sample of 1521 patients recruited, 632 patients completed a questionnaire about depressive symptoms and were included. The remaining patients did not complete psychosocial questionnaires, either due to exhaustion following several medical examinations, or language barrier. Non-respondents were slightly older (54.8 vs. 52.3), less educated (10 vs. 12 years of education), and more likely to be female (22% vs. 14%) than those who had their depressive symptom assessments recorded. Indeed, the percentage difference in females may have impacted the study's representativeness of the population, and again the female percentage was low compared to the other studies included in this review. In addition, there was insufficient data available concerning patient's history of depression. These authors recommended further studies to investigate the impact of depression prior to an acute cardiac event and incident depression, which may potentially trigger a heart event itself (Myers et al., 2012).

Gravely-Witte et al. (2009) aimed to investigate the association between smoking status and depressive symptoms. 1489 CHD patients completed a baseline survey to assess smoking status and depressive symptoms in this study, with a mean age of 66.99±11.42, and a proportion of females of 28.6%. Smoking status was assessed by employing a self-report questionnaire and patients were grouped as current-, former- or non-smokers. The participants' smoking at baseline were identified as current smokers and former smokers and those who had quit prior to a baseline assessment. The BDI was used to assess depressive symptoms when categorising patients with scores >14 that reflect mild to severe symptomatology. Multinomial logistic regression analysis was employed to investigate the association between depressive symptoms and smoking status, after adjusting for age, gender, marital status, weight, work status, and comorbid conditions. This study found current and former smokers had significantly more depressive symptoms than non-smokers. However, the odds ratio was very close to the no effect of 1 (OR: 1.04 P<0.001, OR: 1.02, p<0.02), querying the significance of this result. In addition, the authors conceded the limitation that the assessment of the association between smoking and depression was cross-sectional, and an analysis in the form of a follow up assessment could be of benefit, and this study failed to include one.

In contrast, the other four studies have found smoking was not a significant determinant (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Eastwood et al., 2012; Murphy et al., 2012). The reason for this might be that the overall quality of three of these studies were relatively poor compared to the other studies, which had found that smoking was significantly associated with depressive symptoms. For instance, these studies had lower participation rates from eligible persons, and loss to follow up was higher than in other studies, which could have had an impact on results (Eastwood et al., 2012; Murphy et al., 2012).

2.5.1.2 Physical activity status

Physical inactivity was another common determinant of depressive symptoms. Patients who are physically inactive were found to be more likely to experience depressive symptoms in eight studies (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Ernstsen et al., 2016; Horne et al., 2013; Murphy et al., 2012; Myers et al., 2012; Pajak et al., 2012; Bonnet et al., 2005).

Ernstsen et al. (2016) aimed to examine whether the recommended level of physical activity over time was associated with having depression after a first MI in older adults. In this prospective Norwegian study, 189 MI patients from the Nord-Trøndelag Health Study (HUNT1: 1984-86, HUNT2: 1995-1997, HUNT3:2006-2008), who had reached the age of 60 in the HUNT3 and those with no prior mental illness or CVD at baseline (HUNT2) and those experiencing their first MI before HUNT3 constituted the study sample (Mean age, stable inactive: 61.1±7.2, Stable active: 62.3±7.4), and the proportion of females was 24%. In relation to physical activity status from HUNT1 to HUNT2, four groups emerged from the sample including: persistently active, persistently inactive, from active to inactive and from inactive to active. Post MI depression symptoms measured by HADS in HUNT3 was the primary outcome of the study. A clinical cut off point of 8 was used in the analysis. 11% of patients had depressive symptoms (HADS-D ≥ 8). A binary logistic regression was employed for the multivariate analysis, to compute the odds of elevated depressive symptoms (HADS-D ≥ 8) at the time of HUNT3. Those patients who were persistently active had statistically significantly lower odds of experiencing depressive symptoms compared to patients who were persistently inactive (OR: 0.28, 95%CI: 0.08-0.98). Other physical activity groups were also associated with reduced odds of having depressive symptoms, when compared to patients with persistent physical inactivity, however they failed to reach the required level of statistical significance. The final model was adjusted for age, gender, BMI, systolic blood pressure and comorbidity; however, the results were not reported, which is a common limitation among the studies reviewed as part of this

thesis. However, smoking was not adjusted in the multivariate analysis of this study, which may limit the thoroughness of the study findings, as in the current review, it has been found to be the one of the most commonly reported significant determinant of depressive symptoms. One of the major limitations of Ernstsen et al.'s (2016) study was that although physical activity level was categorised as active and inactive based on whether it was ≥ 150 min/ week or <150 min/week, it was measured with different questionnaires in the HUNT1 and HUNT2 surveys (Kurtze et al., 2008, 2007) which may possibly have introduced bias to this study results. In addition, due to the small sample size there was overlapping CIs and wide CIs within the physical activity groups in the multivariate analysis. Therefore, caution is required when drawing conclusions based on this study.

Murphy et al. (2012) conducted a cross sectional study in Australia. It included a total of 275 patients admitted to hospital after MI or for PCI or CABG, and interviewed them six weeks after hospital discharge. The study aimed to examine the relationship between depression and health behaviours in Australian CVD patients. Patients' depressive symptoms were assessed using the HADS assessment tool. Patients with a HADS depression score ≥8 were classified as having depressive symptoms and 15.2% of patients met this level. In order to measure levels of physical activity, the Active Australia Survey was employed, which is an eight-item survey that is mainly self-reported and measures moderate activity and vigorous activity in the last two weeks, as well as frequency and duration of walking. Total physical activity in minutes per week was calculated for each patient, and then converted from 'minutes per week' to 'multiples of 10 minutes per week' for use in a multivariate analysis. The results of the logistic regression revealed that 10 minutes increased physical activity was associated with 2% reduced odds of experiencing depressive symptoms (OR:0.976, p=0.010). The logistic regression analysis was adjusted for smoking, gender, education, marital status, and insurance status and these variables were reported to be not significant in the text, however the results were not reported. In addition, another separate logistic

regression analysis was run to determine any association between dietary fat intake and depressive symptoms, adjusting for the same variables, and found it to be a significant determinant of depressive symptoms. The mean age of the study participants was 59±9.1 which is much younger than those patients seen in routine practice, where the mean age is 67 years (NACR, 2019). However, the female percentage was 14% (Murphy et al., 2012) which is much lower than the female proportion, which was nearly half, in NACR data (29%) (NACR, 2019). It was also lower compared to the rest of the studies included in this review which may have had an impact on the generalisability of the study results in the wider population. In addition, this study did not include CR, which is an important intervention to provide secondary prevention for CVD patients and the implications of these results remains unknown in the CR setting.

Almamari, Muliira and Lazarus, (2019) was a cross-sectional study conducted in Oman. The study included 180 patients in total (mean age: 62±11.3; female: 31.7%), all of whom were at least 4 weeks post MI diagnosis and attending follow-up care in the cardiology outpatient clinic of two hospitals, during the period September 2017-December 2017. The aim of this study was to investigate the prevalence of depression in post MI patients. The PHQ-9 assessment tool was used to assess depressive symptoms and the patients were categorised as 0-4 = minimal depression, 5-9 = mild depression, 10-14 = moderate depression, 15 – 19 = moderately severe depression, and 20-27 = severe depression. The authors reported the prevalence of major depressive symptoms at 5% (PHQ-9 ≥ 15). The study results reveal that self-reported regular physical activity was the only significant variable inversely associated with depressive symptoms in a multivariate analysis, and other variables such as age, gender, smoking, BMI, and education level were found not to be significantly associated with depressive symptoms. However, the study only recruited a small sample of patients from two hospitals in Oman (Almamari, Muliira and Lazarus, 2019).

Zhu et al. (2019) conducted a cross-sectional study of 4043 Chinese MI/UA patients (Mean age, 61±10, Female: 37%), between November 2014 and January 2017, from 16 rural hospitals in 9 provinces in China. The study aimed to investigate the association between unhealthy lifestyle behaviours and depression. The study participants were assessed in terms of their depressive symptoms and life styles, health behaviours during hospitalisation and four days prior to their discharge. Their average length of stay was nine days. PHQ-9 was used to assess depressive symptoms. There were only a total of 135 patients (3.3%) with elevated depressive symptoms (PHQ-9 ≥10), revealing that a smaller proportion of Chinese patients experienced elevated depressive symptoms compared to patients in the other included studies in the current review. Physical activity was measured by asking whether the patient had engaged in any exercise during the past 3 months, including walking, running, dancing, Tai chi, etc., for at least 30 min each time, using the response categories of frequently, occasionally and seldom. The authors considered a response of seldom as unhealthy. However, this is not a common approach to assessing physical activity and might have impacted the comparability of the findings with other studies. The study findings have shown that physical inactivity and reduced sleep quality were associated with increased levels of depressive symptoms (PHQ-9 ≥10) according to logistic regression results; however, other lifestyle behaviours, including smoking, unhealthy drinking, and BMI were found to be non-significant. In addition, the analysis was adjusted for age, gender, and education level, although the results were not reported. The study was limited to a cross-sectional design and the requirement for better designed studies has been highlighted (Zhu et al., 2019).

Myers et al. (2012) also found that self-reported regular physical activity categorised as regular, irregular or none, was associated with lower odds of experiencing depressive symptoms assessed at initial hospitalisation with BDI in MI patients. Physical activity was also found to be associated with a reduced likelihood of experiencing depressive symptoms in other studies, including different countries in Canada (Horne et al., 2013),

France (Bonnet et al., 2005) and elsewhere (Pajak et al., 2012). In a study by Horne et al., (2013), patients' physical activity was measured with the International Physical Activity Questionnaire short form (IPAQ-short). The patients were required to recall the amount of physical activity accrued over the preceding week in an IPAQ-short. Patients were categorised as either inactive or active (inactive patients, ≤ 600 MET min/week) (Craig et al., 2003; Horne et al., 2013). In Pajak et al. (2012), physical activity was also assessed using the IPAQ; however, how the processes of categorisation and analyses were not clearly described. Conversely, in a study by Bonnet et al. (2005), a different scoring system was preferred for physical activity. For example, a score of 0 was assigned to patients who had carried out regular activity for at least 20 min and who had engaged in at least 3 moderate to intense physical activity bouts (defined as ≥3 - metabolic equivalents - METs). A score of 1 was assigned to patients who exercised once or twice a week for at least 20 min (≥3 METs), and a score of 2 to those who had very weak physical activity (less than 20 min per week) and a score of 3 to those who did not exercise at all. However, this was not a validated and prevailing assessment of physical activity status, which might thereby influence the generalisability of the findings.

2.5.1.3 Age

Age was a significant determinant of depressive symptoms in one of the included studies (Van Melle et al., 2006). Van Melle et al. (2006) conducted a sub-study using data from a large multicentre trial (the Myocardial INfarction and Depression-Intervention Trial (MIND-IT)) based in the Netherlands. The primary aim of the main study was to examine the influence of an antidepressant treatment (mirtazapine), compared to care as usual, for depressive disorder after MI on cardiac prognosis. According to the main study protocol (Van Den Brink et al., 2002), the primary outcome was a combined time-related incidence of new cardiac events including cardiac mortality, hospital admission for MI, UA, HF or ventricular tachyarrhythmia. Secondary outcomes were the effect of antidepressant treatment versus control as usual on

quality of life, and cardiac functioning 1 year after MI. However, in this sub study, the aim was to examine potential determinants of depression in the year following MI, although this was not clearly mentioned in the main trial protocol. In total, data from 2177 MI patients in this study (mean age 63 years, 23% female) was examined. Inclusion criteria was patients ≥ 18 years of age, had an acute MI between September 1999 and November 2002, and admitted to 1 of the 10 study hospitals. The exclusion criteria were being unable to communicate or being unavailable for follow up, any comorbidities that might influence short term survival, already receiving treatment for depression elsewhere, or being a participant to another trial. Eligible patients were screened through BDI to measure their depressive symptoms at 3, 6, 9 and 12 months after their MI event, and patients with depressive symptoms were identified with a BDI ≥10 at these months underwent a standardised psychiatric interview. The presence of post MI depression was assessed with the ICD-10 criteria. According to the ICD-10 criteria, MI patients divided into two groups, those with a depressive disorder and those that remained free of depression. Age was categorised as either <60 and ≥60 years. The study results found that being younger than 60 years old was associated with increased odds of experiencing depression following MI. Having LVEF <30 was another significant determinant of depression in the multivariate analysis. However, hypercholesterolemia and calcium channel blockers were insignificant as determinants in the multivariable analysis. One limitation of the study was that it was unable to include patients with a history of depression, and one of its inclusion criteria was the exclusion of patients being treated for depression, because the trial was mainly designed to establish the effect of antidepressant treatments on cardiac prognosis in patients with post MI depression. Furthermore, this study failed to adjust for the common potential determinants of depression in a multivariate analysis including smoking, physical activity and gender, which might have influenced the results (Van Melle et al., 2006). In addition, the trial data provides a controlled experiential environment; on the other hand, the use of a routinely collected real-world data could facilitate the observation of natural variation in patient characteristics to establish what

determines depressive symptoms in real clinical environment. Whether patients were referred to or had CR is reportedly unknown.

In contrast, three studies did not find age to be a significant determinant when included as a continuous variable (Almamari, Muliira and Lazarus, 2019; Eastwood et al., 2012; Naqvi et al., 2007). In addition, age was adjusted for in the analysis set out in six studies, although their results were not reported (Zhu et al., 2019; Ernstsen et al., 2016; Myers et al., 2012; Pajak et al., 2012; Schrader et al., 2006; Bonnet et al., 2005). This might be due to the authors' intention to examine the impact of specific variables on depressive symptoms; for instance, Ernstsen et al. (2016) sought to investigate the impact of physical activity on depressive symptoms.

2.5.1.4 Gender

Naqvi et al. (2007) investigated the impact of gender on the severity of depressive symptoms after MI. This was a US based study, which included 944 patients with MI and UA (mean age, men: 67±13, women: 71±12; female: 24.1%) between the years 1998 and 2002 admitted to a California-based community hospital. Upon hospital discharge, the Zung Self-Rating depression questionnaire was administered to patients to be returned by mail. Based on the Zung depression scale patients were defined as having major depressive symptoms with a summed depressive symptoms score of >50. Of the patients involved in the study, 35% (n=250) males and 45% (n=103) females had depressive symptoms (P = 0.005). In addition, according to a multivariable logistic regression analysis, female gender was an independent determinant associated with increased odds of elevated depressive symptoms arising (OR: 1.64; 95% CI, 1.19-1.28). Two other variables found to be significant determinants of depressive symptoms in the analysis were smoking (OR = 1.41; 95% CI, 1.01-1.97) and diabetes (OR = 1.42; 95% CI, 1.03-1.97). However, age, hypertension, and peripheral vascular disease were viewed as insignificant determinants. One limitation of this study is that the Zung self-assessment depression scale is a rarely used assessment tool; therefore, a comparison of this study result with other studies might

prove difficult. In addition, Naqvi et al.'s (2007) was a single centre study, therefore caution is necessary before applying the results to the wider population.

On the contrary, gender was not a significant determinant in four of the studies (Almamari, Muliira and Lazarus, 2019; Stafford, Berk and Jackson, 2013; Murphy et al., 2012; Gravely-Witte et al., 2009). Stafford, Berk and Jackson, (2013) carried out a prospective observational study including 193 CHD patients with a mean age of 64.14 ± 10.37; 156 of these patients were male (19% female). According to the multivariate analysis, gender was found to be a non-significant determinant. This was also the case for thin Murphy et al.'s (2012) study. However, the independent variables used in the multivariable analysis were not clearly reported, and the results in general were insufficiently reported. On the other hand, six studies were adjusted for gender in their analysis; however, the results were not reported (Zhu et al., 2019; Ernstsen et al., 2016; Myers et al., 2012; Pajak et al., 2012; Schrader et al., 2006; Bonnet et al., 2005).

2.5.1.5 BMI

Pajak et al. (2012) conducted a cross-sectional study based on The EUROASPIRE III survey undertaken in 22 European countries. This multi-centre study had the largest sample size among the rest of the included studies in the current study; it recruited 8580 MI/PCI/CABG patients, who were examined at least 6 months after hospitalisation due to a cardiac event. The mean age was 62.3 ± 9.5 for males, 65.9 ± 8.9 for females, and the proportion of female participants was 25%. The main aim of this study was to investigate the prevalence of depression in CVD patients in 22 countries from the selected samples, and to examine the association between lifestyle changes, cardiovascular risk factors, and compliance with cardio-protective medication and depressive symptoms. The symptoms of depression were assessed using the HADS tool. The analyses were stratified to gender of the participants. The prevalence of depression (HADS ≥8) differed among the included countries varied from 8%-36% in men and 22% to 64% in women. Depressive symptoms were found to be related to BMI, physical inactivity, smoking, waist circumference and self-reported diabetes in the

multivariate analysis. In addition, the analysis accounted for age, country, diagnostic category and education, however, results were not shown. The participation rate of the survey was 73% after the index event. Samples were chosen from hospitals in the areas defined in some countries; therefore, they may not be representative of the whole country. In addition, it was reported that the patients who had died before the examination may had higher prevalence of depression. The main limitation of this study is its cross-sectional design, which obscures causal relationships. Furthermore, whether these patients had received CR or not was not reported. Therefore, the association of patient characteristics with depressive symptoms pre- and post-CR might be beneficial in future studies. Another limitation is that, in some countries, a small number of females participated in the study. For example, 13 females participated in Greece and 39 females participated in the Netherlands and Belgium, which may have influenced the study results and had an impact on insignificant results. For instance, although the percentage of male and female quitters was similar in the depressive symptom categories, the difference was significant in males, but not in females. In addition, due to the presumably smaller sample size of female smokers, confidence intervals for odds ratios proved to be very wide in the multivariate analysis, OR: 1.53 (0.05 - 45.8).

In contrast, four studies found BMI was not a significant determinant of depressive symptoms (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Stafford, Berk and Jackson, 2013; Eastwood et al., 2012), whereas two studies adjusted for BMI in their analysis, but failed to report the result regarding BMI (Ernstsen et al., 2016; Bonnet et al., 2005).

2.5.1.6 Anxiety

A positive association between anxiety and depressive symptoms emerged in four of the included studies (Horne et al., 2013; Stafford, Berk and Jackson, 2013; Eastwood et al., 2012; Schrader et al., 2006). The US based retrospective observational study of Eastwood et al. (2012) included 622 HF patients (Mean age, 61±13; Female: 30%)

from a HF Quality of Life Collaborative registry. The objective of this study was to determine the demographic, clinical, behavioural, and psychosocial correlates of depressive symptoms in HF patients. The inclusion criteria was patients ≥18 years admitted to cardiology clinics related to academic medical centres in the Northeast, Midwest, South and Southeast of the USA, with a documented diagnosis from a cardiologist of chronic HF, from either preserved or non-preserved ejection fraction. Exclusion criteria were having experienced MI or stroke within the previous 3 months and known cognitive problems (not being able to answer researcher's questions, complete questionnaire or give consent to participate). The Patient Health Questionnaire (PHQ-9) is a self-assessment questionnaire employed to assess the severity of depressive symptoms. The PHQ-9 comprises nine items as stated in its abbreviation. Each item can be scored between 0 (not at all) and 3 (everyday), and minimum and maximum values of 0 to 27 can be received, and higher scores relate to more severe symptoms of depression. The clinical cut off point of 10 is used in the analysis of this study ≥10 to indicate having depressive symptoms. Another assessment tool, namely, the Brief Symptom Inventory (BSI) was used to assess anxiety. This scale consists of 6 items, which are rated by patients according to a score of 0 indicating no distress ranging up to 4 indicating extreme stress. The results of the multivariate analysis revealed that anxiety was a significant correlate of depressive symptoms. The other variables including age, ethnicity, marital status, financial status, smoking, BMI, Charlson comorbidity index scores, NYHA class, functional capacity, and health perception were not found to be statistically significant. However, the inclusion of only the HF population in this study limits the generalisability of the results to the wider population of patients with CVD.

A Canadian prospective observational study conducted by Horne et al. (2013) recruited 436 CABG patients. Mean age was 65 (57-71 range) for patients classified as naive, 67 (58-77 range) for patients classified as at risk, and 64 (58-72 range) for patients classified as depressed according to their PHQ-9 scores, and the percentage of

females was 32.4%. Post-operative stressful events were found to be a significant determinant of depressive symptoms in the study, despite the primary aim of the study being to assess the impact of physical activity on depressive symptoms. However, they failed to describe thoroughly what the stressful events were, or how this variable was used in the analysis. In addition, the independent variables used in the regression analysis were insufficiently reported, and the result of the analysis were similarly not clearly reported.

Schrader et al. (2006) was a prospective Australian study recruiting range of CVD patients, 1444 acute coronary syndrome (ACS) and HF patients. Mean age of participants was 62.2±12.4, and 32% were female. In the multivariate analysis, self-reported past experience of emotional health (depression, anxiety or stress) was found to be a significant determinant of depressive symptoms at 12 months post-hospital discharge, as measured by CES-D self-report questionnaire. Age and gender were adjusted for in the multivariate analysis; however, they were not significant determinants. Stafford, Berk and Jackson's (2013) study identified general anxiety disorder (GAD) as a significant determinant of depression 3 months after discharge from hospital for acute events. Both depression and GAD were assessed using the Mini International Neuropsychiatric Interview Version 5 (M.I.N.I.), which is a diagnostic structured interview tool, similar to the Structured Clinical Interview for DSM-IV. However, the number of patients with GAD was relatively small in this study (10 smoker and 27 non-smoker), making the results of the multivariate analysis questionable, as there should be at least 10 patients for each variable, and this was barely the case for some of the variables included in the analysis.

2.5.1.7 Other variables

Diabetes was significantly associated with depressive symptoms in one of the included studies (Pajak et al., 2012). For example, Pajak et al. (2012) found that self-reported diabetes was associated with higher HADS depression scores in CVD patients at least 6 months after hospitalisation due to CHD, according to a multivariate analysis. In

Naqvi et al.'s (2007) study, diabetes was found to be significantly associated with depressive symptoms as measured by the Zung questionnaire in the univariate analysis. However, this did not apply in the multivariate analysis. In addition, variables observed in the multivariable analysis were not adequately reported, and there were few independent variables employed. In addition, due to a study design excluding patients experiencing ongoing treatment for depression, the generalisability of the findings might be limited. According to a study by Stafford, Berk and Jackson (2013), comorbidity of diabetes, as obtained from medical records, was not a significant determinant of depression. However the limitations of this study were explained previously (section 2.5.1.1). Bonnet et al. (2005) adjusted for diabetes in their analysis, however, they did not report its results.

Two of the included studies revealed dietary fat intake to be a significant determinant of depressive symptoms (Murphy et al., 2012; Bonnet et al., 2005). Murphy et al. (2012) found that higher dietary fat intake was associated with an increased likelihood of experiencing depressive symptoms. In addition, Bonnet et al.'s (2005) study showed that an unhealthy diet was a determinant of increased depressive symptoms in men, but not in women.

The total number of comorbidities was found not to be a significant determinant in two studies (Eastwood et al., 2012; Gravely-Witte et al., 2009). Eastwood et al. (2012) used the Charlson comorbidity index, and reported it was not a significant determinant of depressive symptoms. In Gravely-Witte et al.'s (2009) study it was more broad and a binary variable whether patients had any other comorbid condition or not, however it was also a non-significant determinant in this study. Ernstsen et al. (2016) adjusted for comorbidities but did not report any of the findings.

Three of the included studies found marital status to be a non-significant determinant (Stafford, Berk and Jackson, 2013; Eastwood et al., 2012; Murphy et al., 2012). Stafford, Berk and Jackson's (2013) study categorised marital status into married and

unmarried, and in Eastwood et al.'s (2012) research, single, divorced, and widowed people were individually categorised within single and the other category given was married. However, the limitations of these studies have been described previously. In addition, marital status was adjusted for in Bonnet et al.'s (2005) and Zhu et al.'s (2019) studies, and yet no results were reported.

2.5.2 Strengths and limitations

In the current review, the literature was searched thoroughly using several databases, which is one of its main strengths. A further strength is that the included studies were restricted to those using a multivariate analysis showing an independent association between exposure variables and outcomes. One of the limitations of this critical review was that included studies were restricted to those written in English. Another limitation was that there was great heterogeneity among the studies in terms of the assessment tool used to assess symptoms of depression, variation in sample size, study population. Different study designs, and statistical analyses also resulted in variation across the different studies. Although overall, the quality of the included studies was fair, some studies were poorly reported in terms of study methods and results.

2.6 Conclusion

The current study critically reviewed previous studies that had aimed to investigate the determinants of depressive symptoms in CVD patients. The critical review included 15 studies conducted in different countries (N= 22,930). Huge variation persists among those studies aiming to identify the determinants of depressive symptoms in CVD patients in terms of sample size, patient population, study designs, assessment tools used to assess depressive symptoms, statistical analysis, and covariates used in the multivariable analysis. Smoking, physical inactivity, age, gender, BMI, anxiety, diabetes, and diet were found to be potential determinants of depressive symptoms herein. In addition, well designed, high quality studies that employ appropriate and detailed reporting are essential to enable future high quality reviews to be performed.

As there is a lack of studies determining depressive symptoms in patients undergoing CR, future studies specifically conducted in CR setting involving a large sample size are necessary.

Chapter 3: Methodology

This thesis uses quantitative research methods, meaning the data collected during the study is presented numerically. Quantitative research tests hypotheses by investigating relationships and or causation among variables, and mainly relies on objective measurements (Ingham-Broomfield, 2014). However, the predominant focus of this thesis is on examining the relationships between the characteristics of patients and symptoms of depression; this differs from causation. Quantitative research is appropriate when there is antecedent knowledge, and in situations where it is possible to apply standardised data collection methods, such as survey questionnaires. Although quantitative research is vital for developing guidelines and for policy making, it is often criticised for its reductionist nature, as it typically focuses on one specific element or a particular variable (Farrelly, 2013). However, quantitative research often involves large sample sizes, which can, when good sampling approaches are applied, be representative of a total population (Harvey and Land, 2017). Quantitative research methods were applied to answer the specific research questions posed in this thesis. This research approach seeks to answer questions about the association between depression and other baseline characteristics of patients with comorbid history of depression, and patients with new onset depressive symptoms, and to discover what the determinants of depression are in participants with a comorbid history of depression and in those with new onset depressive symptoms. Due to the specificity of these research questions, and the study aims, a large sample size is required, and quantitative research was therefore selected as the most appropriate way to address this.

Quantitative studies are often used in evidence-based practice (EBP), and for the development of clinical guidelines. EBP is defined as:

> ‘A problem-solving approach to clinical decision making in healthcare that integrates the best evidence from well-designed studies with a clinician’s expertise, which includes internal evidence from patient assessments and practice data, and a patient’s preferences and values’ (Melnyk et al., 2012).

EBP generally leads to a reduction in healthcare costs, an increase in quality of care and an improvement in patient outcomes (Melnyk et al., 2014). Due to its many benefits, healthcare providers and hospitals recommend the implementation of EBP whenever possible (Melnyk et al., 2012). EBP is a key factor in identifying strategies to achieve better and more affordable care, and ensure healthier communities. However, although EBP is acknowledged as a means of reducing mortality, medical errors and variations in the healthcare quality, its successful implementation by healthcare professionals might not be considered consistent or adequate (Pravikoff, Pierce and Tanner, 2005). The major reasons for lack of EBP implementation in healthcare settings might be limited clinicians' knowledge and skills, or their belief that EBP is overly time consuming and an extra burden (Beckett et al., 2011). However, due to its extensive benefits, its practise and application in clinical settings should be encouraged by researchers and heath care professionals alike. Moreover, its importance should also be acknowledged across the healthcare profession (Melnyk et al., 2014).

One principle of EBP requires that a hierarchy of evidence be built, according to which not all evidence is judged at the same level (Murad et al., 2016). A hierarchy of evidence is often presented as a pyramid, and evidence-based healthcare practitioners often employ this pyramid when assessing the literature and applying evidence (Murad et al., 2016) **(Figure 3.1)**.

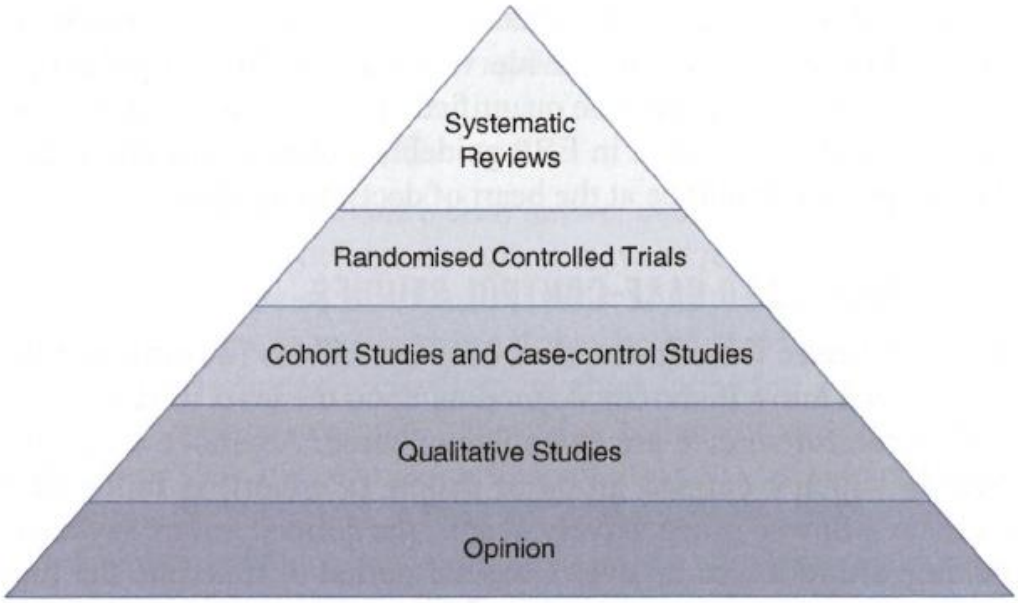

Figure 3.1: Hierarchy of evidence pyramid (Adapted from: Harvey and Land, 2017)

Good quality systematic reviews are at the top of the pyramid, and are considered the best available evidence. High quality robust randomised controlled trials (RCTs), observational studies, qualitative studies and expert opinion follow this hierarchy in sequential order. Although RCTs are ranked higher in the hierarchy of evidence pyramid, they may not always be an appropriate design to fit a study's specific purpose. In addition, the quality of evidence is changeable according to the study design. For instance, an RCT could be of poor quality with a high risk of bias, and therefore a good quality observational study may produce more valid results (Balshem et al., 2011; Guyatt et al., 2008). The differences between the main quantitative study designs (RCT and observational study) and the reasons why the observational study method was chosen over RCT for the purposes of this thesis will be explained in greater detail in the following section.

3.1 Why a retrospective observational study?

A retrospective observational study was conducted to explore the research questions in this thesis. There is published work suggesting that randomised controlled trials (RCTs)

are the “gold standard” (Saturni et al., 2014), and some scientists argue that observational studies by contrast have little to contribute (Black, 1996). Although RCTs and concomitant systematic reviews are located at a higher level on the hierarchy of evidence pyramid (Berlin and Golub, 2014), the nature of this study means it is not logical to design a trial, because not all questions can be suitably answered by RCTs (Saturni et al., 2014; Jepsen et al., 2004). The efficacy and effectiveness of Cardiac Rehabilitation (CR) has been established in more than 60 clinical trials, as has been summarized in three systematic reviews and meta-analyses carried out during the last ten years (Anderson et al., 2016; Taylor et al., 2014; Lawler, Filion and Eisenberg, 2011). The current gap in the literature revolves around how best to implement CR (Doherty and Lewin, 2012). A primary challenge here is the need to identify and evaluate which specific factors determine outcomes. The determinants of change in depression levels following CR, and the characteristics of patients with these conditions are the focus of this thesis. This will be examined in patients with a comorbid history of depression, and in patients with new onset depressive symptoms, and the characteristics of patients with high levels of depressive symptoms at the start of CR will also be investigated by drawing on these populations. Patients with comorbid conditions are often excluded from RCTs (Fortin et al., 2006); therefore, an observational study was considered the best choice to provide valuable insights using a large sample of patients with a comorbid history of depression.

In trials, there should be at least one population that receives a treatment and one that does not (Evans, 2003). However, this will not be the case in this study, because determinants and patient characteristics cannot simply be changed or manipulated, as trials would normally seek to do (Young and Solomon, 2009). This study aims to assess and factor in the baseline characteristics of patients with a comorbid history of depression, and patients with new onset depressive symptoms, and investigate the determinants of depressive symptoms following CR in these populations using routinely collected real life data. Jepsen et al (2004) argued that RCTs might be inappropriate,

unnecessary or even impossible in some cases, and that observational studies may be more effective. As a trial design does not seem appropriate for this research, an observational study will be the best possible approach to answer the research questions posed.

The reason for the study's focus on baseline patient characteristics is to assist clinical teams to adjust interventions to the patient population. Understanding the characteristics of the patient population, and the association of these characteristics with outcomes is therefore crucial. The outcomes were also investigated, but identifying baseline patient characteristics facilitates the researcher's understanding of the determining factors of patients having higher levels of depression in patients with comorbid depression, and new onset depressive symptoms at the start of CR. This will enable the intervention to be tailored more effectively, rather than studying depression outcomes first.

Prior research has suggested that a comorbid history of depression might be important for determining depression outcomes, and is also shown to be associated with adverse cardiovascular events and increased mortality (Albert et al., 2009; Lesperance, Frasure-Smith and Talajic, 1996). One of the aims of this research is therefore to investigate the determinants of depressive symptoms in patients with comorbid depression, and in patients with new onset depressive symptoms for the CR outcome, which will be done by employing the same observational approach. The research takes this approach because numerous RCTs have already proven the effectiveness of CR. There is a wealth of clinical trials that have tackled this issue, listed in Cochrane Reviews, comparing individuals who received CR and those who did not (Anderson et al., 2016). Although a recent low quality systematic review has reported conflicting results in all-cause mortality (Powell et al., 2018), the majority of the literature is consistent in confirming the benefits of CR (Salzwedel et al., 2020; BACPR, 2017; SIGN, 2017; Piepoli et al., 2016; Anderson et al., 2016; Rauch et al., 2016; Lawler, Filion and Eisenberg, 2011). This study will also focus on the variable outcomes of

routinely delivered services to deliver insights into what determines outcomes for patients who begin rehabilitation, and how some patients achieve better or poorer outcomes than others. Hypothetically, the baseline characteristics of patients with a comorbid history of depression that determine their depression levels, following CR, might differ from those of patients with new onset depressive symptoms. It is the objective of the National Audit of Cardiac Rehabilitation (NACR) to improve service quality, so it is essential to ensure CR programmes be made aware of the potential impact of a comorbid history of depression, and new onset depressive symptoms at the start of rehabilitation on patient recovery, and to know what are the determinants of depression levels following CR in patients with a comorbid history of depression, and in patients with new onset depressive symptoms.

The vast majority of RCTs have proven that CR is effective (Anderson et al., 2016), although the RAMIT study showed outcomes are variable (West et al., 2012). The RAMIT study found no statistically significant difference between patients who had received CR, and the control group, in terms of mortality, cardiac events, quality of life and psychosocial health (West et al., 2012). One possible explanation for this might be that although RAMIT was a highly funded study, there were difficulties with recruitment. The researchers attempted to recruit 8000 patients, but eventually only 1813 took part, which may have created self-selection bias. Therefore, the generalisability of the RAMIT findings to real world situations demands careful consideration (Doherty and Lewin, 2012). Problems with recruitment may therefore reduce the ability of a study to demonstrate significant findings (Young and Solomon, 2009). The reason for this low recruitment rate may have been because clinical guidelines and Cochrane Reviews had already established the effectiveness of CR by the time the study took place (Doherty and Lewin, 2012). This means the randomisation of patients might not have been approved by the cardiologists leading the CR programmes, so continuing to attempt randomisation would have led to ethical problems. Young and Solomon (2009) stated that when an RCT is not a feasible option for answering research questions,

observational studies are the most appropriate study design. Observational studies are also faster and cheaper to implement than RCTs (Carlson and Morrison, 2009).

The National Audit of Cardiac Rehabilitation (NACR), funded by the British Heart Foundation (BHF), is a clinical audit that monitors CR services in the UK in terms of service delivery and patient outcomes. The age range in the NACR data is 18 - 109 with a mean age of 67. 30% of participants were female, while for the majority of the RCTs included in the recent Cochrane Review the mean age was 56 and the female percentage included was less than 15% (Anderson et al., 2016). Considering this difference in terms of average age and percentage of female participants, the data shows that RCTs may not reflect real life situations. Conducting an observational study using NACR data therefore seems a much better option; indeed, it is a vital one if we are to understand what happens in real life rather than in a manipulated experimental environment (Faraoni and Schaefer, 2016).

Much like any other form of study, observational studies have known disadvantages. For instance, lack of follow-up can be problematic and may cause attrition bias in observational studies (Song and Chung, 2010; Carlson and Morrison, 2009; Fewtrell et al., 2008). In order to reduce this type of bias, this study will determine whether patient characteristics are similar across the missing populations to those of the participants included in this study. The missing values, and how to deal with them will be discussed below in a separate section (3.8.1), and at this stage I will only highlight its importance to observational studies. Another important issue that relates to observational studies is that causal conclusions cannot be drawn from them. Unlike RCTs, which provide cause and effect relationships based on specific interventions that have been applied, observational studies can only provide estimates of association. Therefore, they are also referred to as correlation studies (Bowling, 2009). The focus of this thesis is therefore on association, rather than causality.

For the reasons given above, a retrospective observational study was selected as the study method. Retrospective observational studies often involve participants' past and current events, attitudes, and behaviours. Secondary data analysis can be conducted in retrospective observational studies, which is often economical in terms of time and resources, and can include a large sample size which can be surveyed quickly, resulting in standardised and generalisable data that is easier to record. Surveys are often applied to collect data for retrospective observational studies, and secondary data analysis is applied afterwards for more specific study purposes.

3.2 Surveys and secondary data analysis

Surveys are used to describe populations, and to study the associations between variables. Surveys are designed to measure events, behaviour or attitudes in the population of interest, and to calculate descriptive measures (Bowling, 2009). Surveys are advantageous as they are often carried out in real life settings. Generally speaking, surveys have two main objectives. The first is the estimation of population parameters in areas such as health status, and the second is to test a hypothesis in a population (Bowling, 2009; Boynton and Greenhalgh, 2004). In order to fulfil either purpose, relevant data from the sample of interest is collected and then statistically analysed. Survey questionnaires enable researchers to quantify patient's experiences using a fixed set of questionnaires supports the repetition and comparison of study findings across different studies using similar tools (Boynton and Greenhalgh, 2004).

3.2.1 Secondary data analysis

Secondary data analysis refers to the use of data sources that already exist and have been collected by others (Bowling, 2009). These data sources are often routinely collected statistics in hospitals, primary care settings, and community health services. There are several accessible survey data sets, which can be used for secondary data analysis and are archived in Europe, in the USA and the UK (Bowling, 2009). The UK NACR data used for the analysis in this thesis is one such data repository, and is

located on NHS Digital secure online platform; after patient identifiers are removed an extract is then sent to the Department of Health Sciences University of York.

Secondary data analysis provides opportunities for researchers to identify convenient answers to their research questions using large data sets, which often include under-represented groups (Donnellan and Lucas, 2013). For the purpose of primary data analysis, research data is collected by researchers designing new studies, whereas existing data can be used in a secondary analysis. There are some advantages and disadvantages to both primary and secondary data analysis techniques. Primary data researchers face challenges recruiting sufficient participants to generate statistical power. Several factors are responsible for low recruitment, such as time and resource constraints, and failure to calculate statistical strength in terms of results (Donnellan and Lucas, 2013).

Existing data sets used for secondary data analysis are much larger and of significantly higher quality than could be collected by a single researcher (Cheng and Phillips, 2014; Johnston, 2014). This enables much more valid generalisability of findings to a specific population. Additionally, large data sets provide sufficient statistical power to conduct complex analyses, and are also convenient for a subgroup analysis of populations that are often poorly represented in sufficient quantities in smaller studies. Therefore, secondary data sets often have considerable breadth, and researchers can also utilise them to measure changes over time (Cheng and Phillips, 2014; Johnston, 2014). An additional reason for using the NACR data for secondary data analysis, rather than generating a new data set, was insufficient time and resources for collecting primary data to deliver a prospective design large enough or to cover a time period sufficiently long enough to answer the research questions (Smith et al., 2011). NACR data provided an opportunity to conduct analyses with a large data set, which had been rigorously collected each year since 2005. The availability of good quality NACR data meant that, ethically, collecting more data could be viewed as questionable. Newly collected data would be less informative, and might result in needless use of resources

for recruitment and data collection, which could have been directed elsewhere. Another reason NACR data was chosen for the analysis is that the sample is nationally representative of CVD patients, which thereby increases the generalisability of the findings presented in the studies conducted in this thesis.

Several skills are required to conduct a high quality secondary data analysis, including scientific judgement, attention to detail, and a thorough knowledge of statistical methodology (Donnellan and Lucas, 2013). One disadvantage of analysing secondary data is the large amount of time and energy required for researchers to familiarise themselves with codebooks and datasets. It is easy to overlook the importance of this issue and therefore to underestimate how long it takes to move from a research concept to a complete and final analysis (Johnston, 2014). Moreover, handling data using large data sets requires knowledge and experience of using statistical software packages. Secondary data researchers also need to understand how the data has been collected, the purpose informing that collection and what was subsequently done with the data (Cheng and Phillips, 2014). Issues relating to data sources, collection, and purpose will be explained further in the following sections (3.3, 3.4, and 3.5).

3.3 Data Source

This thesis aims to evaluate the baseline characteristics of participants associated with high levels of depression, and the determinants of depression outcomes in patients with a comorbid history of depression, and in patients with new onset depressive symptoms. To realise these aims, a secondary analysis using NACR data was conducted. In this section, NACR is further explained in terms of its aims and data collection methods.

3.3.1 NACR Data

Comprehensive audit data is collected by NACR to improve upon secondary prevention, and to monitor CR services in terms of accessibility, quality assurance and clinical outcomes. In addition, it aims to support local teams (community centre or

hospital based) to produce their own reports detailing patient progress (NACR, 2019). NACR is the only audit that collects national data from CR programmes on care quality and outcomes for patients who have experienced a myocardial infarction (MI), a percutaneous coronary intervention (PCI), a coronary artery bypass graft (CABG), and a heart failure (HF). Data from routine clinical practice is collected regarding the service being offered, and its benefits to CR patients to facilitate quality assurance.

The objectives of NACR are to:

- Inform commissioners about whether services are running at the standards expected, with reference to national guidelines.
- Identify inequalities in the provision of CR, to enable local providers to ensure all patients are being offered the same opportunities.
- Describe what patients can achieve with CR; thus, enabling assessment of the performance of individual CR programmes.
- Examine why patient outcomes vary between programmes, thus identifying those services that require attention and can be supported to improve.
- Work collaboratively to share information with national institutions, such as NHS England, National Institute for Health and Care Excellence (NICE), and the British Association for Cardiovascular Prevention & Rehabilitation (BACPR) (NACR, 2019).

Data from the majority of CR programmes in the UK is collected by NACR, and comparisons are then made based on minimum standards of service improvement, and better delivery of resources (NACR, 2019; BACPR, 2017). In addition, NACR reports that CR programme performance is based on minimum clinical standards locally, regionally and nationally, showing whether CR programmes meet or fail to meet minimum clinical standards on typical outcomes, such as identification, referral and recruitment of eligible patient populations; early initial assessment of individuals; early

provision of a structured cardiovascular prevention; and final assessment of individual patient needs among others (NACR, 2019; BACPR, 2017).

3.4 Data collection

Patient data is anonymised and collected to assess a range of clinical variables. Individual patient data on demographics, comorbidity, smoking, physical activity and psychosocial health is entered into the NACR via an NHS digital secure online portal. Healthcare professionals collect data by distributing purpose-designed questionnaires. Patients complete these NACR questionnaires before and after CR. Subsequently, the approved Caldicott Guardian electronically enters the data into the NHS digital database. From there, the link-anonymised patient level data is sent to the University of York for the data validation and quality checks. The University of York team gathers the data and publishes the results, producing annual reports based on the data. CR patient journey and the data collection processes can be seen in **figure 3.2** below.

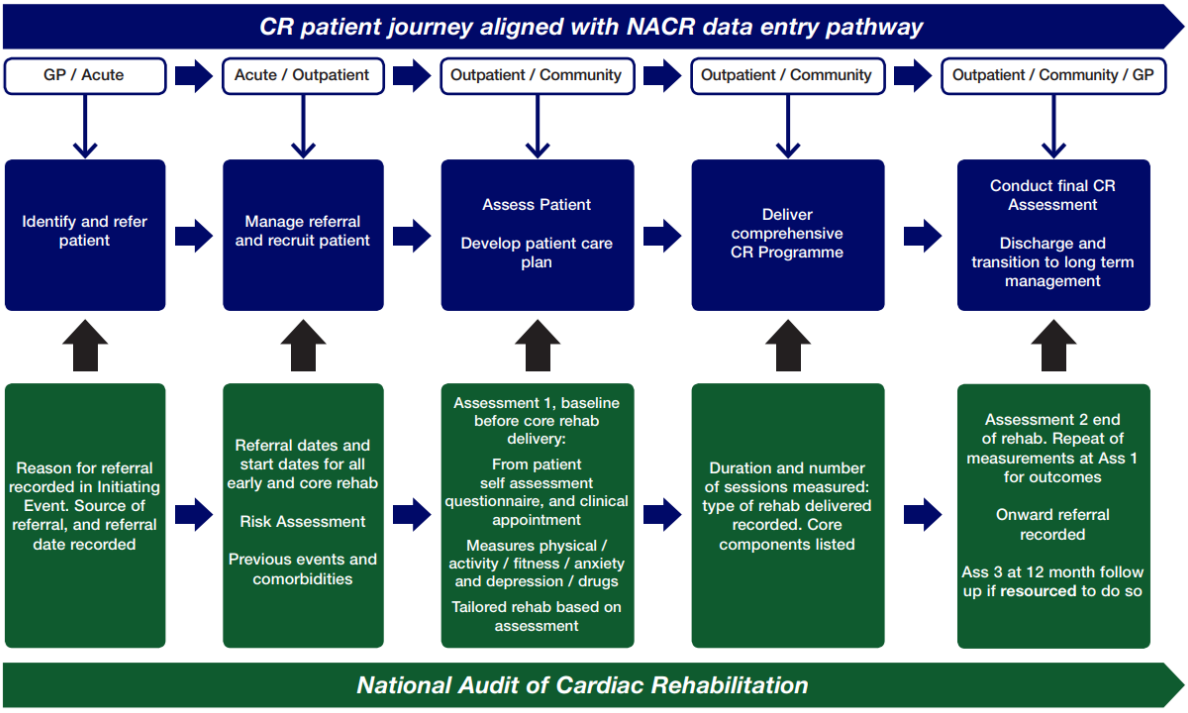

Figure 3.2: NACR patient journey and data collection [Adapted from (BACPR, 2017)].

Patients are initially identified and referred to CR by general practitioners, or from acute care wards. The referral of patients is thereby managed and appropriate patients recruited to CR. Before CR is implemented, patients are assessed and baseline measures are taken such as physical activity, previous events and psychosocial measurements, in order to support a tailored programme of rehabilitation (the questionnaire in **Appendix - 4**). Comprehensive CR programmes are delivered to provide secondary prevention to benefit CVD patients, at the end of which a final assessment is conducted to measure CR outcomes. The total number of services contributing data to NACR is 230, which constitutes 82% of all CR programmes in the UK, including England, Wales and Northern Ireland (NACR, 2019). In the studies conducted for this thesis, baseline and outcome measures are used to investigate associations between set baseline characteristics and depressive symptoms, and the determinants of depression outcomes in the specific population of participants with a comorbid history of depression, and patients with new onset depressive symptoms.

3.5 Data Input

Data input is the process of keying data into a digital system. It is often done manually by registered Caldicott Guardians, who enter patient data into a digital national database system. Registration to the NACR, and data input for audit purposes is one of the BACPR national standards, which aims to establish quality assurance and ensures service development of CR programmes (NACR, 2019; BACPR, 2017). NACR applies extensive data checking for quality appraisal, and data cleaning and matching therefore becomes less of a burden. NICE guidelines and the NHS commissioning and accountability frameworks are taken into account for data quality approaches, such as automated data validation within the portal system, which does not allow the keying of extreme values.

3.6 Study Design

3.6.1 Participants

Individual patient data was extracted from 1 April 2012 to 31 March 2018, based on NACR figures. Male and female participants aged 18 years and over were included in the analysis. Patients experiencing cardiac events, such as MI and heart failure, and patients who had received PCI and CABG treatments were included in the analysis according to recommendations made in the guidelines (NICE, 2018, NICE 2013). All eligible participants with a comorbid history of depression, and patients with new onset depressive symptoms who had undergone pre- and post-HADS depressive symptom screening comprised the study population in the included studies.

3.6.2 Measures

3.6.2.1 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a measurement tool used for screening for anxiety and symptoms of depression in CR programmes across the world (Bjelland et al., 2002). HADS is recommended before and after CR to tailor intervention needs specifically to individual patients (BACPR, 2017). To date, HADS has been used in recent large clinical trials investigating CR (Dalal et al., 2019; Wells et al., 2018). The HADS score is separately rated, between 0 and 21 for anxiety and depression, with higher numbers reflecting worsening symptoms. It has been found to be a valid and reliable measurement for the assessment of both anxiety and depression, and consequently is recommended for use with cardiac patients (Bjelland et al., 2002; Spinhoven et al., 1997; Zigmond and Snaith, 1983). NACR holds a licence for HADS to be used by audit registered services. In this thesis, the HADS depression measurement scale is used for the primary outcome assessment. A clinical cut off point of 8 is used in this analysis, and patients are categorised as either having low levels of depression (< 8) and higher depression groups (≥ 8), for both baseline and outcome analyses (Zigmond and Snaith, 1983). Baseline associations are investigated to

compare patients with low levels of depressive symptoms and those showing higher depressive symptoms, focusing on participants within the comorbid depression group. Key determinants of HADS depression outcomes are examined using a logistic regression to ascertain what determines change (improvement) in depressive symptoms following CR, and specifically in patients with a comorbid history of depression. A similar approach was followed for patients with new onset depressive symptoms, as will be explained in detail in the study chapters.

3.6.2.2 Comorbid depression

Comorbid depression is measured with a case note review, and the question: 'Have you ever been told by a doctor that you have definitely had or been treated for depression?' This question is included in the NACR data questionnaire, which includes the patient's history of depression prior to a cardiac event. It is answered with a 'yes' or 'no' option. Patients with comorbid depression constituted the population of the first study, and patients with new onset depressive symptoms the second study.

3.6.2.3 Other variables

HADS Anxiety baseline measurement was used as a continuous variable with a value set between 0 and 21. Its structure is explained above (section 3.6.2.1). Age was also used as a continuous variable. Gender was categorised as either male or female. The total number of comorbidities variable shows the number of possible comorbidities present. In the NACR data, 19 different comorbidities are present, including hypertension, hypercholesterolemia, diabetes, angina, arthritis, osteoporosis, asthma, chronic bronchitis and other. Weight is measured in kilograms. Baseline smoking measurements are categorised to establish whether a patient currently smokes or not. Marital status is categorised according to whether the patient is partnered or single. Baseline physical activity is measured with the question: 'Do you take regular moderate physical activity of at least 30 minutes duration on average 5 times a week? (or its equivalent, 150 minutes over 7 days)' and the response options provided were 'yes' or

'no'. Moderate activity is explained in the questionnaire as anything requiring as much effort as brisk walking or housework, carrying a light bag on level ground, mowing the lawn, painting and decorating, sports like easy swimming, easy cycling, or hobbies such as ballroom dancing.

Although only briefly mentioned here, the included variables will be explained in detail in each study.

3.7 Ethics

Gaining the informed consent of patients to support the management of acute cardiac events is difficult, and creates an additional burden on healthcare professionals and services. To resolve this issue, exemption from individual consent is given by the NHS, with sufficient safeguards applied. Permission is granted for the NACR to use patients' data by the Health Research Authority's Confidentiality Group under section 251 of the NHS Act 2006, which permits hospitals to collect identifiable patient data without the requirement for individual consent. However, the purpose of the audit is explained to patients through questionnaires they have completed, or via face to face interactions. Patients are also informed of the right to withdraw at any time.

Postgraduate researchers are allowed to use NACR data with permission from the Chair of the NACR audit, for the purposes of research. However, there are number of regulations that must be adhered to, and these regulations are strictly imposed by the Data Sharing Agreement between NHS Digital and NACR. An Online Information Security Training Course provided by University of York must be successfully completed before access to the data is granted. Confidential patient information is included in the NACR, so those to whom access is granted must comply with these general data protection regulations.

There are other ethical issues that require careful attention from researchers to avoid breaching data protection rules. Firstly, no publication that includes data results can be published without an acknowledgement from the Director of the NACR. Secondly,

original data sets must not be copied or removed from the secure network of the University of York Health Science Department database, called the 'I drive'. Lastly, data must not be presented that includes the names or locations of CR programmes without the express permission of the NACR chair. When the research period for postgraduate study finishes, access to the Department of Health Sciences online data network will be terminated and all data must be returned to the NACR team to be archived.

3.8 Statistical analysis

The analysis was performed using the IBM statistical package for social sciences software statistics (SPSS) Version 24 (New York, USA). The study population comprised patients with a comorbid history of depression, patients with new onset depressive symptoms and those with pre- and post- HADS depression measurements. A 5% significance level was applied to the statistical analyses. The mean and standard deviations and proportions were used for the summary statistics. Independent sample t-tests and chi square tests were carried out to investigate baseline characteristics in the population with comorbid depression, and those with new onset depressive symptoms. Effect sizes were calculated and reported for continuous and categorical variables. For the outcome analysis, binary logistic regression was conducted to determine the change in HADS depressive symptoms based on the variables as defined from both the literature and baseline assessments in the sub-populations of patients with a comorbid history of depression and patients with new onset depressive symptoms. Statistical analyses were explored broadly under each study, and as such are only briefly mentioned here.

Another statistical issue that demands attention relates to dealing with missing data and outliers, which is an important aspect of any analytical procedure when working with large data sets (Kwak and Kim, 2017). Appropriate approaches to dealing with

these factors was viewed as a necessary part of the procedure, and is further explained below.

3.8.1 Missing values

Missing data arises when there is no available value stored for a variable during an observation. Missing values can impact study validity and potentially cause biased estimates (Graham, 2009). Having missing data is not rare, and is viewed as almost inevitable in observational studies. Missing values can arise as a consequence of drop out or non-response. Observational studies with a large sample population are subject to frequent missing data (Kaplan, Chambers and Glasgow, 2014; Kang, 2013).

Missing data is classified into three categories; missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). MCAR means the absence of a value is not related to the observed subject data. For instance, blood pressure measurements could be missing due to a breakdown in automatic sphygmomanometer (Sterne et al., 2009). MAR means the absence of data is related to the subject, but the value can be predicted according to other available information that exists for this subject. For example, when a child does not attend an exam because he or she is ill, their absence could be predicted based on other data regarding that child's health (Bland, 2015). MNAR means there is a systematic pattern in absences, which are directly related to what is missing. An example could be when a subject does not attend a drug test due to having taken drugs the night before (Bland, 2015). This is a worst case scenario, and one which we seek to avoid, as it may bias the study results as there is a clear pattern in the absence. Ideally, we do not want any absences or blank values in the data set, so studies must be well designed from the outset to prevent this from happening. However, this is very difficult in practice, and MCAR is the most preferred type of missing data when absences are inevitable. This is because when a missing data meets MCAR assumptions, it can be seen as a random sample of the full dataset (Dong and Peng, 2013). As a result, ignoring missing data under this assumption will not introduce bias, although standard error of sample

estimates could increase due to a reduced sample size. This means that in the final analysis, MCAR poses less of a threat to inferences drawn from sample populations than MAR or MNAR (Dong and Peng, 2013).

There are different approaches given to deal with missing data. One possible approach is the so-called “complete case” or “available data” analysis. All incomplete cases are omitted and the analysis is performed using only the available variables that are. This is a valid approach, and less likely to provide biased estimates when missing data is MCAR (Sterne et al., 2009). A recent study suggests that for MAR or MCAR data, available data analysis estimates are generally unbiased and achieve a level of precision similar to or better than multiple imputation methods (Mukaka et al., 2016). Therefore, in this thesis, available data analysis will be favoured where possible to obtain estimates that are closer to real data, reflecting the measures collected during routine NHS practice.

Another technique for dealing with absence is to use the sample mean to replace missing data, or carrying forward the last known observation when we conduct more than one observation over time. Here, the observation prior to the missing one is being used as an estimate. However, neither of these methods are preferable, as they are more likely to bias results, and so are not recommended by statisticians (Bland, 2015; Kang, 2013).

Other more complex techniques for dealing with missing data include maximum likelihood and multiple imputation. When data is missing, however relatively complete the dataset is, the maximum likelihood method can be used to estimate the missing data by examining the conditional distribution of other variables (Kang, 2013). Another technique to address missing data is multiple imputation. Multiple imputation is a useful and robust technique for handling missing data (Sterne et al., 2009). Rather than substituting a single value for each missing value, a set of plausible values is utilised, which allows for natural variability and uncertainty among real values. This natural

variability is performed by observing the different variabilities between the imputed data sets to produce differing versions of the missing data. Pooling these results, a single overall result is produced (Kang, 2013). For that reason, when an available data analysis is not the best application, such as when there are high rates of data absence, the multiple imputation method is used to replace missing values in this thesis.

3.8.2 Outliers

Outliers are observations that are distinct from the rest of the data (Kwak and Kim, 2017; Ghosh and Vogt, 2012). These values could be based on real observations from patients with extreme levels of variable (Osborne and Overbay, 2004), or might reflect typographic errors or incorrect unit choices. Therefore, all suspicious values need to be examined. Detecting outliers is crucial as they can influence the results of a multivariate data analysis (Ghosh and Vogt, 2012; Cousineau and Chartier, 2010). For instance, in most data sets, a woman whose height is 220cm could appear as outlier. However, although this is an extreme value for the height of a woman, it could represent a real value (Petrie and Sabin, 2009). The researcher needs to investigate further and check other variables, such as age and weight before deciding whether or not it is a valid value. Changes should only be applied if there is strong evidence the value is not correct (Petrie and Sabin, 2009). The inclusion of outliers may alter study results (Kwak and Kim, 2017; Ghosh and Vogt, 2012; Cousineau and Chartier, 2010), and the data needs to be managed appropriately to avoid this. One strategy to manage outliers can be the audit data entry system itself, which prohibits the input of extreme values. Another strategy is manual cleaning of extreme values which may not be real, and the exclusion of values that are beyond three standard deviation from the mean (Osborne and Overbay, 2004). These strategies will be applied when performing the analyses in this thesis.

Chapter 4: Determinants of depression in patients with comorbid depression following cardiac rehabilitation (CR)

4.1 Abstract

Background

Comorbid depression, which this study defines as a history of depression prior to a cardiovascular event, is associated with poor outcomes, including increased mortality and a higher than average likelihood of major adverse cardiac events. However, there is a lack of evidence concerning the factors that determine the extent of benefit attained by following a cardiac rehabilitation (CR) programme. Therefore, this study examines the determinants of CR depression outcomes in patients with a prior history of depression.

Methods

Routine clinical data obtained from the British Heart Foundation (BHF) National Audit of Cardiac Rehabilitation (NACR) between April 2012 and March 2017 was analysed, focusing on the population of CR patients with a comorbid history of depression. Independent t-test and chi-square tests were employed to investigate baseline characteristics. To determine improvement in depression outcomes, measured by Hospital Anxiety and Depression Scale (HADS), following CR, a binary logistic regression was applied.

Results

A total of 2,715 CR participants with comorbid depression are included in the analysis, with a mean age of 62.27 years, 33.6% of whom are female. At baseline, patients with comorbid depression, and those with a high level of depressive symptoms were found to be younger (Mean Difference (MD): 2.71, 95%CI: 1.91, 3.50), and to have an increased total number of comorbidities (MD: -0.50, 95% CI: -0.66, -0.34), a high HADS anxiety score (MD: -5.17, 95% CI: -5.47, -4.87), a higher body mass index (BMI) (MD: -

0.71, 95%CI: -1.13, -0.28), increased weight (MD: -1.94, 95% CI: -3.35, -0.52), and comorbid anxiety (52.4%, $p < 0.001$), together with being smokers (12.7%, $p < 0.001$), physically inactive (150 minutes of moderate physical activity a week 27.5%, $p < 0.001$), and less likely to be partnered (63.6%, $p < 0.001$), when compared with patients with low levels of depressive symptoms.

The determinants of post-CR HADS depression measurements associated with better outcomes were found to be not smoking at the baseline (OR 1.774, 95% CI: 1.086, 2.898); physical inactivity (OR 0.707, 95% CI: 0.514, 0.971); a higher total number of comorbidities (OR 0.914, 95% CI: 0.854, 0.979); HADS anxiety score (OR 0.883, 95% CI: 0.851, 0.917); and male gender (OR 0.721, 95% CI 0.523 to 0.992).

Conclusion

The baseline characteristics of the patients with comorbid depression, such as physical inactivity, smoking, higher anxiety, higher total number of comorbidities, and male gender were determinants of the depression levels following CR. In order to optimise outcome in patients with a history of comorbid depression, CR programmes should tailor the intervention, and provide support around these determinants.

4.2 Introduction

Cardiovascular disease (CVD) is the world's number one cause of death, with 17.9 million deaths recorded worldwide in 2016 (WHO, 2017b), and 152,405 deaths in the United Kingdom (UK) in 2017 (BHF, 2018). According to the European Society of Cardiology, 83.5 million people are currently living with CVD in its member countries (Timmis et al., 2017). As a consequence of improved survival rates in CVD, and an aging population, the number of comorbidities present with CVD has increased over time, creating significant challenges for service delivery (Uhlig et al., 2014). Depression is one common comorbidity in patients with CVD (Arnett et al., 2014), with a prevalence of approximately 20% in patients clinically diagnosed via structured interviews, while the proportion is larger when assessed using self-answered questionnaires (Thombs et

al., 2006). Evidence demonstrates that depression is an independent risk factor for cardiac mortality (Correll et al., 2017; Lichtman et al., 2014) and all-cause mortality (Correll et al., 2017; Sokoreli et al., 2016; Meijer et al., 2013). Therefore, the American Heart Association's (AHA) recent scientific statement acknowledges depression to be a risk factor for poor prognosis in CVD patients (Lichtman et al., 2014). Moreover, a systematic review demonstrated that depression in CVD patients is associated with higher hospital admission rates and greater overall healthcare costs (Baumeister et al., 2015). Furthermore, a state of the art review that included recent papers related to depression in CVD patients highlighted that depression makes optimal management of CVD more difficult, by worsening cardiovascular risk factors, and reducing adherence to the management of lifestyle risk factors (Jha et al., 2019).

According to European guidelines, CR serves as a class 1 level A recommendation for CVD patients (Piepoli et al., 2016); further, according to the recent Cochrane review (Anderson et al., 2016), CR is an effective intervention that certain meta-analyses demonstrated reduces depressive symptoms (Zheng et al., 2019; Rutledge et al., 2013). Recent guidelines recommend that CR should be a multicomponent intervention, including the assessment and management of psychosocial health (BACPR, 2017; SIGN, 2017; Piepoli et al., 2016). In the UK CR context, to assess and manage the depressive symptoms of CR patients, HADS is used pre- and post-CR to tailor the intervention according to the patient's needs. This scale is a reliable and validated tool for screening depressive symptoms in CVD patients (Wang, Lopez and Martin, 2006; Spinhoven et al., 1997; Zigmond and Snaith, 1983). However, previous studies have only focused on the psychosocial health measures associated with the acute cardiac event, with a paucity of focus on patients with comorbid depression (Meijer et al., 2013). Some studies have however demonstrated that a history of depression prior to a heart event is associated with increased risk of mortality and poor cardiac prognosis (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016; Albert et al., 2009; de Denus et al., 2004). Nevertheless, there is a lack of research

concerning historic comorbid depression among the CR population. Therefore, the present study aims to identify and evaluate the sociodemographic and clinical characteristics that determine depression outcome following CR in patients with a history of depression.

4.2.1 Rationale for the study

Given the importance of depression associated with CVD and mortality, assessing depressive symptoms, as measured by HADS is important not only within the general population, but also in the CR setting. There is currently a dearth of studies identifying the potential determinants of depressive symptoms among CR patients with a comorbid history of depression. Therefore, this study sought to:

1) Examine the sociodemographic and clinical factors associated with depressive symptoms at the start of CR;

2) Identify the factors that determine the changes in depressive symptoms in patients with comorbid depression, following CR.

4.2.2 The research questions

The research questions posed were:

- What are the factors associated with depressive symptoms in patients with comorbid depression attending CR, at baseline?

- Which baseline characteristics determine depression in patients with comorbid depression, following CR?

The first hypothesis tested whether age, gender, smoking, physical activity, weight, marital status, anxiety, and total number of comorbidities were associated with high levels of depressive symptoms in patients with comorbid depression at baseline. Meanwhile, the second hypothesis tested which of these baseline characteristics of patients with comorbid depression determined their depression levels following CR.

4.3 Methods

This study investigated the factors associated with depressive symptoms at baseline, together with the determinants of CR depression outcome in patients with a comorbid history of depression.

4.3.1 Data source

A secondary data analysis was conducted using the BHF NACR data. The NACR is used to monitor the UK's CR services, and aims to improve the quality of cardiovascular secondary prevention and rehabilitation programmes across the UK. The NACR is operated in collaboration with the UK's National Health Service (NHS) digital and data governance between NHS Digital and NACR is reviewed annually. Individual patient level data is collected by CR programmes via validated questionnaires under Section 251 approval of the NHS Act 2006, and then the data is entered onto a secure online platform hosted by NHS Digital. In accordance with this approval, NHS Digital collects identifiable patient data, which is then anonymised to enable the data to be extracted and made available to NACR for audit purposes. Due to the data used by NACR being anonymised, and the established data governance processes between NHS Digital and NACR, it was not a requirement to gain individual patient consent for the present study, as the data used was already anonymised, and complied with data protection regulations. The PhD related studies are, in accordance with NACR purposes, therefore no separate NHS ethical requirements were necessary. The NACR is representative of the UK's CR programmes, with 224 CR services currently entering data electronically, representing 74% of all programmes (NACR, 2017). The data includes patient demographics, risk factors, treatment, and the outcomes of patients who undergo CR in the UK.

4.3.2 Design and inclusion criteria

A retrospective observational study of routine practice across the UK was conducted using the data extracted from the BHF NACR for the period 1 April 2012 to 31 March

2017. The data was the most recently available data during time of study conducted, and the results were published in that year before the new data was available. As the study has already been published in the journals mentioned at the start of thesis, the aim was to keep the analysis same as in previously published papers, to avoid confusion. Patients were included in the analyses if they were adults (≥18), had experienced a myocardial infarction (MI) or heart failure (HF), and had received treatment in the form of a percutaneous coronary intervention (PCI) and a coronary artery bypass graft (CABG). In the data, a diagnosis of comorbid depression was verified by CR practitioners via case note reviews, together with being measured using a self-answered questionnaire provided by the NACR data, which required the patients to identify whether they had ever been told by a doctor that they definitely had, or had been treated for depression. Therefore, this study defined comorbid depression as a history of depression prior to the heart event. All the eligible patients in the study timeframe with comorbid depression, who had undergone pre- and post-HADS assessments in CR, were included. The flow diagram in **Figure 4.1** shows the total population in the timeframe, together with the study's sample size.

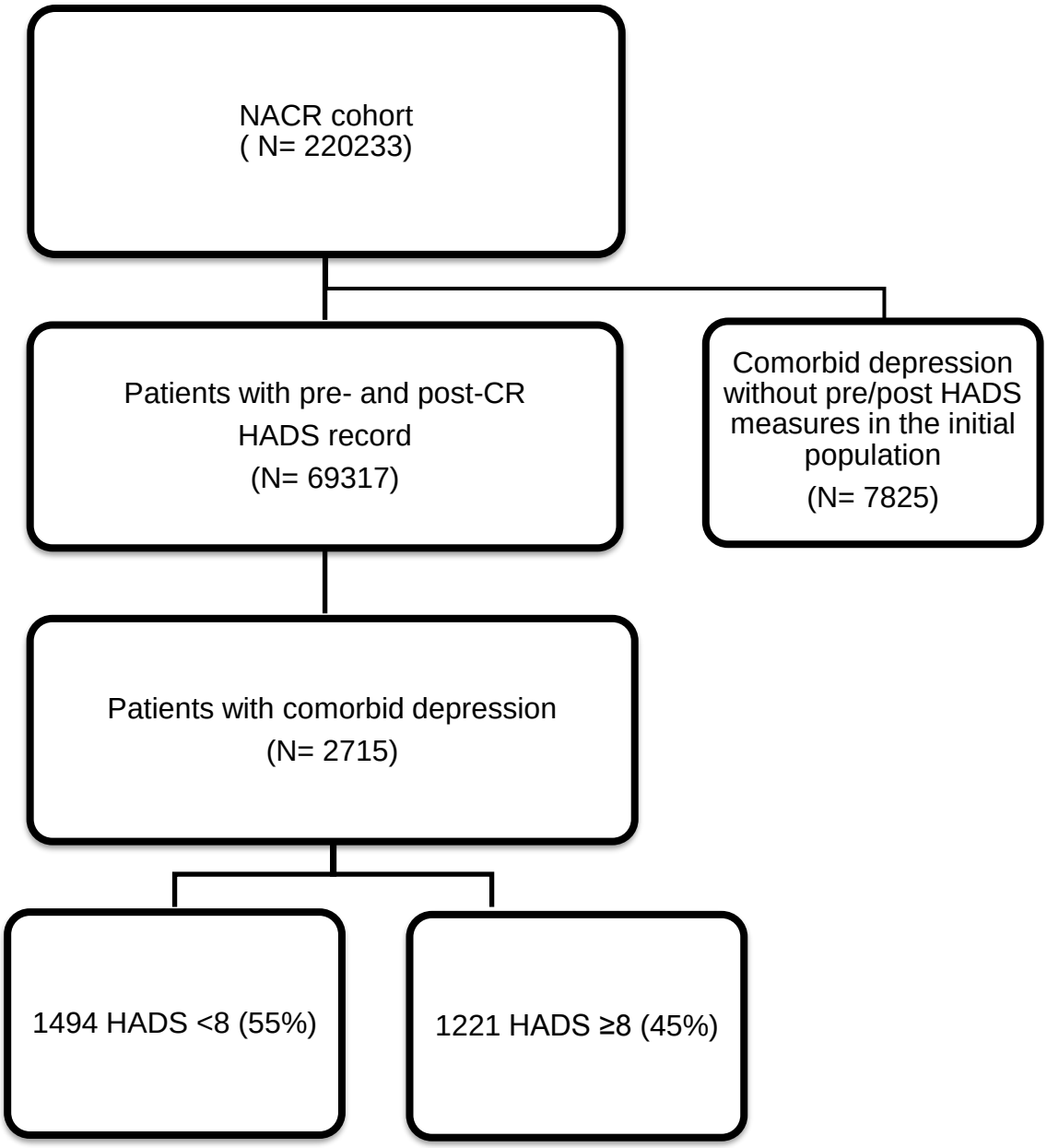

Figure 4.1. Flow diagram representing the study sample.

4.3.3 Variables investigated in the analyses

4.3.3.1 Outcome variable

HADS is a screening tool in the form of a self-answered questionnaire that is employed to measure depressive symptoms in clinical practice. It was found to be a reliable means of assessing depression and anxiety symptoms, in terms of its internal

consistency and test-retest reliability, and is considered a valid measure, and is therefore recommended for use with cardiac patients (Wang, Lopez and Martin, 2006; Spinhoven et al., 1997; Zigmond and Snaith, 1983). Although HADS has been critiqued in terms of its ability to differentiate between constructs of anxiety and depression (Cosco et al., 2012), the recent British Association of Cardiac Prevention and Rehabilitation (BACPR) guidelines recommended the use of HADS, and its assessment both before and after CR, so as to tailor the CR intervention to the patient population (BACPR, 2017). In accordance with the BACPR guideline recommendation and due to being the most commonly used measurement tool in the UK CR programmes registered to NACR, HADS was employed here.

In total, HADS includes 14 items, seven of which cover anxiety symptoms, and seven for depression symptoms. Each item can be assigned a score from 0 to 3, hence a minimum of 0 and a maximum of 21 can be recorded for each of the separate anxiety and depression scores. The tool is licensed to NACR for use by services registered with NACR. This study employed the CR baseline, and the outcome of HADS depression measurements in the analysis, and a clinical cut-off point of eight was used to categorise patients as experiencing low level depression (< 8) and higher level depression (≥ 8) groups (Zigmond and Snaith, 1983). The reason for this is that a systematic review conducted by Bjelland et al. (2002) demonstrated that an optimal balance between sensitivity and specificity for HADS as a screening tool was often achieved at a cut-off score of eight for both HADS anxiety and HADS depression, considering the sensitivities and specificities of both scales at roughly 0.80. The analyses employed in the present study then compared the patients with HADS < 8 and HADS ≥ 8 in a subgroup of patients with a comorbid history of depression. In addition, a comparison was performed between the baseline HADS anxiety scores for patients with low and higher levels of depressive symptoms. A recent study conducted by Lemay et al. (2019) found that the minimum clinically important difference (MCID) was 1.7 in HADS for CR participants. Their study involved a sample of 591 patients

with CVD, of whom 74% of participants were male, with a mean age of 63 ± 10. The MCID for HADS was estimated with a robust approach by triangulating distribution-based methods of effect size, standard deviation, and standard error of measurement; anchor-based methods of linear regression and receiver operator characteristics curve; and Delphi methodology in the form of a clinical consensus. The baseline HADS anxiety mean difference was compared with the current study, and reported accordingly.

4.3.3.2 Explanatory variables

All the variables included in this chapter were selected in line with the extant literature and preliminary baseline assessments. These variables are age, gender, marital status, total number of comorbidities, weight, anxiety, smoking, and physical activity (Schuch et al., 2018; Ernstsen et al., 2016; Horne et al., 2013; Stafford, Berk and Jackson, 2013; Murphy et al., 2012; Myers et al., 2012; Pajak et al., 2012; Eastwood et al., 2012; Luppino et al., 2010; Gravely-Witte et al., 2009; Naqvi et al., 2007; Van Melle et al., 2006; Schrader et al., 2006; Bonnet et al., 2005).

In the analyses, age was employed as a continuous variable, gender was categorised as either male or female, and marital status in terms of whether the patient was partnered or single. Married patients, or those in a permanent partnership were categorised as partnered, and single, divorced, widowed or separated patients were categorised as single. A diagnosis of comorbid anxiety was confirmed by CR practitioners via a case note review, and a questionnaire determined whether the patients had ever been told by a doctor that they definitely had, or had been treated for, anxiety, employing responses of ‘yes’ or ‘no’. Thus, comorbid anxiety provided a measure of patients’ anxiety history, prior to the heart event. Weight was measured in kilogrammes, and body mass index (BMI) calculated as weight in kilogrammes divided by squared height in metres, were used as continuous variables in the analyses. Pre-CR baseline smoking measurements were categorised according to whether the patient was currently a smoker or non-smoker. Baseline physical activity was

measured by asking, ‘Do you take regular moderate physical activity of at least 30 minutes duration, on average five times a week? (or its equivalent, 150 minutes over 7 days)?’ and the response options were ‘yes’ or ‘no’. Moderate activity was explained as anything that constituted the same degree of effort as brisk walking or housework, carrying a light bag over level ground, mowing the lawn, and painting and decorating, for example. The total number of comorbidities was defined as the sum of number of patients’ comorbidities including, e.g. hypertension, hypercholesterolemia, diabetes, angina, arthritis, osteoporosis, asthma, and chronic bronchitis. The NACR list includes 19 different comorbidities.

4.3.4 Data analysis

The analyses were performed using the IBM Statistical Package for Social Sciences software statistics (SPSS), version 24, with $P<0.05$ considered to be statistically significant. The summary statistics were presented as mean, standard deviation, and percentages. The descriptive statistics were calculated, and the baseline characteristics compared between patients with high and low levels of depressive symptoms within a subgroup of patients with comorbid depression, using t-tests for continuous variables, and chi-square tests for categorical variables. The Cohen’s d effect size for continuous variables was also calculated, and the Phi effect size for categorical variables was reported.

In some statistical tests, for instance t-tests, the assumption is that the sampling distribution is normally distributed. Normality can be inspected visually, and one of the best methods for assessing normality graphically is a Normal Q-Q Plot. When data is normally distributed, the circular dots representing the data points are aligned on a diagonal line in the Q-Q Plot, although with ‘real world’ data these may not be perfectly positioned approximately along the diagonal line. In reality, there is high probability of some deviation from the line, even when data is normally distributed (Ghasemi and Zahediasl, 2012). In this study, after drawing the Q-Q plots, the presence of normal

distribution was observed, and data points were found to be positioned along the diagonal line.

A confidence interval (CI) is usually interpreted as the range of values that include the true population parameter, as estimated by a certain statistic, with given probability (Nakagawa and Cuthill, 2007). For instance, when a sample is taken from a population multiple times, there is approximately a 95% chance that 95% CI calculated from these samples will include the true value of the parameter (with a 5% chance of it being wrong). It can also be inferred that CIs provide a range within which the parameter value of interest is likely to lie (Nakagawa and Cuthill, 2007). The mean is one parameter used in t-tests, and CIs were also generated for it in the current study. When the mean represents the true mean well, there should be a narrow CI for that mean. As 95% CI contains the true mean, if the CI is narrow, it can be assumed the sample mean must be very close to the true mean of the population. In contrast, if the CI is very wide, the sample mean could differ from the true mean, indicating a poor representation of the population (Field, 2013; Nakagawa and Cuthill, 2007). For these reasons, the CI is provided in the study analysis.

In statistics, an effect size is simply an objective measure of the magnitude of an observed effect. Cohen's d is used here to describe the mean difference of an effect, and this value can therefore be used to compare effects across studies. The values obtained range from 0 to infinity, and a common interpretation given of Cohen's d effect size refers to values as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) (Lakens, 2013). However, according to Thompson (2007), these values are variant, and so should not be interpreted immutably. In some cases, small effect sizes can have a large impact, for instance an intervention that reduces suicide rates reliably, with an effect size of d = 0.1 (Lakens, 2013). In large samples, p values can even detect minimal differences; therefore, using effect size is recommended to provide a better estimate to determine the magnitude of an effect. Hence, Cohen's d effect sizes were calculated for the t-tests in this study, and are reported in **Table 4.1**.

Phi is a measure of the strength of association between two categorical variables. It is used with a 2 × 2 cross tabulation when there are two categorical variables and each variable has only two groups (Field, 2013). As all the categorical variables employed in the analyses in this study were binary, the Phi effect sizes are reported for the chi-square tests in **Table 4.2**. Phi effect size is interpreted as either small (0.1), medium (0.3), or large (0.5).

A binary logistic regression model was constructed in this study to investigate which variables determined change in HADS depressive symptoms. The baseline characteristics that determined moving to low levels of depressive symptoms group were compared with those demonstrating a continuance of higher depressive symptoms, after CR was investigated. Model goodness of fit was tested using the Hosmer and Lemeshow test, which demonstrates whether the predicted probabilities are close to the observed data, by grouping cases into similar percentiles of predicted values. A Pearson chi-square test is then run to examine whether discrepancies between the predicted values and observed values are statistically significant, with $P > 0.05$ indicating that the model fits the data well (Hosmer, Lemeshow and Sturdivant, 2013). Pseudo - R^2 is calculated using the maximum likelihood method in logistic regression, by dividing the log likelihood of the full model by the log likelihood of the original model prior to entering any predictors. The values in the R^2 range are between 0 and 1; and the closer the value to 1, the greater the predictive power of the model. The best model is one that better fits the data, with fewer predictors, and higher R2 values (Palmer and Connell, 2009).

The odds ratio (OR) measures the association between exposure and outcome. Such ORs are most common in observational studies, and can be defined as the odds that an outcome will occur, given a particular exposure, compared with the odds of an outcome occurring in the absence of exposure (Szumilas, 2010). Hence, ORs are used to compare the likelihood of the occurrence of an outcome, given exposure to the variable of interest, and can also be used to determine whether exposure is a risk

factor for a particular outcome, and to compare the magnitude of various risk factors for that outcome. If the OR=1, it can be interpreted that exposure does not affect the odds of the outcome; however, when OR>1, exposure is associated with higher odds of that outcome; and if OR<1, exposure is associated with lower odds (Szumilas, 2010). In logistic regression, OR is an indicator of the change in odds of an outcome resulting from a unit change in an exposure variable. The odds of improved depressive symptoms are reported in this chapter, and are in line with the logistic regression results in **Table 4.3**, and 95% CI is used for the precision of OR. A wide CI indicates a low level of precision in the OR, whereas a narrow CI indicates a higher level of precision for the OR.

The missingness in the data is often evident in retrospective observational studies. Due to the population sampling in the current study, which was selected in order to answer the research question regarding the determinants of depression in patients with comorbid depression following CR, the majority of variables were not missing, since age, gender, HADS anxiety, and total number comorbidities were not missing (all 0%); smoking was 3.7%; weight was 4.7%; marital status was 9.4%; and 150 minutes of physical activity was 10.6%. In addition, Little's MCAR test was performed, and resulted in chi-square= 9.223 (P=0.161). Therefore, a valid case/available case analysis was employed.

4.4 Results

The study population consisted of 2,715 patients with comorbid depression, all of whom had completed CR with valid pre- and post-HADS assessments. Of these 2,715 participants, 45% had high levels of depressive symptoms (HADS ≥8), and 55% had low levels of depressive symptoms (HADS <8). These patients' baseline characteristics are presented in **Table 4.1** according to their HADS levels.

Table 4.1: **Baseline characteristics of the participants, using t-tests for the mean differences between high and low HADS depression groups.**

Variables	HADS <8 group (n=1494)	HADS ≥8 group (n=1221)	Diff	95% CI	P value	d
	Mean + SD	Mean + SD				
Age	63.49 ± 10.50	60.77 ± 10.53	2.71	1.91 to 3.50	< 0.001	0.26
Total comorbidities	4.39 ± 2.10	4.90 ± 2.19	-0.50	-0.66 to -0.34	< 0.001	0.24
Weight	83.62 ± 17.04	85.56 ± 19.08	-1.94	-3.35 to -0.52	= 0.001	0.11
BMI	28.83 ± 5.14	29.54 ± 5.73	-0.71	-1.13 to -0.28	<0.001	0.13
HADS anxiety score measurement	6.43 ± 3.80	11.60 ± 4.05	-5.17	-5.47 to -4.87	<0.001	1.32

Key: SD = standard deviation; P = probability; Diff = difference, d = Cohen's d effect size.

In order to determine the mean differences in age, total number of comorbidities, BMI, weight, and HADS anxiety score measurements between patients with low depression levels (HADS <8), and higher depression levels (HADS ≥8), independent sample t-tests were employed. Patients with higher level of depressive symptoms were found to be younger, had a higher BMI, increased weight, a higher total number of comorbidities, and more anxiety symptoms than patients in the group showing lower levels of depressive symptoms.

Chi-square test of association were conducted between the categories of gender, marital status, comorbid anxiety, physical activity, smoking, and depressive symptoms. All the test variables, aside from gender, were found to be statistically significantly associated with depressive symptoms at the baseline. The patients with a history of depression and higher depressive symptoms at the outset of CR were more likely to be

single, smokers, physically inactive, and to have comorbid anxiety. The results of the chi-square tests are presented in **Table 4.2** below.

Table 4.2: Results of the chi-square test of association for low and high HADS levels of depressive symptoms at the baseline.

Variables	**HADS <8 group %**	**HADS ≥8 group %**	**P value**	**Phi effect size**
Female	33.6	33.6	0.99	0
Comorbid anxiety (Yes)	41.8	52.4	< 0.001	0.11
150 minutes physical activity a week (Yes)	43.6	27.5	< 0.001	0.17
Smoking (Yes)	7.7	12.7	< 0.001	0.08
Partnered (Yes)	71.5	63.6	< 0.001	0.08

Key: P = probability.

A binominal logistic regression was performed to ascertain the impact of patient demographics and clinical factors on the likelihood that the patients moved to the low levels of depression group, over those who remained in the higher levels of depression symptoms group, following CR. The model was statistically significant, $X^2(8) = 72.193$, $p < 0.001$, and correctly classified 63.3% of cases. According to the Hosmer and Lemeshow test, the model was a good fit ($p = 0.288$). Among the determinant variables, five were statistically significant: the HADS anxiety score measurement, the total number of comorbidities, smoking, physical activity, and gender. **Table 4.3** illustrates the regression model.

Table 4.3: Coefficients of the model determining a change in depression, in terms of whether a patient moved to the low levels of depressive symptoms group, following CR.

Variable	B	SE	P value	Odds ratio (OR)	Lower 95% CI for OR	Upper 95% CI for OR
Age	-0.002	0.008	0.765	0.998	0.983	1.013
Total number of comorbidities	-0.090	0.035	0.010	0.914	0.854	0.979
Weight	-0.004	0.004	0.363	0.996	0.988	1.004
HADS anxiety score measurement	-0.124	0.019	<0.001	0.883	0.851	0.917
150 minutes a week physical activity (No)	-0.347	0.162	0.033	0.707	0.514	0.971
Smoking (No)	0.573	0.250	0.022	1.774	1.086	2.898
Gender (Male)	-0.328	0.163	0.045	0.721	0.523	0.992
Marital status (Single)	-0.088	0.155	0.570	0.916	0.677	1.240

Key: B = regression coefficient; P = probability; SE = standard error; CI = confidence interval for odds ratio.

An increased HADS anxiety score measurement was associated with a reduced likelihood of experiencing low levels of depressive symptoms after CR (OR 0.883, 95%CI: 0.851, 0.917). Meanwhile, CR participants with a higher total number of comorbidities had 0.914 times lower odds of moving into the low levels of depressive symptoms group, following CR (OR: 0.914, 95%CI: 0.854, 0.979). Physical inactivity and being male were also associated with a decrease in the odds of relocating to the low depression level category (OR: 0.707, 95%CI: 0.514, 0.971 and OR: 0.721, 95%CI: 0.523, 0.992 respectively). Meanwhile, being a non-smoker at baseline was associated with an increased likelihood of achieving low depression levels, after CR (OR: 1.774, 95%CI: 1.086, 2.898).

4.5 Discussion

Certain elements of the association between depressive symptoms, patient demographics and lifestyle risk factors have been addressed in previous studies, although the extent of their association with comorbid depression remained unclear. Therefore, the present study examined the impact of comorbid depression in CVD patients to a greater extent, by applying a robust study design and statistical approach. The research questions explored were: What are the factors associated with depressive symptoms in patients with comorbid depression attending CR, at the baseline, and which of these baseline characteristics determine depression in patients with comorbid depression following CR? The study's hypothesis evaluated whether age, gender, smoking, physical activity, weight, marital status, anxiety, and total number of comorbidities were associated with high levels of depressive symptoms in patients with comorbid depression at baseline. Meanwhile, the second hypothesis tested whether these baseline characteristics of patients with comorbid depression determined their depression levels following CR.

The findings of this study revealed that the baseline characteristics of patients with a history of depression determined the outcome following CR. These characteristics

included having a higher anxiety score, total number of comorbidities, physical inactivity, smoking, and being male, all of which were found to be significant determinants of HADS depression outcomes after completing CR. However, age, marital status, and weight were not able to statistically significantly determine depressive symptoms following CR in patients with a history of comorbid depression.

The findings of the current study support previous cohort studies that have demonstrated an association between depressive symptoms and smoking (Stafford, Berk and Jackson, 2013; Gravely-Witte et al., 2009), as well as physical inactivity (Ernstsen et al., 2016; Horne et al., 2013). In addition, at baseline, the mean HADS anxiety scores were not only found to be statistically significant, but also clinically meaningfully higher in patients with comorbid depression and high depressive symptoms at the baseline, compared with patients presenting with low levels of depressive symptoms (MD: -5.17, 95% CI: -5.47, -4.87). A recent study conducted by Lemay et al. (2019) found that the MCID was 1.7 in HADS for CR participants. This Canadian retrospective cohort study included 591 CVD patients, and employed a combination of methods to estimate the MCID, including distribution-based, anchor-based methods, and Delphi methodology. In the present study, at baseline, the mean difference among patients with high and low levels of depressive symptoms was three-fold higher than for HADS MCID. Another notable finding of the current study was that baseline anxiety scores were influential on the depression outcomes ($p < 0.001$, OR: 0.883, 95%CI: 0.851, 0.917). A recent retrospective cohort study revealed that when anxiety is concomitant with depression, it is associated with higher rates of death after CR (HR = 2.41, P = 0.04) (Kachur et al., 2016). This cohort study involved 1,150 CVD patients, and employed Kellner Symptom Questionnaires to assess anxiety and depression, which is not a frequently used measurement. The HADS, which is a more common measurement of anxiety and depressive symptoms, was employed for the current study, which contributed to the study's aforementioned findings by demonstrating that the baseline anxiety scores of patients with comorbid depression

determined the outcome following CR. In other words, patients with comorbid depression were less likely to improve their depression levels, and to move in to the low levels of depressive symptoms group when presented with high anxiety scores at the baseline. Thus, baseline anxiety levels might prove to be an important intervention focus in CR, and serve as a way to reduce mortality rates. In addition, it would be valuable to assess those interventions in future studies.

Patients with high levels of depressive symptoms at the commencement of CR were found to possess a higher total number of comorbidities than patients with low levels of depressive symptoms (MD: -0.50, 95% CI: -0.66, -0.34). In addition, the present study also found the total number of comorbidities was a significant determinant of depressive symptoms following CR (OR: 0.914, 95%CI: 0.854 to 0.979), which contrasted with findings from a United States-based, prospective cohort study of 53 to 63 year old adults (n = 10,150) targeting the general population, and conducted by Forman-Hoffman et al. (2008). Moreover, according to recent studies, a higher number of comorbidities reduces CVD patients' quality of life, and can be mediated by limiting their physical capacity (Tušek-Bunc and Petek, 2016; Mitchell et al., 2015). It might be that patients develop higher levels of depressive symptoms resulting from this process. The association of comorbidities with depressive symptoms was also supported by a study conducted among the general population of older adults residing in western European countries (Braam et al., 2005).

A recent meta-analysis of prospective cohort studies revealed physical activity had a protective effect on incidence of depression in the general population (OR: 0.83, 95%CI: 0.79, 0.88) (Schuch et al., 2018). This study involved a sample of 267,000 individuals derived from 49 studies, including participants in all age groups who were initially free of depressive symptoms. Physical activity was measured using a self-report questionnaire (i.e. the International Physical Activity Questionnaire), with single or multiple questions concerning physical activity, or objective physical activity measures, such as accelerometers. This meta-analysis included studies reporting 150

minutes of moderate physical activity per week, which was the same physical activity measurement employed in the current study. However, the current study contributed to the findings by demonstrating that cardiac patients with a history of depression, who are physically inactive at baseline, were 30% less likely to improve their depression levels following CR (OR: 0.707, 95%CI: 0.514, 0.971).

Another noteworthy finding of the present study was that smoking, as an important lifestyle risk factor determines depression outcomes following CR, as the study demonstrated that patients who are non-smokers at baseline were 77% more likely to improve their depression levels, and to move to the low levels of depressive symptoms group, following CR (OR: 1.774, 95%CI: 1.086, 2.898). A recent systematic review of 148 cohort studies revealed smoking is associated with depressive symptoms in the general population (Fluharty et al., 2017). The association of smoking with subsequent depression was investigated in a third of the studies included in the review, ascertaining that 73% of them found evidence to support this association. The authors of the review were unable to conduct a meta-analysis, because in the general population samples available, there was substantial heterogeneity, in terms of age, location, the covariates used, the frequency of outcomes sampled, and follow-up time, therefore it was necessary to employ a narrative synthesis approach (Fluharty et al., 2017). In addition, the mean age of the participants, and the percentage of females in the studies included were not reported. The findings of the present study supported an association between smoking and depressive symptoms in CVD patients who attended CR programmes in routine practice.

In contrast, age was unable to significantly determine depressive symptoms (OR: 0.998, 95%CI: 0.983 to 1.013), although some studies demonstrated that patients with higher levels of depressive symptoms were younger (Mikkelsen et al., 2019; Mallik et al., 2005). This relationship was apparent at baseline in the current study; however, after adjusting for other covariates, age did not appear to determine outcome. Moreover, unlike previous studies (Luppino et al., 2010), the present study found

weight did not determine depressive symptoms. The reason for this might be the total number of comorbidities accounted for in the analyses, which could have influenced changes in weight (Forman-Hoffman et al., 2007). In addition, the marital status of patients did not have an impact on depressive symptoms (OR: 0.916, 95%CI: 0.677, 1.240), a finding which differed from those observed in the general population (Yan et al., 2011). Although single patients were observed to be more likely to exhibit depressive symptoms at baseline, in the multivariate analysis, this variable did not achieve statistical significance in the final model. A recent Finnish prospective study found that increased marriage dissatisfaction is associated with risk of sudden cardiac death in males (HR: 1.90, 95%CI: 1.09, 3.32) (Isiozor et al., 2018). However, the NACR data does not include information regarding patients' satisfaction in their marriage; nevertheless, this might represent an important factor for future studies to examine.

Another finding of the present study was that males were less likely than females to improve their depression status in the sample of patients with a history of depression (OR: 0.721, 95%CI: 0.523, 0.992). This result differed from the findings in a study conducted by Pajak et al. (2012). Although more females were included in the present study (33.6%), their mean age was lower by three years, which makes the result difficult to explain. However, a possible explanation could be that the proportion of male smokers was higher than that of female smokers in the current sample, which may have had an impact on the finding, as smoking was found to be associated with higher levels of depressive symptoms (Stafford, Berk and Jackson, 2013; Gravely-Witte et al., 2009).

One important finding of the present study for CR practice was that 65% (N=5110) of the patients in routine practice with comorbid depression had no recorded pre- and post-CR HADS measurements. Clinical guidelines across the world recommend the assessment of health status before and after CR (BACPR, 2017; Piepoli et al., 2016). The current study was the first to demonstrate in the UK CR context that HADS measurements in patients with a history of depression do usefully inform patient

outcomes. Thus, it is essential for CR programmes to conduct and record psychosocial assessments pre- and post-CR.

4.6 Study limitations

Due to this study's aim being to test which characteristics of patients with comorbid depression determine their CR outcome, the population involved was a subgroup of patients with a pre-existing diagnosis of depression. As the study's focus was on patients with comorbid depression, representing only around 20% of the CR patients in the UK, the findings were only relevant to this population, and so cannot therefore be generalised to the wider CR population. However, the study population was representative of all the available patients with comorbid depression, as the patient demographics in the current study sample are similar to those for all available participants with comorbid depression, with a mean age of 62 years, compared with 61 years, when comparing between the two groups, and 33.6% females compared with 35%; this proportion did not differ by more than 5% for the other variables. Although the sample was nationally representative of those patients with a comorbid history of depression, it is important to note that not all CR programmes conducted in the UK provide complete patient records. In the NACR data, 38% of patients did not have a follow-up assessment, which might have influenced the sample's representativeness (NACR, 2017). However, the analysis of routinely collected patient data was useful for providing a real world understanding. Furthermore, the data included patients with multi-comorbidities, and included more female patients than previous randomised controlled trials (RCTs) (Anderson et al., 2016).

4.7 Conclusion

This project was undertaken to investigate which factors determine depressive symptoms in patients with comorbid depression following CR. The results indicated that the baseline characteristics of patients with a history of depression, such as higher anxiety, a higher total number of comorbidities, physical inactivity, smoking, and male

gender, were associated with higher depression levels, following CR. Therefore, CR programmes and practitioners must heed patients with a history of depression, and their characteristics, in order to improve outcomes, and to factor these characteristics into tailored CR interventions. As part of routine clinical practice, CR programmes should aim to assess and record HADS measurements in patients with a comorbid history of depression. Using routine clinical practice, this study investigated for the first time the inter-relationship between comorbid depression and clinical outcomes, following CR. Additional studies concerning the determinants of depression, and the development of interventions that could improve depression levels in patients with comorbid depression are recommended, to build on the findings of the current study.

Chapter 5: Part 1: To what extent is multi-morbidity associated with new onset depression in patients attending cardiac rehabilitation?

5.1 Abstract

Background

Depression is associated with mortality and adverse cardiac events in patients with cardiovascular disease (CVD). However, little is known regarding the medical comorbidities associated with new onset post heart event depressive symptoms, or other patient characteristics in the case of cardiac rehabilitation (CR) attenders. This study investigates the comorbidities and patient characteristics associated with new onset depressive symptoms at baseline, in patients participating in CR programmes.

Methods

An observational study extracting and using the routine practice data of British Heart Foundation (BHF) National Audit of Cardiac Rehabilitation (NACR) between April 2012 and March 2018. The study population constituted patients with new onset post heart event depression, and no previous documented history of depression. The association between new onset depressive symptoms and patient variables including demographics, comorbidities, and clinical measures was compared using an independent samples t-test and chi square tests. Following this, employing a log-likelihood ratio statistic, a binary logistic regression was conducted to investigate the determinants of new onset depressive symptoms.

Results

The total of 109,055 CR patients with new onset depression measured by Hospital Anxiety and Depression Scale (HADS) were included in the analyses. At baseline assessment, comorbidities associated with new onset depressive symptoms were identified such as diabetes, chronic back problems, stroke, angina, etc. In addition, key

patient characteristics such as being younger, female, physically inactive, more likely to smoke, from areas with higher social deprivation etc. were associated with new onset depressive symptoms in univariate analysis. After multivariate adjustments were performed, related to characteristics at the start of CR, ten significant determinants of new onset depressive symptoms remained including for example physical inactivity, high HADS anxiety score, increased weight and total number of comorbidities.

Conclusion

The findings of this study established new insights into patient characteristics and clinical variables that determine new onset post heart event depressive symptoms, at the start of CR. Patients with new onset depressive symptoms need to be assessed skilfully due to having a complex multi-morbid condition and psychosocial risk factors recognised to impede CR engagement.

5.2 Introduction

Depression is a common condition following CVD, and is associated with increased mortality rates and poor prognosis (Lichtman et al., 2014). Around 1 in 5 patients experience major depression after an acute heart event (Thombs et al., 2006). The coexistence of depression and CVD, with concomitant increased costs of health care utilisation and hospital readmission rates, is of concern to commissioners and health care providers alike (Baumeister et al., 2015). In addition, depression is not only associated with disability, but also noncompliance with treatment and loss of productivity in CVD patients (Egede, 2007).

Secondary prevention of CVD risk factors and psychosocial health are core components of comprehensive CR programmes (BACPR, 2017). A recent Cochrane review recommended CR as an effective intervention for CVD patients (Anderson et al., 2016). In line with this, some meta-analysis has shown CR leads to a reduction in depressive symptoms (Zheng et al., 2019; Rutledge et al., 2013). Under the virtue of being a multicomponent intervention, assessment of depression is recommended by

recent CR and prevention guidelines as a risk factor for adverse medical outcomes in CVD patients (BACPR, 2017; SIGN, 2017; Piepoli et al., 2016, 2014; Lichtman et al., 2014). In the UK, so as to manage psychosocial health, HADS is employed at baseline prior to CR, to enable tailoring of the intervention to meet patients' individual needs and goals (NACR, 2018). In addition, HADS is accepted as a valid and reliable tool for the assessment of depressive symptoms in CVD patients, not only in the UK but also in other countries (Bjelland et al., 2002; Zigmond and Snaith, 1983).

There is emerging evidence, which particularly focuses on the time of onset of depressive symptoms in relation to poor cardiac prognosis and mortality outcomes (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016; Dickens et al., 2008; de Jonge et al., 2006). Some studies have shown that patients with a history of depression prior to a heart event are at increased adverse cardiac events and mortality risk (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016); on the other hand, additional research has shown that new onset depressive symptoms after a heart event are particularly related to increased mortality and poor cardiac prognosis (Dickens et al., 2008; de Jonge et al., 2006). This literature has been further developed in a recent paper, which used NACR data, and found patients with a prior history of depression, and who present with high level of depressive symptoms at the start of CR, tend to experience increased weight, BMI, anxiety symptoms, smoking, physical inactivity, and were also younger and more likely to be single compared to patients with a history of depression but absence of acute depressive symptoms at the start of CR (Sever, Golder and Doherty, 2018) (the results are presented and discussed in detail in Chapter 4). This study aims to build on previous work in this field with a unique population yet to be addressed, i.e. patients without a history of depression, meaning patients with new onset post heart event depressive symptoms, to examine which patient characteristics are associated with developing new onset depressive symptoms in relation to CVD. Therefore, this study for the first time examines the demographic and clinical characteristics associated with new onset depressive symptoms in patients

attending CR using a greater number and type of comorbidities than previous studies. The findings will enable CR practitioners to better understand patient profile as well as the determinants of new onset depressive symptoms.

5.2.1 Study Rationale

Due to the association between depression and its known detrimental effect on the health of CVD patients, and on their mortality rates, it is important that depressive symptoms are fully-recognised and not under-treated in CVD patients attending CR. Currently, there is a lack of studies identifying the potential determinants of new onset depressive symptoms in patients starting CR. Knowing the potential determinants that inform new onset depressive symptoms may provide essential evidence for policy makers, clinicians, and health organisations, to enable them to understand its impact on CR service utilisation. Further, this information might then enable better provision of services by decision-makers, as well as optimising uptake and adherence to CR programmes.

Thus, this study aimed to:

3) Identify the patient characteristics associated with new onset depressive symptoms at the start of CR.

4) Investigate which of these characteristics act as determinants of new onset depressive symptoms at the start of CR.

5.2.2 The research questions

The research questions posed this study were:

- What are the factors associated with new onset acute depressive symptoms in patients attending CR, at baseline?
- Which factors determine new onset acute depressive symptoms at the start of CR?

The hypothesis will also test whether the total number of comorbidities and comorbid conditions, such as diabetes, stroke, and others, age, gender, smoking, physical activity, weight, marital status, and anxiety, were associated with new onset acute depressive symptoms in CR patients at baseline. This was in accordance with the findings of a critical review in chapter 2, and recently published NACR studies conducted in patients with a comorbid history of depression population (Sever et al., 2019; Sever, Golder and Doherty, 2018).

5.3 Methods

The main methodological approach taken in the current study chapter is a retrospective research design. Data routinely collected from UK CR services, i.e. NACR data, was analysed to investigate the determinants of new onset depressive symptoms at the start of CR in part 1 of this chapter.

5.4 Retrospective approach

5.4.1 Data source

A secondary data analysis was conducted using patient data held in the NACR database. The NACR aims to monitor CR services and improve the quality of UK cardiovascular secondary prevention and rehabilitation programmes. Individual patient level data is collected by CR programmes via validated questionnaires under section 251 approval of the NHS Act 2006, and entered into a secure online system hosted by NHS Digital. NHS Digital has approval to collect identifiable patient data, which is then anonymised before data can be extracted and made available to the NACR for audit purposes. Therefore, there was no need to gain patient consent from individuals due to this data governance process. NACR is operated in collaboration with the UK's National Health Service (NHS) Digital, and the data governance agreement between NHS Digital and NACR is reviewed every year by NHS digital. In the current study, as the data used corresponds with NACR's purposes, and complies with data protection regulations, no separate ethical approval was required from the NHS. There are 229

CR services entering data electronically, comprising 80% of all programmes (NACR, 2018). The data includes patients undergoing CR in the UK, the initiating event, demographics, risk factors, treatment, medication and outcomes.

5.4.2 Design and inclusion criteria

In part 1 of this chapter, a retrospective observational methodology was used to examine the factors determining new onset depressive symptoms in CVD patients attending a CR assessment. The NACR's routine practice data across the UK was extracted and analysed for the dates from 1 April 2012 to 31 March 2018. The reason this data range differs from the previous study is that when the study was conducted new data became available, and the analysis was later expanded to include newly available NACR data. The reason for this was that the data improves every year, so the inclusion of newly available data strengthens the analysis. Patients were included in the analyses if they were adults (≥18), had experienced a myocardial infarction (MI) or heart failure (HF), and had received treatment in the form of a percutaneous coronary intervention (PCI) and a coronary artery bypass graft (CABG) as recommended in the clinical guidelines (NICE, 2018, NICE 2013). All the eligible patients (N= 109055) with baseline HADS assessments recorded in CR, and who did not present with a prior history of depression, were selected as participants in the study period in the current section. The flow diagram in **Figure 5.1** shows the total population over the study time period, and the sample size of the current study.

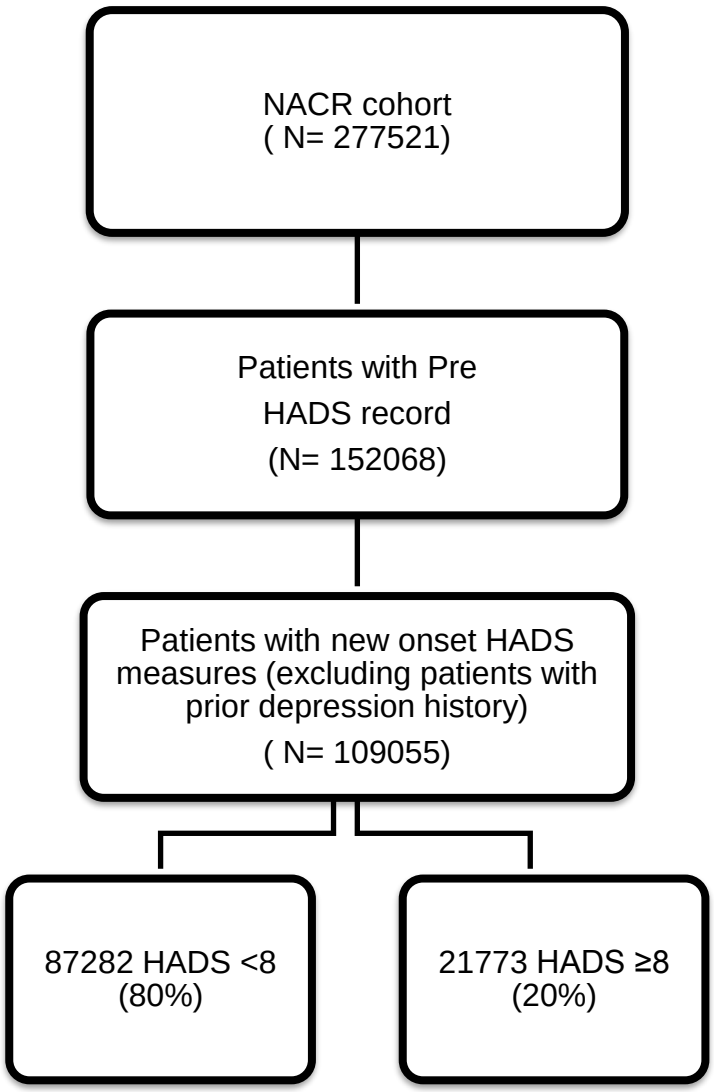

Figure 5.1: Flow diagram of the study sample

5.4.3 Variables investigated in the analyses

5.4.3.1 Outcome variable

The HADS depression measurement was used as an outcome in the current study. The HADS is a self-answered screening tool, which is employed to assess depressive symptoms. In line with recent guidelines, HADS is assessed before and after CR to allow the tailoring of CR intervention services to meet the individual needs of the patients (BACPR, 2017). A total of 14 items are included in HADS, which is divided into two subscales; each question includes four possible responses, and each response has a tick box next to it. Patients are asked to select the response that is most relevant to them. Each question can be scored from 0 through to 3. A CR practitioner adds up

the scores separately for anxiety and depression resulting in a total score between 0 and 21 for separate anxiety and depression scales. Higher scores represent more unfavourable symptoms. The HADS tool is easy to apply and can be rapidly interpreted by CR team members. HADS is a well-established reliable and valid assessment tool for anxiety and depression, both in general and among the CVD population (Wang, Lopez and Martin, 2006; Bjelland et al., 2002; Zigmond and Snaith, 1983). A clinical cut-off point of 8 was employed to categorise patients into presence of new onset acute depressive symptoms (≥ 8) and absence of new onset depressive symptoms (< 8) (Zigmond and Snaith, 1983). Following this, comparisons were made between CR participants with HADS < 8 and HADS ≥ 8 in patients with no history of depression. In addition, baseline HADS anxiety scores, routinely reported as part of HADS, were also compared in patients with absence and presence of new onset depressive symptoms.

5.4.3.2 Explanatory variables

Total number of comorbidities and comorbidity types

Total number of comorbidities is a summative variable detailing the number of comorbidities a patient presented with following their cardiac event. In the NACR data, comorbidities refer to a medical history of conditions confirmed by a case note review of CR practitioners as well as by patients, whether or not they have definitely been treated for a condition or diagnosed by a doctor. The comorbidities presented in this study are as follows: hypertension, hypercholesterolemia, diabetes, angina, arthritis, osteoporosis, asthma, chronic bronchitis, emphysema (COPD), cancer, rheumatism, stroke, claudication, chronic back problems, anxiety, a family history of heart disease and erectile dysfunction.

Other variables

The patient demographics included in the analyses were age, gender, and marital status (partnered/single). Another patient demographic used was The English Index of Multiple Deprivation (IMD) (measure of deprivation in England). The IMD measure is constructed by combining seven domains; namely, education skills and training, health deprivation and disability, employment, income, barriers to housing and services, crime and living environment (Department for Communities and Local Government., 2015). A total of 32,844 sub-areas were identified and ranked from the most to least deprived areas. IMD was used to group patients into quintiles, the first quintile, reported as the 'lowest quintile', represents the most deprived areas and higher quintiles refer to the less deprived in the analysis. Body mass index (BMI), weight (kg), and moderate physical activity (150 min a week, Yes/No) were other variables, and smoking was categorised as either current smoker or non-smoker. The inclusion of these variables was decided from preliminary baseline assessments and the literature search (in Chapter 2).

5.4.4 Data analysis

SPSS software statistics version 25 (IBM Corp, Armonk, New York, USA) was used to conduct the data analysis. The study population included patients who did not present with prior history of depression and instead have new onset pre-HADS assessments. A p value of <0.05 was accepted as statistically significant (Dahiru, 2008). Means, standard deviations, and percentages were used to depict the summary statistics. Mean difference was investigated by employing t-tests for presence of new onset depressive symptoms and absence of new onset depressive symptoms for the variables of age, total number of comorbidities, weight, BMI, and HADS anxiety score. Chi-square tests were employed to explore associations between gender, smoking, IMD, physical activity, marital status, a variety of comorbidities and new onset depressive symptoms. To report effect sizes, Cohen's d (for continuous variables) and Phi (categorical variables) effect sizes were used. Statistically significant determinants

of new onset depressive symptoms (HADS ≥ 8) were investigated using a binary logistic regression, at the start of CR, for a multivariate analysis.

There are some statistical tests, t-tests for example, which need to meet the assumption of sampling distribution to be normally distributed. A visual inspection of this assumption can be done by applying different methods, and one of the best methods involves checking the Q-Q plot. If the data is normally distributed, data points, represented by circular dots in the plot, need to be aligned on the diagonal line. However, in real world data, data points might not always be perfectly positioned on a diagonal line. In fact some deviation from the line is common even if data is normally distributed (Ghasemi and Zahediasl, 2012). In the current study, Q-Q plots showed a normal distribution and the data points were positioned along the diagonal line.

Some elements of the data analysis were previously explained in detail in previous chapter 4 section 4.3.4. Therefore, it has only been briefly summarised here.

In large samples, even minimal differences can be detected by p values, for that reason, reporting an effect size is often recommended as a way to provide a clearer estimate of the magnitude of effect (Field, 2013). Thus, Cohen's d effect sizes were calculated and reported for the t-tests in the current study. In addition, for the binary categorical variables, for chi-square tests, Phi effect sizes were reported.

Hosmer and Lemeshow's test was used to test the goodness of fit of the model. This test clarifies whether predicted probabilities are close to the observed data, and is done by grouping cases into similar percentiles of predicted values. Following this, a Pearson chi-square test is run to investigate whether there is any statistically significant difference between predicted and observed values, and $P > 0.05$ indicates the model is a good fit to the data (Hosmer, Lemeshow and Sturdivant, 2013). In logistic regression, a maximum likelihood method is used to calculate Pseudo-R^2, and is applied by dividing the log likelihood of the full model by the log likelihood of the original model before any predictor variables are entered. The R^2 values range between 0 and 1, and

the model has a greater predictive power as the value moves closer to 1. The model that best fits the data, has higher R^2 values and fewer predictors, and is then assumed to be the best model (Palmer and Connell, 2009).

An odds ratio (OR) is often used in observational studies, and is a measure of the association between exposure and outcome. OR illustrates the change in the odds of a specific outcome occurring, given a unit change in the exposure variable (Szumilas, 2010). The odds of improvement in depressive symptoms are reported in the current study, and so 95% CI related to the OR. A wide OR means less precision of the OR, and a narrow CI relates to higher level of precision of the OR.

5.5 Results

The study population was inclusive of 109,055 patients without a prior history of depression, who had started CR with a valid HADS assessments. From these 109,055 CR attenders, 20% had new onset depressive symptoms (HADS≥8), whereas 80% had absence of new onset depressive symptoms (HADS<8). **Table 5.1** below shows the patients' baseline characteristics based on their HADS levels (HADS<8 absence of new onset depressive symptoms, HADS≥8 presence of new onset depressive symptoms).

Table 5.1: Baseline characteristics with t-tests for mean difference for the presence and absence of new onset acute HADS depressive symptoms groups

Variables	HADS <8 Non acute group (n=87282)	HADS ≥8 Acute group (n=21773)	Diff	95% CI	P	d
	Mean ± SD	Mean ± SD				
Age	66.24 ± 10.96	64.01 ± 11.69	-2.23	-2.40 to -2.06	< 0.001	0.20
Total Comorbidities	2.36 ± 1.46	2.60 ± 1.58	0.24	0.22 to 0.27	< 0.001	0.16
Weight	82.67 ± 16.86	83.80± 19.05	1.13	0.84 to 1.42	< 0.001	0.07
BMI	28.21 ± 4.97	29.00 ± 5.77	0.79	0.70 to 0.88	<0.001	0.16
HADS Anxiety Score Measurement	4.48 ± 3.37	9.86 ± 4.12	5.38	5.33 to 5.44	<0.001	1.52

SD = standard deviation; CI = confidence interval; Diff = difference; d = Cohen's d.

Patients from the new onset acute depressive symptoms group had increased anxiety scores, a higher total number of comorbidities, increased weight, a higher BMI, and were younger compared to patients with an absence of new onset depressive symptoms.

Moreover, patients with new onset acute depressive symptoms at the commencement of CR were more likely to be physically inactive, more likely to smoke, be female, single

and from areas of higher social deprivation. **Table 5.2** shows the results for the chi-square tests.

Table 5.2: Results from chi square test of association for presence and absence of new acute onset HADS depressive symptoms groups

Variables	**HADS <8 Non-acute group (n=87282)**	**HADS ≥8 Acute group (n=21773)**	**P**	**Effect size**
Female	24.9	30.6	< 0.001	0.05
150 min. Physical Activity a Week (Yes)	44.0	26.4	< 0.001	0.14
Smoking (Yes)	6.6	11.8	< 0.001	0.08
Partnered	78.2	72.7	< 0.001	0.05
IMD (Most deprived)	11.4	18.0	< 0.001	0.08

Examining the comorbidity profile of the patients, at the start of CR, patients with presence of new onset depressive symptoms were more likely to have the comorbidities of diabetes, stroke, emphysema, chronic bronchitis, asthma, angina,

arthritis, osteoporosis, rheumatism, claudication, anxiety, and chronic back problems compared to patients with absence of new onset depressive symptoms. Yet, patients with new onset depressive symptoms were less likely to have hypercholesterolemia, or a family history of CVD and cancer. **Table 5.3** shows the comorbidity profile of CR attenders.

Table 5.3: The comorbidity profile of patients reported by the presence and absence of acute depressive symptoms categories

Comorbidity	**HADS <8 Non-acute group (n=87282)**	**HADS ≥8 Acute group (n=21773)**	**P**	**Effect size**
Angina	18.6	19.5	0.004	0.01
Arthritis	16.3	18.9	< 0.001	0.03
Cancer	7.8	7.2	0.003	0.01
Diabetes	20.5	26.7	< 0.001	0.06
Rheumatism	2.6	3.7	< 0.001	0.03
Stroke	4.5	6.6	< 0.001	0.04
Osteoporosis	2.1	2.7	< 0.001	0.02
Hypertension	49.5	49.8	0.43	0
Chronic bronchitis (COPD)	2.6	4.2	< 0.001	0.04

Emphysema	2.0	3.1	< 0.001	0.03
Asthma	8.4	10.4	< 0.001	0.03
Claudication	2.5	3.7	< 0.001	0.03
Chronic back pain	11.4	14.3	< 0.001	0.04
Anxiety	2.7	5.2	< 0.001	0.06
Family history of CVD	24.8	21.6	< 0.001	0.03
Erectile dysfunction	4.9	5.2	0.08	0.01
Hypercholesterolemia	28.8	27.9	0.006	0.01

A binominal logistic regression was conducted to investigate the impact of comorbidities and other patient characteristics on the likelihood of having new onset acute depressive symptoms. The logistic regression model was statistically significant, $X^2(12) = 12429.216$, $p < 0.001$. The model accurately classified 84.9% of the cases. The statistically significant variables were physical activity, HADS anxiety score measurement, weight, IMD, age, gender, and marital status, total number of comorbidities, stroke, diabetes, and chronic back problems. The regression model has been shown in **Table 5.4.**

Table 5.4: Multivariable adjusted odds ratios for new onset acute depressive symptoms

Variable	B	SE	P value	Odds Ratio	Lower 95% CI	Upper 95% CI
Age	0.009	0.001	<0.001	1.009	1.006	1.012
Weight	0.002	0.001	0.040	1.002	1.000	1.004
HADS anxiety	.360	0.004	<0.001	1.443	1.422	1.445
150 min. activity (No)	0.626	0.031	<0.001	1.870	1.761	1.985
Smoking (Yes)	0.097	0.052	0.062	1.102	0.995	1.221
Gender (Male)	0.227	0.035	<0.001	1.254	1.170	1.344
Marital Status (Single)	0.138	0.034	<0.001	1.148	1.074	1.227
Diabetes (Yes)	0.260	0.036	<0.001	1.297	1.209	1.392
Stroke (Yes)	0.434	0.063	<0.001	1.543	1.363	1.745
Chronic back pain (Yes)	0.091	0.046	0.049	1.095	1.000	1.198
Total comorbidities	0.029	0.11	0.007	1.029	1.008	1.051
IMD (Most deprived)	0.239	0.042	<0.001	1.270	1.169	1.378

B = regression coefficient; P = probability; SE = standard error; CI = confidence interval for odds ratio.

At the start of CR, CR patients who are physically inactive were found to be 87% more likely to have new onset depressive symptoms (OR 1.870, 95%CI: 1.761, 1.985). In addition, an increased HADS anxiety score measurement was associated with increased odds of experiencing new onset depressive symptoms (OR 1.443, 95%CI: 1.422, 1.445). Patients with a comorbidity of stroke, diabetes and chronic back problems were more likely to have presence of new onset depressive symptoms (OR 1.543, 95%CI: 1.363, 1.745; OR 1.297, 95%CI: 1.209, 1.392; OR 1.095, 95%CI: 1.000, 1.198 respectively) similar to patients having a higher total number of comorbidities (OR 1.029, 95%CI: 1.008, 1.051). Furthermore, CR participants from areas of the higher level of deprivation had 27% increased odds of having new onset depressive symptoms at the start of CR (OR 1.270, 95%CI: 1.169, 1.378), and males had 25% increased odds of having depressive symptoms (OR 1.254, 95%CI: 1.170, 1.344).

5.6 Discussion

Prior studies have addressed the association between new onset depressive symptoms, poor cardiac prognosis and mortality. Yet, the determinants of new onset depressive symptoms at the start of CR have not been investigated comprehensively. The current study informs clinical practice in terms of those factors associated with new onset depressive symptoms, at the start of CR, as well as the determinants of new onset depressive symptoms at baseline in a multivariate analysis. The study findings revealed that high HADS anxiety symptoms, increased weight, physical inactivity, higher total number of comorbidities, and variety of comorbidities were significantly associated with new onset depressive symptoms. In terms of patient demographics, patients with new onset depressive symptoms were found to be more likely to be single, male and from areas with higher social deprivation.

The current study found patients with new onset depressive symptoms also have a higher number of total comorbidities than patients with absence of depressive symptoms following their cardiac event. Correspondingly, adjusting for other

covariates, a higher number of comorbidities was associated with an increased likelihood of having new onset depressive symptoms among patients attending CR (OR: 1.029, CI: 1.008, 1.051). Furthermore, the comorbidities of diabetes, stroke, emphysema, chronic bronchitis, asthma, angina, anxiety, arthritis, osteoporosis, rheumatism, claudication, and chronic back problems were shown to be more prevalent in patients experiencing new onset depressive symptoms. Contrary to this, Vitinius et al. (2019) (an RCT data driven study) was unable to confirm an association between comorbidities and depressive symptoms. This perhaps can be explained by the younger study population (mean age 59.1 ± 19.8) relative to the current study (65.79 ± 11.14). The RCTs were recommended to be more inclusive of older, multi-morbid populations, as they sometimes recruit a younger population (Anderson et al., 2016). In addition, there is a great challenge for health care providers and services here, because patients with multiple comorbidities are less likely to be referred to or uptake CR (Brown et al., 2009; Suaya et al., 2007). A higher number of comorbidities might have a negative impact on patient's physical functioning, leading to an increase in depressive symptoms (Kang et al., 2015). Nonetheless, attending CR may be beneficial for patients with multiple comorbidities, as it improves both their psychosocial conditions and their functional capacity (Milani and Lavie, 2007).

In the current study sample, diabetes was one of the most common comorbidities in patients with new onset depression (26.7%, $p<0.001$). Moreover, the findings demonstrated that patients with diabetes were 29% more likely to experience new onset depressive symptoms at the start of CR (OR: 1.297 95%CI: 1.209, 1.392). At the beginning of CR, patients with diabetes had both more cardiovascular risk factors and reduced physical capacity (Mourot et al., 2010). Previous studies have shown diabetic patients benefited from CR in terms of reduced mortality rates (Jiménez-Navarro et al., 2017; Armstrong et al., 2015). CR services are also recommended to actively seek to recruit patients with diabetes, both because of their lower CR participation rate and their greater CVD risk profile (Sumner, Grace and Doherty, 2016; Lopez-Jimenez et al.,

2013; Banzer et al., 2004). In addition, due to the rising prevalence of diabetes (Einarson et al., 2018), its medical management could be of benefit which may eventually reduce depressive symptoms.

Having the comorbidity of stroke is associated with 54% increased odds of having new onset depressive symptoms at the start of CR (OR 1.543, 95%CI: 1.363, 1.745). The comorbidity of stroke was associated with reduced odds of a referral (Brown et al., 2009), and attendance in CR (Suaya et al., 2007). Despite that, CR programmes have been shown to improve the functional capacity of stroke patients (Tang et al., 2009); thus, these patients would benefit from CR services if they were to participate. The current study has demonstrated that, in a baseline univariate analysis, patients with respiratory related conditions, including emphysema, chronic bronchitis and asthma were more likely to have new onset depressive symptoms. Breathlessness and disability are the major problems experienced by patients with CVD and COPD, therefore recommendations have been made for CR programmes requiring sufficient flexibility to include patients with COPD (Man et al., 2016).

Other comorbidities, such as osteoporosis, rheumatism, arthritis, and back pain were also more prevalent in patients with presence of new onset depressive symptoms compared to patients with absence of new onset depressive symptoms following a cardiac event. The results of a cohort study revealed patients who have these comorbid conditions were less physically active, and had relatively lower levels of cardiovascular fitness than patients without such comorbidities at the start of CR (Marzolini, Candelaria and Oh, 2010), which might explain their increased levels of depressive symptoms. Similarly, patients with a comorbidity of chronic back pain had an increased likelihood of experiencing new onset depressive symptoms at baseline (OR 1.095, 95%CI: 1.000, 1.198). This is the first study detailing a variety of comorbidities and their association with new onset depressive symptoms among patients starting CR.

A statistically significant difference of 0.79 has been observed as a result of BMI by being higher in patients with new onset depressive symptoms when compared with patients with absence of new onset depressive symptoms. However, both groups were in the same overweight range; i.e. BMI 29.00 vs 28.21. However, one American study conducted with CR patients was unable to attain a statistically significant result (Milani and Lavie, 2007). A possible explanation for this may have been that their study had not factored in patients with new onset depressive symptoms, as the characteristics of such patients might differ. The current study has also shown that patients with new onset depressive symptoms had increased weight by 1.13 kilogrammes compared to patients with absence of new depressive symptoms. Furthermore, according to the results of multivariate analysis, weight measure remained to be significantly associated with depressive symptoms when other covariates were adjusted for in the analysis.

The current study supports the association of anxiety symptoms with depression. There is a statistically significant and clinically meaningful difference in that the mean HADS anxiety scores are higher in patients with new onset depressive symptoms than patients with absence of new onset depression, MD: 5.38, 95%CI 5.33 to 5.44. A recently published study by Lemay et al. (2019) has demonstrated a minimum clinically important difference in HADS of 1.7 for CR patients. Considering this minimum clinically important difference, there was a more than threefold higher mean difference among these groups than there was a minimal clinically important difference. In addition, an increased HADS anxiety measurement was associated with 44% increased odds of experiencing new onset depressive symptoms in a multivariate analysis.

Physical inactivity and smoking were two modifiable risk factors for CVD found to be associated with new onset depressive symptoms, which is also a finding of clinical relevance. These findings correspond to previous systematic reviews among the general population that have found physical inactivity and smoking to be prospectively associated with depression (Schuch et al., 2018; Fluharty et al., 2017), as have some

cohort studies conducted with CVD patients. However, prior studies have not differentiated between new onset depressive symptoms and a history of depression (Stafford, Berk and Jackson, 2013; Ye et al., 2013; Gravely-Witte et al., 2009). The results of the current study contributed to the current literature by adding that, at the start of CR, patients with new onset depressive symptoms after a heart event are more likely to be physically inactive and smoke compared to patients with absence of new onset depressive symptoms. Moreover, the results of the multivariate analysis has shown that patients who are physically inactive are 87% more likely to have new onset depressive symptoms than patients attending CR (OR 1.870, 95%CI: 1.761, 1.985). However, smoking did not attain statistical significance in the multivariate analysis.

In terms of the demographic characteristics of patients determining new onset depression, being single was identified as a determinant, in common with previous studies (Yan et al., 2011), and being older and male were other determinants. The current study also included the English Index of Multiple Deprivation (IMD) as another demographic. Recently, one US based study investigated the impact of neighbourhood socioeconomic context on CR uptake and found that a lower neighbourhood socioeconomic context was associated with reduced odds of CR participation (Bachmann et al., 2017). The neighbourhood deprivation index was used in this American study. However, in the current study, IMD measure was employed and it is the first research to show that patients with new onset depression at the start of CR were more likely to be from areas with higher levels of social deprivation. In addition, in a multivariate analysis, adjusting for other covariates, patients from areas of increased social deprivation were 27% more likely to have new onset depressive symptoms (OR 1.270, 95%CI: 1.169, 1.378). There is a relationship between deprivation and unhealthy lifestyle behaviours, such as smoking and physical inactivity (Stimpson et al., 2007), which could explain the depressive symptom initiated in these patients. Furthermore, patients from areas with higher deprivation might be expected to experience barriers to participation in CR, due to the inequalities they face (Bachmann

et al., 2017). Therefore, CR programmes and policy makers may need to develop strategies to involve these patients in CR services. In addition, at the start of CR, screening for depressive symptoms in patients from areas with greater levels of deprivation can be beneficial for the early detection of high risk patients, which could also be an area of investigation for further studies.

Finally, the results of the current study correspond to the European Society of Cardiology's (ESC) Position statement on the psychosocial aspects of CR, agreeing that patients from areas of greater deprivation are more likely to experience depressive symptoms which therefore may lead to adverse cardiac events (Pogosova et al., 2015). The current study affirms the importance of identifying patients, either with new onset depressive symptoms or other psychosocial risk factors, to offer tailored CR interventions delivered by trained health care providers (Pogosova et al., 2015).

5.7 Study limitations

To fulfil the aim of examining factors associated with new onset depressive symptoms, patients with a prior history of depression were excluded from the population of this study. Yet, when the characteristics of the study sample were investigated, it was found to represent all available patients during the study time scale (n=277521), and the proportion of females was 26% compared to 27%, with the mean age being 65.79 compared to 65.06 and other variables showing similar characteristics. The study sample was comprehensive and representative of patients with new onset depressive symptoms nationally in the UK. The analysis of routine practice data was beneficial for providing a real world understanding, which is a key strength of an observational study. In line with this, a higher percentage of females and more of the multimorbid patient population were included in the data than in previous RCTs (Anderson et al., 2016). Nevertheless, it is not possible to draw causal conclusions based on observational studies.

5.8 Conclusion

Based on the results of the multivariate analysis, the patient characteristics associated with new onset depressive symptoms were having a stroke, diabetes, chronic back problems, and a higher total number of comorbidities, a high HADS anxiety scores, physical inactivity, increased weight, being single, male and from areas of greater deprivation. CR programmes should be informed that tailored CR intervention may be required for patients with new onset depressive symptoms because of their multimorbid condition and worse patient characteristics such as high anxiety scores, increased weight, physical inactivity and others. Future studies are needed to investigate the determinants of CR outcomes in patients suffering with new onset acute depressive symptoms.

Chapter 5: Part 2: Is improvement in depression in patients attending cardiac rehabilitation with new onset acute depressive symptoms determined by patient characteristics?

5.9 Abstract

Background

Experiencing, depressive symptoms is common among CVD patients and it is related to adverse heart events and higher mortality rates. Investigations into the baseline characteristics of CR patients to determine outcome of depression might be expected to facilitate adjustments in the delivery of CR services.

Objectives

The current study examines whether comorbidities, demographic and clinical characteristics of patients with new onset acute depressive symptoms determine improvement in their depression after CR.

Methods

An observational study was conducted analysing the routine practice of NACR data, funded by BHF, between April 2012 and March 2018. The study population was patients with new onset depressive symptoms and no previously documented history of depression. Baseline characteristics were investigated with t-tests and chi-square test and after this, a binary logistic regression analysis was conducted in order to determine change in HADS depression outcome.

Results

A total of 64,658 CR patients with new onset depressive symptoms (66.24±10.69 years, 75% male) constituted the study sample. The comorbid conditions found to determine reduced odds of improvement in depressive symptoms, following CR, were such as: emphysema, angina, stroke, and diabetes. Other statistically significant key

determinants leading to a reduced likelihood of improvement were a higher HADS anxiety score, increased weight, physical inactivity, smoking at baseline, etc.

Conclusion

The current study found baseline comorbid conditions of patients with new onset depressive symptoms were determinants of poorer HADS outcomes following CR. Smoking, increased weight, physical inactivity etc., were other determinants of reduced likelihood of improvement in depression. CR programmes should try to tailor the CR intervention to align with patient characteristics.

5.10 Introduction

The association of depression with increased mortality and worse cardiac prognosis has been well established by previous meta-analyses in the CVD population (Meijer et al., 2013, 2011). A scientific statement from the American Heart Association (AHA) recommended depression be seen as a risk factor for mortality and morbidity in cardiac patients (Lichtman et al., 2014). Depression is common in CVD patients, and 20% of cardiac patients experience depression (Thombs et al., 2006). Globally, depression is one of the leading causes of years lived with a disability (Vos et al., 2017), and relates to non-compliance with treatment, and loss of productivity in CVD patients (Egede, 2007; Gehi et al., 2005; Ziegelstein et al., 2000). Similarly, according to World Health Organization (WHO), depression is predicted to be a leading cause of burden of disease in 2030 (WHO, 2008). Furthermore, depression and CVD often coexist (Van der Kooy et al., 2007) and depression leads to both increased inpatient and outpatient health care utilisation costs (Sullivan et al., 2002).

The time to onset of depressive symptoms has been investigated in recent cardiac morbidity and mortality studies (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016; Dickens et al., 2008; de Jonge et al., 2006). While some research shows patients with a history of depression before a heart event experience increased cardiac morbidity and mortality, other studies have found that patients with new onset

depressive symptoms following a heart event were ultimately more likely to experience adverse heart events and death (Dickens et al., 2008; de Jonge et al., 2006). Recently, a study conducted using the UK National Audit of Cardiac Rehabilitation (NACR) data has augmented this body of literature, demonstrating that the baseline characteristics of patients with a history of depression, such as physical inactivity, higher anxiety, smoking, higher total number of comorbidities, and being of male gender were determinants of depression levels after CR (Sever et al., 2019) (see chapter 4). However, there remains an unaddressed population; that is, patients with new onset depressive symptoms, whose characteristics can differ from patients with a prior history of depression. Furthermore, the different types of comorbidities, and their impact on depression outcome has failed to be thoroughly investigated by previous papers in the CR setting, in addition, they were unable to adjust for HF and cardiac treatments. Therefore, the current study will be first to investigate the association of comorbidities and other patient characteristics with the outcome of depression in UK CR programmes.

The second objective of this study was to examine variations in the psychosocial support delivered to CR patients in the routine UK CR programmes. In a recent BACPR guideline, the core components of CR programmes were revealed, and psychosocial health was one of these (BACPR, 2017). However variation exists among CR programmes (Cowie et al., 2019; BACPR, 2017; SIGN, 2017) and emphasis has been placed on the fact that CR programmes need to deliver core components to ensure clinical effective care and sustainable health benefits (Cowie et al., 2019). The recommendation was made in BACPR guideline that if appropriately trained psychological practitioners exists within the CR programme, patients with clinical signs of depressive symptoms can be managed within the programme (BACPR, 2017). However, in the absence of dedicated psychological practitioners, patients should be offered access to trained psychological practitioners (BACPR, 2017), or referred to services outside of the core CR team. However both in this guideline and the recent

NACR data, there is a limited evidence regarding what CR programmes offer to CR patients in terms of psychosocial support, the percentage of CR programmes delivering psychosocial support within a programme, or referring individuals to outer services, and how psychosocial support is delivered (NACR, 2018). Therefore, the latter aim of the current study is to address these issues and explain the variation in the UK CR programmes in terms of the psychosocial support offered to patients.

5.10.1 Rationale for the study

As the negative impact of depression on worse CVD prognosis and mortality is now widely recognised, the study investigates determinants of improvement in depression after CR. The aim being to ensure CR programmes can better manage the depression levels of patients with new onset depressive symptoms, to help these patients gain the most from CR programmes and improve their depressive symptoms by tailoring CR intervention based on these determinants. No previous study has been able to investigate the determinants of change in depression in patients with new onset depressive symptoms following CR. Therefore, identifying the determinants of achieving improved HADS levels in patients with new onset depressive symptoms, following CR, was the principal aim of this chapter. The determinant variables identified in the critical review chapter (Chapter 2) and the potential variables designated in the NACR data were employed in the analyses performed in the current study.

5.10.2 The research questions

The research questions posed in this study were:

- ‘Is improvement in depression in patients attending cardiac rehabilitation with new onset depressive symptoms determined by patient characteristics?’ Or can be rephrased as ‘What are the baseline patient characteristics that determine improvement in depression in patients with new onset depressive symptoms, following CR?’

- What psychosocial support is available for the CR patients in routine CR practice in the UK?

The study hypothesis tested which baseline characteristics of patients with new onset depressive symptoms were determinants of their depression levels following CR. In addition, a prospective survey hypothesis tested the variation present in UK CR programmes, focusing on how psychosocial support is delivered in these programmes, in the prospective survey part.

5.11 Methods

A retrospective research design was the ruling methodological approach in the current part of the chapter, with the addition of a prospective approach (national survey) as a sub-set of this part to clarify key aspects of CR service delivery in the context of psychosocial support. In order to identify what factors inform change in depressive symptoms following CR in patients with new onset depressive symptoms, routine practice data from NACR was analysed. In addition, a prospective survey was also employed to gain insight into the psychosocial support offered to CR patients at a programme level.

5.12 Retrospective approach

5.12.1 Data source

In the current study, the NACR data was used for secondary data analysis. The data source was previously explained in detail in chapter 5, part 1, section 5.4.1.

5.12.2 Design and inclusion criteria

The current study employed a retrospective observational methodology to investigate the determinants of improvement in depressive symptoms following CR. The analysis was based and extracted from the BHF NACR routine practice data from the 1st April 2012 to 31st March 2018. The study population included adult patients (≥18), with MI and HF having received PCI and CABG (NICE, 2018, NICE 2013). All the eligible

patients were selected as participants in the study period if they had no prior history of depression and had pre and post HADS assessment scores recorded in CR (N= 64,658). In other words, patients who had no reported prior history of depression, and possessed a HADS measurement pre and post CR were screened through the NACR data set. This approach defined the eligible population constituting our study sample. The flow diagram show the sample size of the study and the total population during the study time period in this part of the chapter **(Figure 5.2)**.

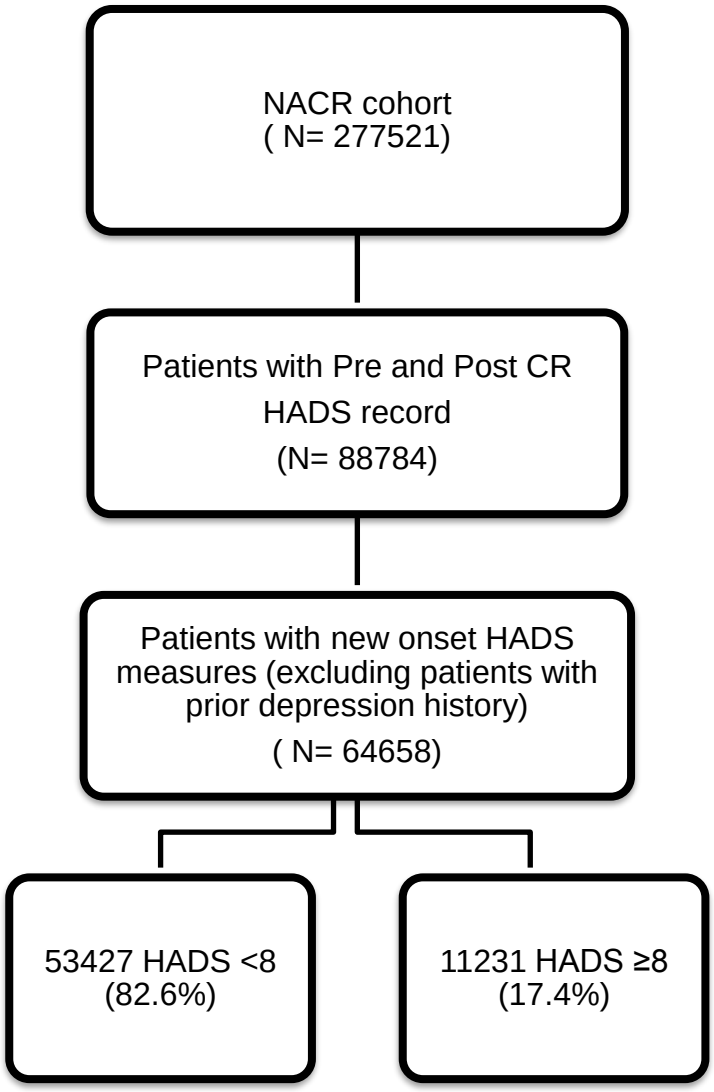

Figure 5.2: Study flow diagram for part 2

5.12.3 Variables in the analysis

5.12.3.1 Outcome variable

HADS is used for the screening of depressive symptoms it was the outcome measurement in this chapter. The elements of HADS and its validity were explained in detail previously, in chapter 5, part 1, section 5.4.3. A clinical cut off point of 8 was used in the current study, as part 1 of the chapter, to categorise patients according to presence of new onset depressive symptoms group (≥ 8) and patients with absence of new onset depressive symptoms (< 8) (Zigmond and Snaith, 1983). The patients with HADS < 8 and HADS ≥ 8 were compared in the analyses of a subgroup of patients without a history of depression. Furthermore, baseline HADS anxiety scores, which are routinely reported as part of HADS, were used to examine the determinants of depression outcomes following CR.

5.12.3.2 Explanatory variables

Total number of comorbidities represents the sum of the number of comorbidities present in the patients. The comorbidities in the NACR data were emphysema, stroke, angina, diabetes, chronic back problems, and others previously described in detail in chapter 5-part 1 section 5.4.3. Age, gender, marital status (categorised as partnered or single) and the English Index of Multiple Deprivation (IMD) were the demographic variables used in the analysis (the English IMD categorised as the most deprived and less deprived areas) (Department for Communities and Local Government., 2015). Other variables were smoking (current smoker/non-smoker), weight (kg), BMI, moderate physical activity (Yes/No) (which is measured by the question of ‘Do you take regular moderate physical activity of at least 30 minutes duration on average 5 times a week? (150 min in a week)), presence of heart failure (Yes/No), and cardiac treatment (PCI/CABG/other/none). A detailed description of these variables can be found in chapter 5-part 1 section 5.4.3.

5.12.4 Data analysis

To perform the data analyses, SPSS version 25 (IBM Corp, Armonk, New York, USA) was used. The study population were patients without a prior history of depression and valid pre and post HADS assessments. Statistical significance was accepted as having a p value of <0.05. The summary statistics were presented using percentages, means and standard deviations. A comparison of baseline characteristics was made among the groups of patients with presence of new onset depressive symptoms and absence of new onset depressive symptoms, by employing t-tests for continuous variables, and chi-square tests for categorical variables. For the continuous variables, Cohen's d was calculated as effect size, phi effect size was reported for binary categorical variables, and Cramer's V effect size was reported for categorical variables with more than two categories. The effect sizes were interpreted as small medium and large for Cohen's d (d=0.2,0.5,0.8, respectively) (Lakens, 2013). Phi and Cramer's V effect sizes were reported as small, medium and large with 0.1, 0.3, 0.5, respectively. To investigate which variables determined improvement in the HADS depressive symptoms following CR, in patients with new onset depressive symptoms, a binary logistic regression model was conducted. The data analysis was briefly summarised here. A detailed explanation of the data analysis can be found in chapter 5, part 1, section 5.4.4.

In retrospective observational studies, the missingness in the data is not unusual. In order to answer the research questions, only patients with new onset depressive symptoms comprised the current study sample. As a result of the sampling approach the majority of the study variables were well represented, for instance, age, gender, HADS anxiety, total number comorbidities, and other comorbidities included in the analyses were not missing with all at 0%, and other variables such as weight 7.1% and moderate physical activity 13% were missing; thus, a valid case/available case analysis was conducted.

5.13 Prospective approach

A psychosocial health survey designed to clarify the variation in psychosocial support offered to CR patients at a programme level as part of routine clinical practice. The NACR survey questions were designed to capture the diversity of psychosocial support at programme level and to answer the question of 'What psychosocial support is available for the CR patients in routine CR practice?'.

This survey was sent out to 332 CR users present on the CR registry in March 2019. A copy of the survey (web-based questionnaire) is given in **appendix - 5**. The survey was piloted and initially sent out to six health care professionals, and according to their suggestions, alterations were made to the survey questions which increased the validity of the questionnaire. The health care professionals were chosen from different specialisms, such as exercise specialists, cardiac specialist nurses, and cardiac rehabilitation co-ordinators. After alterations were made based on the suggestions of CR practitioners, the survey was sent out to the UK CR programmes. A reminder e-mail was distributed to non-responders via e-mail on two occasions. Descriptive statistics were applied using frequencies (%). SPSS 25.0 (IBM Corp, Armonk, New York, USA) statistical software package was used to perform calculations.

5.13.1 Population

The primary contacts at the UK CR programmes received the survey which was a total of 332 recipients. These primary contacts were chosen from CR programmes registered with NACR, and entered in an online registry.

5.13.2 Questionnaire

An online survey was applied via survey monkey (https://www.surveymonkey.co.uk/). CR programmes were asked whether their programme offer psychosocial support to manage patients' psychosocial health. The survey asked the programmes stated whether they provide psychosocial support to patients by referring patients internally,

referring them externally, both internally and externally, or offer no support at all. According to their responses, a further series of questions were asked. These questions were: how do patients receive psychosocial support; i.e. one-to-one session, group sessions, or a mixture?; who delivers the psychosocial support?; what interventions are offered for psychosocial support?; if patients are referred externally what external services are they referred to, and what is patient referral based on?; and if programmes do not offer support for patient's psychosocial health, what are the reason for it? And so on **(see Appendix - 5)**.

5.14 Results

5.14.1 Retrospective study results

The study population were 64,658 patients without a prior history of depression, who had completed CR with valid pre and post HADS assessments. Among this population of 64,658 participants, 17.4% presented with new onset depressive symptoms (HADS≥8) and 82.6% had absence of new of new onset depressive symptoms (HADS<8). At baseline assessment, at the commencement of CR, patients with new onset depressive symptoms were more likely to be single, younger, female, had increased weight, a higher total number of comorbidities, were more likely to smoke, had increased anxiety score, were physically inactive, presence of heart failure, less likely to receive cardiac treatments, and more likely to have the following comorbidities: emphysema, diabetes, angina, chronic back problems, and stroke, compared to those with an absence of new onset depressive symptoms group. Patient's baseline characteristics were grouped based on their HADS levels (HADS≥8 presence of new onset depressive symptoms, HADS<8 absence of new onset depressive symptoms), as shown in **table 5.5**.

Table 5.5: Baseline characteristics for presence and absence of new onset HADS depressive symptoms groups

Variables	**HADS <8 Non-acute group (n=**53427)	**HADS ≥8 Acute group (n=**11231)	**P**	**Effect Size**
	Mean ± SD	**Mean ± SD**		
Age	66.56 ± 10.54	64.73 ± 11.29	< 0.001	0.17
Total Comorbidities	2.34 ± 1.44	2.58 ± 1.56	< 0.001	0.16
Weight	82.35 ± 16.46	83.11± 18.40	< 0.001	0.05
HADS Anxiety Score	4.38 ± 3.31	9.56 ± 4.03	<0.001	1.50
BMI	28.04 ± 4.82	28.68 ± 5.52	<0.001	0.13
Gender female %	24.1	29.3	< 0.001	0.05
150 min. Physical Activity a Week (Yes) %	46.2	28.5	< 0.001	0.14
Smoking (Yes) %	4.7	8.3	< 0.001	0.06
Single %	20.1	24.8	< 0.001	0.04

IMD (most deprived) %	9.6	15.0	< 0.001	0.07
Heart Failure (Yes)%	6.4	10.1	< 0.001	0.06
Comorbidity				
Angina %	18.4	19.5	0.008	0.01
Diabetes %	19.1	24.6	< 0.001	0.05
Stroke %	4.2	5.9	< 0.001	0.03
Emphysema %	1.7	2.6	< 0.001	0.03
Chronic back problems %	11.5	14.3	< 0.001	0.03
Cardiac treatment				
No treatment %	8.5	11	< 0.001	0.05
PCI %	50.3	44.5		
CABG %	16.6	16.2		
Other treatment %	24.6	28.3		

HADS = Hospital Anxiety and Depression Scale; SD = standard deviation

A binominal logistic regression was performed to ascertain the impact of gender, age, marital status, total number of comorbidities, HADS anxiety measurement, smoking, weight, physical activity, heart failure, cardiac treatments and comorbidities of emphysema, stroke, diabetes, angina, and chronic back problems, on the likelihood that participants' depression symptoms improved over the ones who remain within the higher levels of HADS depression symptoms after CR. The logistic regression model was statistically significant, $X^2(18) = 359.814$, $p < 0.001$. The model correctly classified 63.3% of cases. The Hosmer and Lemeshow test shows that the model was a good fit ($p = 0.208$). Of the sixteen potential determinant variables, thirteen were statistically significant: marital status, weight, physical inactivity, smoking, HADS anxiety score measurement, presence of heart failure, CABG or other treatments, total number of comorbidities, and comorbidities of emphysema, stroke, angina, diabetes, and chronic back problems (As shown in **table 5.6**).

Table 5.6: Coefficients of the model determining change in depression whether a patient has improved depressive symptoms after CR

Variable	**B**	**SE**	**P**	**Odds Ratio**	**Lower 95% CI**	**Upper 95% CI**
Age	-0.005	0.003	0.138	0.995	0.990	1.001
Total Number of Comorbidities	-0.071	0.024	0.004	0.932	0.888	0.977
Weight	-0.008	0.002	<0.001	0.992	0.989	0.996
HADS anxiety score	-0.105	0.008	<0.001	0.900	0.885	0.915

150 min. a week physical activity (No)	-0.196	0.067	0.003	0.822	0.721	0.937
Smoking (Yes)	-0.281	0.118	0.018	0.755	0.599	0.952
Gender (Male)	-0.119	0.075	0.112	0.888	0.767	1.028
Marital Status (Single)	-0.273	0.073	<0.001	0.761	0.660	0.877
IMD (most deprived)	-0.015	0.088	0.864	0.985	0.829	1.171
Angina (Yes)	-0.251	0.083	0.003	0.778	0.661	0.916
Diabetes (Yes)	-0.186	0.077	0.016	0.830	0.714	0.965
Stroke (Yes)	-0.332	0.136	0.015	0.718	0.550	0.937
Emphysema (Yes)	-0.407	0.207	0.049	0.665	0.443	0.999
Chronic Back Problems (Yes)	-0.208	0.095	0.028	0.812	0.674	0.977

Heart Failure (Yes)	-0.289	0.105	0.006	0.749	0.610	0.919
Cardiac treatment (reference: no treatment)						
PCI	0.078	0.116	0.499	1.082	0.862	1.357
CABG	0.362	0.132	0.006	1.436	1.108	1.861
Other treatment	0.313	0.119	0.008	1.367	1.084	1.725
Constant	2.720	.320	<0.001	-	-	-

B = regression coefficient; SE = standard error; CI = confidence interval.

An increased HADS anxiety score measurement was associated with reduced odds of improvement in depressive symptoms following CR (OR: 0.900, 95%CI: 0.885 to 0.915). Physical inactivity was also associated with a reduced likelihood of moving into the non-acute HADS depressive symptoms category (OR: 0.822, 95%CI: 0.721 to 0.937). Smoking was associated with reduced odds of improvement in the HADS range following CR (OR: 0.755, 95%CI: 0.599 to 0.952). Patients with a higher number of comorbidities had a reduced likelihood of experiencing an improvement in their HADS levels following CR (OR: 0.932, 95%CI: 0.888 to 0.977). Increased weight and being single were also negative determinants of change in depression (OR: 0.992, 95%CI: 0.989 to 0.996) and (OR: 0.761, 95%CI: 0.660 to 0.877) respectively. Patients with the comorbidity emphysema had 0.665 times lower odds of experiencing improved depressive symptoms, sequentially, patients with comorbidity stroke had 0.718 times, comorbidity angina had 0.778 times, comorbidity chronic back problems 0.812 times, and comorbidity diabetes had 0.830 times lower odds of improvement in their depressive symptoms after CR. Patients that had heart failure were 25% less likely to

improve their depressive symptoms following CR (OR: 0.749, 95%CI: 0.610 to 0.919). Furthermore, patients receiving CABG and other treatments were 43% and 36% more likely to experience an improvement in their depressive symptoms (OR: 1.436 95%CI: 1.108 to 1.861; OR: 1.367 95%CI 1.084 to 1.725, respectively).

5.14.2 Prospective survey results

In the UK, the total number of CR programmes delivering core CR is 332, and 229 of them enter data electronically to the NACR portal (NACR, 2018). The survey was sent out to all 332 programmes, and 186 (56%) responded. Of these 186 programmes 140 (75%) were NACR users and 46 (25%) were not. **Figure 5.3** provides a flow diagram detailing the respondent CR programmes, showing those reported as NACR users and the remainder.

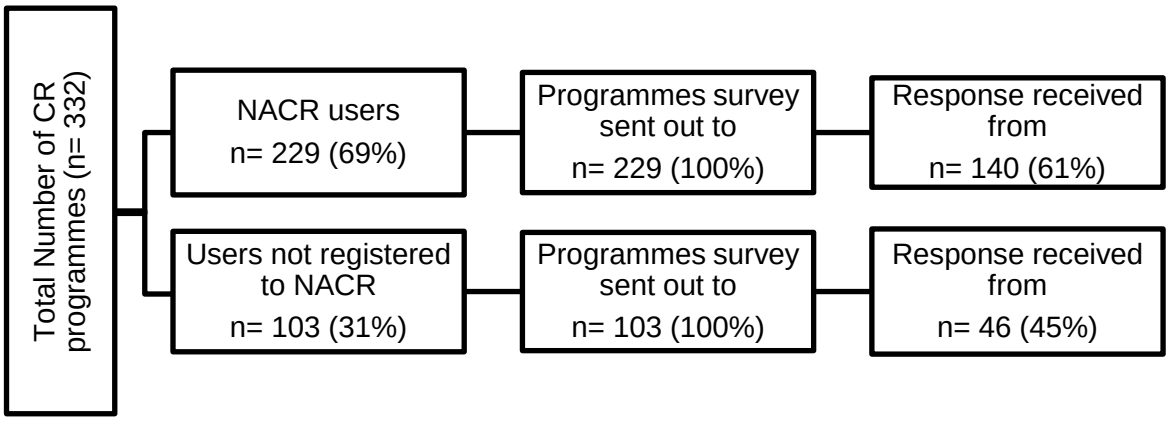

Figure 5.3: Number of responses received for survey

Of the 186 CR programmes responding to the questionnaire, 97 (52.2%) offered support for psychosocial health both internally and externally. 42 (22.6%) programmes offered psychosocial support within their programme and 37 (19.9%) referred patients out. However, 10 (5.4%) programmes were unable to offer any support for psychosocial health **(Figure 5.4)**.

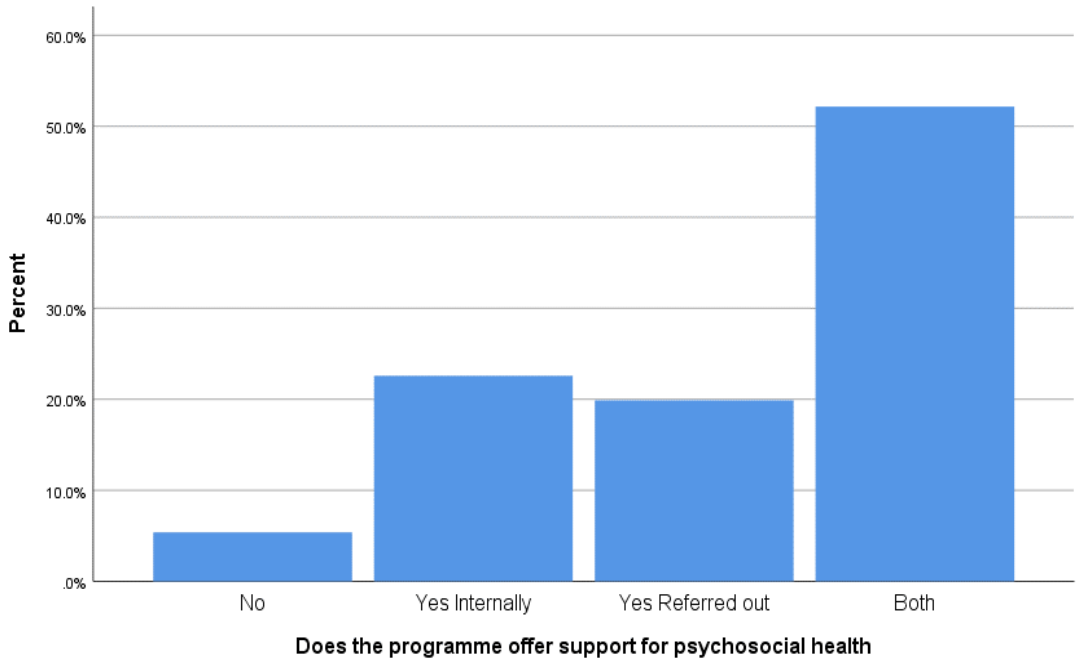

Figure 5.4: Whether the programme offers support for psychosocial health

Respondents were also asked if patients receive psychosocial support within the programme, such as a one-to-one session, group session, or a mixture of the two (n=139). A mixture of one-to-one and group sessions were used by the highest number of programmes 80 (57.6%), 28 (20.1%) programmes utilised one-to-one sessions only, and 27 (19.4%) group sessions **(Figure 5.5)**.

Among the CR centres offering psychosocial support within their programmes (n=139), around three quarters 102 (73.4%) stated psychosocial support was delivered by the CR team including nurses, physiotherapists, occupational therapists and other team members, whereas in 46 (33.1%) centres it was delivered by a qualified clinical psychologist, and in 23 (16.5%) by a health psychologist, in 11 (7.9%) by a CBT therapist, and in 9 (6.5%) by a counsellor.

One finding of this survey was that among those CR services offering psychosocial health within their programme (n=139), psychosocial support medications were mainly prescribed by general practitioners (GPs) according to reports regarding 97 (70%) CR programmes. 20 (14.4%) programmes stated that a member of the CR team including

nurses, occupational therapists, or other members were responsible for this, and in 16 (11.5%) programmes this was managed by a qualified clinical psychologist.

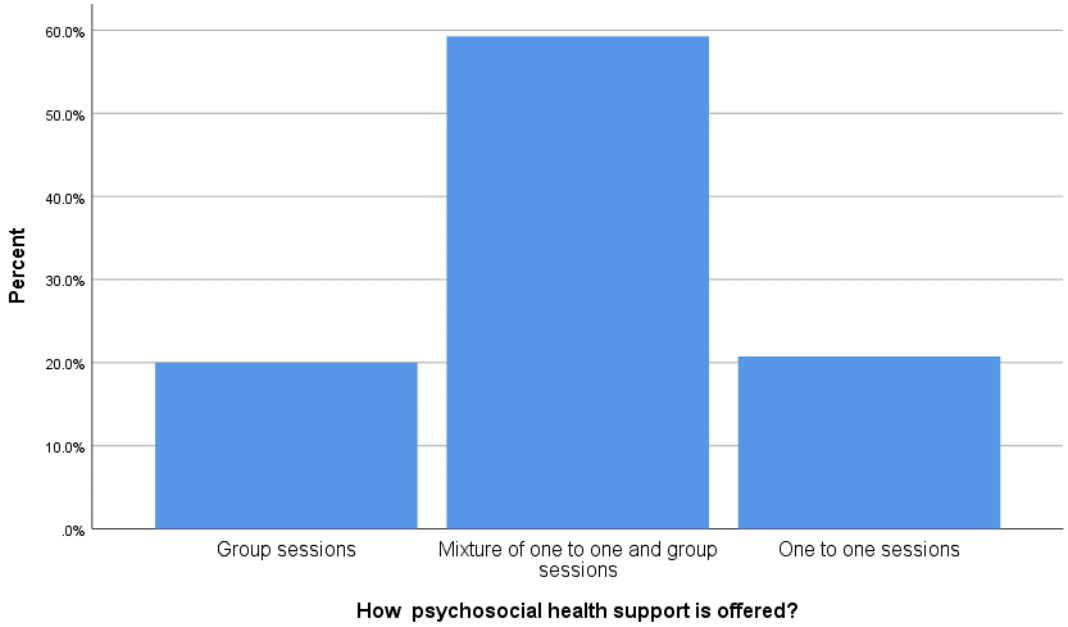

Figure 5.5: How psychosocial health is offered to patients within the programme

Once the interventions available at CR centres for psychosocial support were examined (n=139), it was found the great majority of the CR programmes 128 (92.1%), offer anxiety/ stress management to patients. In addition, 82 (59%) programmes were able to offer behavioural therapies, such as cognitive behavioural therapy (CBT) and behavioural activation (BA). Furthermore, 15 (11%) programmes also provide access to other types of interventions, such as counselling, motivational interviewing, etc.

CR centres, when referring patients to external services (n=134), mainly refer patients to GP's 78 (58.2%), followed by Improving Access to Psychological Therapies (IAPT), 75 (56%), and 47 (35.1%) to a psychologist. According to the 120 programmes that responded, these referrals were principally based on patient's Hospital Anxiety and Depression Scale (HADS) scores at 90 (75%) programmes and the minority were based on Generalised Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9) with 15 (12.5%) programmes and the Beck's Depression Inventory in only 1

(0.8%) programme. In addition, 18 (13.4%) programmes mainly referred patients after individual 1:1 assessments, or simply after talking to patients **(Figure 5.6).**

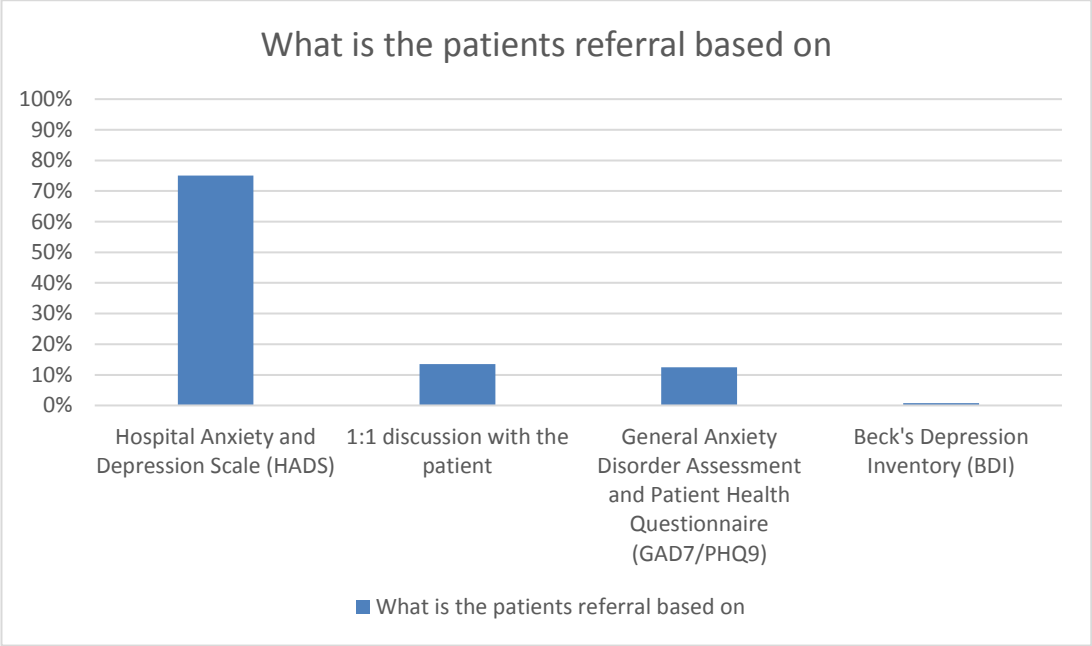

Figure 5.6: What patients' referral are based on

What informs whether a patient receives a CR programme psychosocial intervention, or whether they are referred out has been examined for programmes offering psychosocial support both within programme and referring them out (n=97). The severity of patient's condition, for instance being clinically anxious or depressed, was the most common reason for referral to external services, as was stated by 75 (77.3%) CR centres. Patient preference also informed referral out according to 51 (52.6%) centres, followed by programme availability as mentioned by 14 (14.4 %) centres, and funding constraints, reported by 4 (4.1 %) centres.

Programmes that were unable to offer any form of psychosocial support (n=10) were asked the reasons for this. 7 (70%) programmes acknowledged there were no psychologists available. 4 (40%) programmes cited funding constraints, and in 3 (30%) programmes psychosocial support was provided in other services **(Figure 5.7)**.

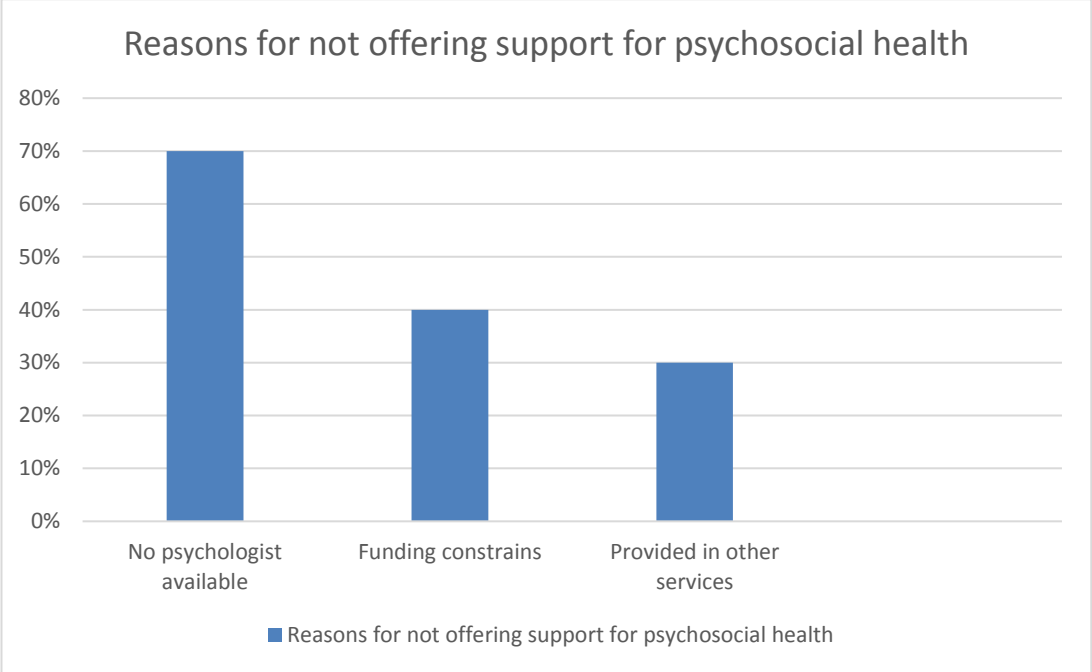

Figure 5.7: Reasons for not offering support for psychosocial health

5.15 Discussion

This discussion relates to the retrospective and prospective studies referred to in part two of this chapter.

Depression is well established in the literature to be associated with adverse cardiac events cardiac mortality and overall mortality. However, there remains a need for further comprehensive investigation of patient characteristics, such as comorbidities, demographics and clinical characteristics associated with new onset depressive symptoms. Consequently, the current study involved an in-depth investigation into patient characteristics, determining outcomes in CR patients with new onset depressive symptoms. The results of this study based on regression findings, demonstrated that the baseline characteristics of patients with new onset acute depressive symptoms include having the comorbidities of emphysema, diabetes, stroke, angina, chronic back problems, and having a higher number of comorbidities, higher anxiety scores, physical inactivity, increased weight, smoking, CABG treatment, presence of heart failure, and being single were significant determinants of depression outcome after CR. In contrast,

age, gender and IMD were not significant determinants of depressive symptoms following CR in patients with new onset depressive symptoms.

The current study found that having a higher total number of comorbidities significantly negatively influenced improvement in depressive symptoms (OR: 0.932, 95%CI: 0.888 to 0.977). A study of the general population included 7620 primary care participants from 30 general practices in Australia (66% females, mean age 51±14) and found a dose–response relationship between the number of chronic conditions and depressive symptoms (Gunn et al., 2012). The current thesis study confirmed that a higher number of comorbidities was a determinant of change in depressive symptoms in the CR population. However, another study conducted in a CVD population was unable to confirm this association (Vitinius et al., 2019), which could be explained by their population being younger (mean age 59.1 ± 19.8) compared to the current study (66.24 ± 10.69), as older age is associated with multimorbidity (Marengoni et al., 2011), the current study may have included more multi-morbid population. Furthermore, having multiple comorbidities has been linked to a reduced likelihood of being referred to or taking up CR, which creates a challenge for CR services and practitioners (van Engen-Verheul et al., 2013; Aragam et al., 2011). Nevertheless, CR patients with multiple comorbidities might be expected to benefit from participating in CR programmes, due to improvements in their BMI and functional capacity (Listerman et al., 2011).

A finding of note was that the comorbidity of diabetes was associated with 17% reduced odds of improvement in depressive symptoms after CR (OR: 0.830 95%CI: 0.714 to 0.965). At the start of CR, patients with diabetes had increased cardiovascular risk factors and a reduced physical capacity, relative to patients without diabetes (Mourot et al., 2010). However, all the patients had improved exercise capacity following CR, and the extent of their improvement was similar in diabetic and non-diabetic patients (Mourot et al., 2010). In addition, diabetic patients who either attend or complete CR also benefited from reduced mortality rates compared to non-attenders, or patients who failed to complete CR (Jiménez-Navarro et al., 2017; Armstrong et al.,

2015). It is recommended that CR programmes aim to recruit patients with diabetes into CR, due to their increased cardiovascular risk and reduced CR programme attendance rate (Sumner, Grace and Doherty, 2016; Lopez-Jimenez et al., 2013; Banzer et al., 2004). Considering the rise in the prevalence of diabetes in recent years (Einarson et al., 2018), the management of diabetes might be relevant, and could eventually lead to improvements in depressive symptoms.

Another finding was that the comorbidity of stroke was a statistically significant negative determinant of improvement in depressive symptoms following CR (OR: 0.718, 95%CI: 0.550 to 0.937). Prior studies have demonstrated that patients with stroke comorbidity had a reduced likelihood of referral to (Brown et al., 2009) and uptake of CR (Suaya et al., 2007). Yet, some studies have shown stroke patients who participated in CR have shown improved cardiac fitness and functional capacity (Marzolini et al., 2014; Prior et al., 2011; Tang et al., 2009), thus, involving stroke patients in CR might be of benefit.

The comorbidity of emphysema had the largest impact on the change in depressive symptoms after CR. Patients with a comorbidity of emphysema at baseline were 34% less likely to improve their depressive symptoms following CR (OR: 0.665, 95%CI: 0.443 to 0.999). Patients with chronic obstructive pulmonary disease (COPD) and CVD, experience problems such as breathlessness and disability; therefore, CR programmes should ideally offer tailored interventions for COPD patients, covering their needs in the context of multimorbidity (Man et al., 2016). Corresponding to this, some studies have recently emerged considering a better adaptation of CR interventions to patients with COPD (Jones et al., 2019; Triest, Singh and Vanfleteren, 2016; Evans et al., 2010). Furthermore, angina and chronic back problems were also associated with reduced likelihood of improvement in depressive symptoms OR: 0.778, 95%CI: 0. 0.661 to 0.916 and OR: 0.812, 95%CI: 0.674 to 0.977. Overall, all of the aforementioned comorbidities were negative determinants of improvement in depression outcomes after CR in patients with new onset depression.

A further finding of clinical relevance was that modifiable risk factors of CVD, such as physical inactivity, smoking and weight had an unfavourable impact on depression levels following CR. These factors were determinants of reduced odds of improvement in depression in patients with new onset depressive symptoms after CR (OR: 0.822, 95%CI: 0.721 to 0.937; OR: 0.755, 95%CI: 0.599 to 0.952; OR: 0.992, 95%CI: 0.989 to 0.996 respectively). Earlier systematic reviews conducted in the general population support these findings (Schuch et al., 2018; Fluharty et al., 2017; Luppino et al., 2010), as do other cohort studies which recruited patients with CVD (Stafford, Berk and Jackson, 2013; Ye et al., 2013). Yet, these studies also failed to be inclusive of CR patients, in particular, patients with new onset acute depressive symptoms. However, in the current study, patients who participated in CR were included and the outcome of change in depressive symptoms assessed. Previous studies tended to focus on the association of CR uptake and depression with a lack of evidence on the factors determining outcomes in patients with new onset depressive symptoms.

In patients with new onset acute depressive symptoms, an increased HADS anxiety score at baseline was associated with 10% reduced odds of improvement in depressive symptoms following CR (OR: 0.900, 95%CI: 0.885 to 0.915). This finding reveals that anxiety and depression are interrelated, and associated with poor outcomes, which was in agreement with a previous publication (Eastwood et al., 2012). In this American study, a total of 622 HF patients constituted the study population, and showed that anxiety, measured by Brief Symptoms Inventory, was associated with depressive symptoms in males and females. In the current study, the HADS anxiety measurement was used for assessment instead and yet, supported this association. Furthermore, the current thesis identified patients with heart failure as less likely to improve their depressive symptoms by 25%. According to recent trial results, there were no significant improvements in depressive symptoms among the HF population (Dalal et al., 2019), perhaps, this could be explained by the results of the current study showing that HF patients are less likely to improve their depressive

symptoms. Therefore, CR teams may need to provide additional psychosocial support for HF patients which can be further investigated in future studies. In addition, in the current study, the multivariate analysis adjusted for cardiac treatment and the findings demonstrated that patients who receive treatment of CABG had 43% increased odds of improvement in their depressive symptoms.

A further finding was that in terms of patient demographics, being single was a significant negative determinant of improved depressive symptoms following CR (OR: 0.761, 95%CI: 0.660 to 0.877). Patients might therefore benefit from the support of a partner to cope with their illness, which results in the noted improvements in their depressive symptoms. Yan et al. (2011) conducted a meta-analysis, and found that being single was associated with increased depressive symptoms. 24 cross sectional and 8 cohort studies were included with a total of 52803 participants from the general population of people aged ≥ 55 years. In the current study, other patient demographics of age, gender and IMD were not able to statistically determine depression outcome. However, the adjustments were made for other comorbidities and cardiac risk factors in the multivariate analysis, which may have impacted this finding.

In relation to this prospective survey, 186 out of 332 CR programmes responded the survey, which is a reasonable response rate (56%). The respondents provided important information from which to understand what psychosocial support is available in UK CR programmes, in routine practice. Based on this data 52.2% of programmes offered support for psychosocial health both internally and externally, 22.6% offered psychosocial support within their programmes, and 19.9% referred out. However, 5.4% programmes did not offer any support for psychosocial health. The two main reasons these programmes did not offer any form of psychosocial support were; there were no psychologists available, and there were funding constraints. According to the BACPR guideline, if there are trained psychological practitioners available in the CR service, patients with clinical signs of anxiety or depression due to a heart event can be managed internally (BACPR, 2017). However, in the absence of psychological

practitioners in the CR programme, participants with clinical levels of anxiety and depression or other severe mental health problems, need to be able to access trained psychological practitioners (BACPR, 2017). The current study has successfully identified the percentage of programmes that manage the psychosocial health of patients within their programmes, and to refer them out due to lack of capacity. Based on a recent study, patients' and nurses' views supported that psychosocial support should be embedded within CR programmes, rather than being provided in parallel outer services (Turner et al., 2017). In addition, the integration of psychosocial and physical healthcare into whole system approaches are considered the most appropriate way to assist patients living with physical and psychosocial morbidity (Coventry et al., 2015).

Psychosocial support was mostly delivered as a mixture of one-to-one and group sessions by mainly CR team members. In addition, anxiety and stress management were the most common interventions offered in CR programmes, however there were less programmes that were able to offer behavioural therapies in the current study. The most recent SIGN guideline recommends all individuals be offered psychosocial care based on a cognitive behavioural model, as a main component of CR (SIGN, 2017). Therefore, recruitment of more psychologists into CR services might be beneficial as a means to increase number of services providing behavioural therapies, such as CBT and BA, thereby, this could have a positive impact on the management of depressive symptoms in CR programmes (BACPR, 2017; SIGN, 2017; Woodruffe et al., 2015). What draws attention in this prospective survey is that variation exists among the CR programmes in terms of the delivery of psychosocial health support. In order to reduce inequalities among services, and improve the psychosocial support that patients receive, in line with the inclusion of the multidisciplinary team (MDT) as one of the key standards of the recent BACPR guideline (BACPR, 2017), recruitment of more psychologists into CR programmes might prove beneficial, especially for services that do not offer any form of psychosocial support.

5.16 Study limitations

In order to answer the specific research question posed in the current study, whether improvements in depression in patients attending CR with new onset depressive symptoms are determined by patient characteristics? Patients with a prior history of depression were excluded from the study sample. However, when the characteristics of the study sample was inspected, it was found to be representative of all available patients over the study time period (n=277521); mean age was 66.24 compared to 65.06, 25% female compared to 27%, and other variables did not differ more than 4%. The sample can be acceptable as nationally representative of patients with new onset depressive symptoms in the UK; however, not all CR programmes provide full patient records after completion, for instance in the NACR data, 36.6% included no follow up assessment which might have influenced the representativeness of the sample (NACR, 2018). The analysis of routinely collected clinical data, by undertaking an observational approach, was a strength of this study and useful as a means to generate real world understanding. Nevertheless, due to the nature of observational studies causal conclusions cannot be drawn, only associations.

5.17 Conclusion

The primary objective of the current study was to investigate whether comorbidities, demographic and clinical characteristics of patients with new onset post heart event depressive symptoms determine improvement in their depression after CR. The baseline characteristics of patients with new onset depressive symptoms, such as a higher total number of comorbidities and comorbid conditions of angina, diabetes, stroke, emphysema, and chronic back problems, smoking, increased weight, physical inactivity, presence of heart failure and being single were negative determinants of improvement in depressive symptoms following CR. Conversely, receiving CABG or other treatments were positive determinants of improvement. These findings could promote CR programmes to adjust CR intervention around comorbidity, weight

management, physical activity status, and smoking cessation in patients with new onset depressive symptoms.

In terms of the prospective survey, there was considerable variation among CR programmes in terms of the delivery of psychosocial health support. To reduce inequalities among the services, and improve the psychosocial support patients receive, recruitment of more psychologists into CR programmes could prove beneficial, specifically for the services that do not offer any form of psychosocial support.

Chapter 6: Synthesis Chapter

6.1 Introduction

Depression occurs in patients with cardiovascular disease (CVD) at a rate of around 20% (Lichtman et al., 2014; Thombs et al., 2006). Many of these patients have a prior history of depression; however, some are experiencing new onset depressive symptoms following the cardiac event. Recently, interest has arisen with regard to the time of onset of depressive symptoms in relation to mortality and cardiac prognosis (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016; Dickens et al., 2008; de Jonge et al., 2006). Some studies have found that patients with a history of depression prior to a cardiac event have increased mortality and worse cardiac prognosis (Sundbøll et al., 2017; Stenman, Holzmann and Sartipy, 2016). However, other research suggests that patients with new onset depressive symptoms after a cardiac event are more likely to experience adverse cardiac events and mortality (Dickens et al., 2008; de Jonge et al., 2006). Nevertheless, both patient groups seem to be at risk for relatively poor cardiac prognosis and outcomes. As stated previously, recent clinical guidelines recommend depression is carefully assessed and managed (BACPR, 2017; SIGN, 2017; Piepoli et al., 2016; Lichtman et al., 2014). The purpose of the current thesis was to identify and critically review the determinants of depressive symptoms in CVD patients in chapter 2; as well as to examine the sociodemographic and clinical factors associated with depressive symptoms in patients with a history of depression at the start of CR, as well as to identify those factors that determine changes in depressive symptoms in patients with a history of depression following CR in chapter 4. In addition, chapter 5 part 1, identified patient characteristics known to be associated with new onset depressive symptoms at the start of CR. In chapter 5 part 2, the aim was to answer the research question ‘What are the baseline patient characteristics that determine improvement in depression in patients with new onset depressive symptoms, following CR?’. Patient characteristics that determine depression levels following CR vary in patients with a history of depression and in patients with new

onset depressive symptoms. It is important to identify which characteristics determine better improvement in these populations, to understand their characteristics and provide tailored approaches to these specific populations within CR programmes, as this will enable them to benefit as much from CR as other patients. In addition, it is important to understand what patient characteristics determine changes in depression levels following CR.

Although the previous chapters independently investigated the determinants of depression in terms of starting CR and patient outcomes it is important, where feasible, for a thesis to synthesise findings across all chapters to gain a deeper understanding of the factors determining depressive symptoms in CR patients with a history of depression and new onset depressive symptoms. This synthesis will briefly summarise each study and discussion in the context of previous literature, to improve understanding of the factors that determine depression outcomes in patients with a history of depression and new onset depressive symptoms. Finally, this will enable the thesis to draw overarching conclusions and recommendations with regard to possible service level adjustments and tailoring of CR, based on factors associated with depressive symptoms at baseline, as well as the identified determinants of change in cases of depression following CR among populations of patients with a history of depression and new onset depressive symptoms.

6.2 Methods

For the current thesis, the studies conducted were mainly retrospective observational studies using NACR data. This synthesis chapter compares data from the studies in chapter 4 and chapter 5, examining the baseline characteristics associated with depressive symptoms in patients with a history of depression prior to cardiac event and in patients with new onset post heart event depressive symptoms. The prevalence of patients with high levels of depressive symptoms in those with a prior history of depression and new onset depressive symptoms will be compared to ones with low

levels of depressive symptoms. In addition, the characteristics of patients determining improvement in depression levels following CR in those specific populations of patients with a history of depression and patients with new onset depressive symptoms will also be compared. Finally, overall findings will be synthesised, and discussed referring to previous critical review literature (chapter 2).

6.3 Results and Discussion

6.3.1 Patients included in the study

The first study population in chapter 4 consisted of 2,715 patients with a comorbid history of depression, with valid pre- and post-CR HADS assessments. Of these 2,715 participants, 45% had high levels of depressive symptoms (HADS ≥8), and 55% had low levels of depressive symptoms (HADS <8) (see **figure 4.1** in chapter 4). The second study population included 64,658 patients with new onset HADS measures recorded (patients without a prior history of depression who had completed CR with valid pre and post HADS assessments), as described in chapter 5 part 2. Among this population of 64,658 patients, 17.4% presented with new onset acute depressive symptoms (HADS≥8), and 82.6% had absence of new onset depressive symptoms (HADS<8) (see **figure 5.2** in chapter 5).

The number of patients with a history of depression (n=2715) was considerably smaller than patients with new onset post heart event HADS measures recorded (n=64658). In addition, patients with a history of depression had higher prevalence of having elevated depressive symptoms at the start of CR with 45%, more than twice the proportion of patients with new onset depressive symptoms in comparison, 17.4%. This demonstrates that patients with a history of depression are more likely to experience high levels of depressive symptoms at the start of CR than patients with new onset post heart event depressive symptoms. A study by Ernstsen et al. (2016), investigating the impact of physical activity on depression after MI reported the prevalence of elevated depressive symptoms to be 11% in patients with HADS-D≥8 group in a

Norwegian population, which was less than that found in the studies of the current thesis. This proportion was 15.2% in a cross sectional study from Australia HADS-D≥8 (Murphy et al., 2012). However, the sample size for both studies was much smaller (n=189, n=275 respectively) than that for studies conducted in the current thesis, which might explain the differences in these proportions, as they may not be representative of cardiac patients with high levels of depressive symptoms (Ernstsen et al., 2016; Murphy et al., 2012). Another explanation could be that these studies were conducted in countries other than the UK, which could have led to some differences in the prevalence of elevated depressive symptoms.

6.3.2 Comparisons of baseline characteristics

In this section of the chapter, the baseline characteristics of patients with a history of depression, and with high levels of depressive symptoms at the start of CR, were compared with patients presenting with new onset depressive symptoms at the start of CR (Chapter 4 **table 4.1**, chapter 5 part 2 **table 5.5**). A synthesis of the baseline characteristics of the study populations with a comorbid history of depression and new onset depression is presented in **table 6.1.**

Patients with a history of depression and high levels of depressive symptoms at the start of CR were found to be younger, had increased weight, higher total number of comorbidities, anxiety, be physically inactive, more likely to be smokers and single than patients with lower level of depressive symptoms. However, gender was not found to be statistically significant at baseline (chapter 4 **table 4.1**). At the start of CR (defined as baseline assessment), patients with new onset acute depressive symptoms were single, younger, had increased weight, a higher total number of comorbidities, were more likely to smoke, had higher anxiety scores, and were physically inactive when compared to patients with absence of new onset depressive symptoms (chapter 5 part 2, **table 5.5**). These results suggest that patients with a history of depression, and those with new onset, share common characteristics, with the exception that patients with new onset depressive symptoms were more likely to be female. In addition, the

impact of comorbidities, presence of heart failure and cardiac treatment were further investigated in patients with new onset depressive symptoms, and it was found that patients with new onset depressive symptoms were more likely to have comorbidities of angina, diabetes, stroke, emphysema and chronic back problems, and were more likely to have presence of heart failure and less likely to receive cardiac treatments compared to those with HADS<8 group.

Table 6.1: Synthesised baseline characteristics among comorbid depression and new onset depressive symptoms study populations

	Comorbid depression study population		**New onset acute depression study population**	
Variables	**HADS <8 group (n=**1494)	**HADS ≥8 group (n=**1221)	**HADS <8 Non-acute group (n=**53427)	**HADS ≥8 Acute group (n=**11231)
	Mean + SD	**Mean + SD**	**Mean ± SD**	**Mean ± SD**
Age	63.49 ± 10.50	60.77 ± 0.53	66.56 ± 10.54	64.73 ± 11.29
Total comorbidities	4.39 ± 2.10	4.90 ± 2.19	2.34 ± 1.44	2.58 ± 1.56
Weight	83.62 ± 17.04	85.56 ± 19.08	82.35 ± 16.46	83.11± 18.40
BMI	28.83 ± 5.14	29.54 ± 5.73	28.04 ± 4.82	28.68 ± 5.52
HADS anxiety score measurement	6.43 ± 3.80	11.60 ± 4.05	4.38 ± 3.31	9.56 ± 4.03

In patients with a history of depression, mean difference in age between high level of depressive symptoms and low depression levels was 2.71 years by patients having high level of depressive symptoms being younger (P<0.001, 60.77 ± 10.53 compared to 63.49 ± 10.50) (Chapter 4 **table 4.1**). This difference was 1.83 in patients with new onset HADS measures, showing that patients with new onset acute depressive symptoms were 1.83 years younger on average than patients with non-acute HADS measures (HADS<8) in the study population (P<0.001, 64.73 ± 11.29 compared to 66.56 ± 10.54, respectively). Similarly, these mean differences were statistically significant in both populations of patients with a history of depression and those with new onset depressive symptoms.

Turning to differences in mean total number of comorbidities; patients with a history of depression, and patients with high levels of depressive symptoms had a 0.50 higher mean total number of comorbidities than those with low levels of depressive symptoms (P<0.001, 4.90±2.19 compared to 4.39±2.10). This difference in the total number of comorbidities was 0.24 in patients with new onset acute depressive symptoms and the non-acute group (P<0.001, 2.58±1.56 compared to 2.34±1.44).

Patients with a history of depression and high levels of depressive symptoms at baseline were 1.94 kilograms heavier than patients with a history of depression and low levels of depressive symptoms, and this mean difference was statistically significant (P<0.001, 85.56±19.08 compared to 83.62±17.04). Patients with new onset acute depressive symptoms at the start of CR were 0.76 kilograms heavier than the new onset non-acute group (HADS<8) (P<0.001, 83.11±18.40 compared to 82.35±16.46).

What stands out from the analysis is that patients with a history of depression and high levels of depressive symptoms at the start of CR also had higher HADS anxiety measurement scores with a mean difference of 5.17, than patients with low HADS levels (P<0.001, 11.60±4.05 compared to 6.43±3.80). This difference was similar (5.18)

between patients with new onset acute depressive symptoms (HADS≥8) and non acute depressive symptoms (HADS<8), P<0.001, 9.56±4.03 compared to 4.38±3.31.

The proportion of females was the same in patients with a history of depression among low and high levels of depressive symptoms group (33.6% in both). However, for patients with new onset post heart event depressive symptoms, the female proportion was 5.2% higher compared to patients with absence of new onset acute depressive symptoms (P<0.001, 29.3% in the new onset depression group, compared to 24.1% in the non-acute new onset depressive symptoms group).

Comparing physical activity recommendations there were a lower proportion of patients with a history of depression and high levels of depressive symptoms at baseline meeting physical activity recommendations (27.5%), whereas in patients with a history of depression and low levels of depressive symptoms at baseline, this proportion was 16% higher with 43.6% meeting the recommendations (P<0.001). In patients with new onset acute depressive symptoms, 28.5% of patients undertook moderate physical activity, while for patients with non-acute new onset depressive symptoms (HADS<8) this proportion was 46.2% (P<0.001). Overall, these proportions were similar for patients with a history of depression, and patients with new onset depressive symptoms.

Turning to the proportion of patients currently smoking at baseline, those with a history of depression and high depression levels were more likely to smoke at 12.7%, whereas in the case of patients with low levels of depressive symptoms this was 7.7% (P<0.001). In terms of patients with new onset acute depressive symptoms, the proportion of smokers was 8.3%, and in patients with non-acute new onset depressive symptoms this was 4.7% (P<0.001). At baseline, the proportion of patients with high HADS levels (HADS≥8) who smoked was higher than in patients with a history of depression than patients with new onset depression according to HADS measures.

The proportion of single patients was higher in patients with a history of depression and high levels of depressive symptoms (36.4%) than patients with a history of depression but low levels of depressive symptoms (28.5%) (P<0.001). Patients with new onset depressive symptoms were also more likely to be single (24.8%), compared to patients with absence of new onset depressive symptoms (20.1%) (P<0.001).

In summary, the patient characteristics significantly associated with high levels of depressive symptoms were similar in the two distinct population of patients with a history of depression and patients with new onset acute depressive symptoms. Patients with a high level of depressive symptoms (HADS≥8) were more likely to be younger, be of higher weight, have a greater total number of comorbidities, anxiety, be physically inactive, more likely to be smokers and single in both patients with a history of depression and those with new onset depressive symptoms at baseline assessment.

6.3.3 Synthesis of determinants

In the current section of this chapter the determinants of improvement in depressive symptoms following CR in patients with a history of depression, and in patients with new onset depressive symptoms will be synthesised. In addition, the findings of the critical review in chapter 2, and those from the studies detailed in chapter 4 and 5 will be compared. Furthermore, any disagreements and similarities between the literature and the studies conducted in the current thesis using clinical data will be reported.

The baseline characteristics that determine improvement in patients' depression levels following CR in patients with a history of depression given in chapter 4 **table 4.3** and in patients with new onset depressive symptoms presented in chapter 5 part 2 **table 5.6** will be compared. The current study is the first to synthesise findings that relate to patients with a history of depression and new onset depressive symptoms and which baseline patient characteristics determine improvement in their depression levels following cardiac rehabilitation. In addition, this study is also the first to synthesise

evidence from the literature with routine clinical practice data in the aforementioned populations.

6.3.3.1 Age

Age was not found to be a significant determinant of improvement following CR both in patients with a history of depression (OR: 0.998, 95%CI: 0.983, 1.013) and also for the patients with new onset depressive symptoms (OR: 0.995, 95%CI: 0.990, 1.001). According to the studies included in the critical review in chapter 2, age was one of the most commonly reported variables in 11/15 studies. Two studies found being younger was associated with depressive symptoms, whereas three studies found no statistical significance, and six studies adjusted for age but did not present their results.

Age was reported to be a significant determinant of depressive symptoms in a sub-study of a Dutch multicentre trial of 2177 MI patients (mean age 63 years, 23% female) (Van Melle et al., 2006). Age was categorised as either <60 or ≥60 years, and the findings showed being younger than 60 years old was associated with an increased likelihood of having depression following MI. However, this study was limited to post MI patients with depression, and did not include patients with a history of depression. The main reason for this was that the primary aim of the trial was to investigate the effect of antidepressant treatment on cardiac prognosis in patients with post MI depression. However, the study was unable to adjust for smoking, physical activity and gender in the multivariate analysis, which were all found to be potential determinants of depression in chapter 2; therefore, this may have had an impact on the study findings (Van Melle et al., 2006). Contrary to this study, based on data collected in a controlled experimental environment, the studies in the current thesis are based on data provided in routine clinical practice that captures observed natural variation in patient characteristics, making it possible to establish what determines depressive symptoms in a real world clinical environment. In agreement with the studies in the current thesis, two American studies were included in the critical review, one secondary retrospective observational study, and a cross sectional study, found that age was not a significant

determinant of depression, and these studies included age as a continuous variable in their analysis (Eastwood et al., 2012; Naqvi et al., 2007), as did a cross sectional study conducted in Oman (Almamari, Muliira and Lazarus, 2019). Although age was adjusted in the other studies, the results were not reported (Zhu et al., 2019; Ernstsen et al., 2016; Myers et al., 2012; Pajak et al., 2012; Schrader et al., 2006; Bonnet et al., 2005).

6.3.3.2 Gender

The impact of gender on CR depression outcome was inconsistent in patients with a history of depression, and those with new onset depressive symptoms. Among those patients with a history of depression, males were 18% less able to improve their depression levels following CR (OR: 0.721 95%CI: 0.523 to 0.992). However, for patients with new onset depressive symptoms, gender was not found to be a significant determinant of improvement in their depression levels after CR (OR: 0.888 95%CI 0.767 to 1.028). According to the studies included in the review, being female was seen as a statistically significant determinant of depressive symptoms in one study (Naqvi et al., 2007). However, four studies reported no significant associations (Almamari, Muliira and Lazarus, 2019; Stafford, Berk and Jackson, 2013; Murphy et al., 2012; Gravely-Witte et al., 2009).

An American cross-sectional study by Naqvi et al. (2007) examined the influence of gender on depressive symptoms after MI, including 944 patients with MI and unstable angina (UA). A Zung self-answered questionnaire were given to patients to assess presence of depressive symptoms upon hospital discharge. Patients were asked to return their responses by mail. Based on the Zung depression scale, patients were categorised as having major depressive symptoms when their total score was >50. According to a multivariate analysis results, female gender was found to be associated with an increased likelihood of having depressive symptoms (OR: 1.64; 95% CI, 1.19-1.28). However, this was a single centred study, and the generalisability of its results to wider population is questionable. In addition, the Zung self-rating assessment tool is

not commonly used to assess depression; therefore, difficulties might arise when comparing the results of this study with other studies.

Conversely, four studies noted that gender was not a significant determinant (Almamari, Muliira and Lazarus, 2019; Stafford, Berk and Jackson, 2013; Murphy et al., 2012; Gravely-Witte et al., 2009). An Australian prospective observational study by Stafford, Berk and Jackson (2013) included 193 patients with MI/PCI/CABG (mean age: 64.14 ± 10.37, female: 19%), and gender was found to be a non-significant determinant in their multivariable analysis. This finding was also in line with a study by Murphy et al. (2012), which also found gender was not a significant determinant. However, the independent variables included in the multivariate analysis were not clearly reported, and nor were the study results. In addition; in the review studies adjustments were made for gender in six studies, however the details of findings leading the researchers to make the adjustment were not reported (Zhu et al., 2019; Ernstsen et al., 2016; Myers et al., 2012; Pajak et al., 2012; Schrader et al., 2006; Bonnet et al., 2005). The current thesis was the first to differentiate between patients with a history of depression and those with new onset post heart event depressive symptoms in CR patients.

6.3.3.3 Smoking

The thesis findings with regard to smoking were consistent. In patients with a history of depression, smoking was associated with a 44% reduced likelihood of improvement in patient's depression levels following CR (OR: 0.563, 95%CI: 0.345 to 0.921). Smoking was also a determinant of 25% reduced odds of improvement in patients experiencing new onset depressive symptoms with a lower effect size in comparison (OR: 0.755, 95%CI: 0.599 to 0.952). The data from clinical practice corresponded to the six studies included in the critical review (Chapter 2) (Stafford, Berk and Jackson, 2013; Myers et al., 2012; Pajak et al., 2012; Gravely-Witte et al., 2009; Naqvi et al., 2007; Bonnet et al., 2005). However, it contrasted with one retrospective secondary data analysis study

(Eastwood et al., 2012), and three cross sectional studies (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Murphy et al., 2012).

The results of an Australian prospective cohort study of 193 cardiac patients (mean age: 64.14±10.37, female: 19%) supported the findings presented in the studies conducted in the current thesis, and found that being a smoker at the time of the cardiac event was associated with an increased likelihood of being diagnosed with depression (assessed with clinical interview) at three months (OR: 4.30, 95% CI: 1.12-16.46; $p < 0.05$) (Stafford, Berk and Jackson, 2013). However, due to the relatively small sample size compared to other studies, the confidence interval was very wide, which may have a negative impact on the precision of the estimate of effect size. This also confirmed another prospective observational study from Israel, which recruited 632 patients (mean age: 52±8.6, Female: 14%) who had been admitted for their first-ever MI (Myers et al., 2012). However, mean age and percentage of females was considerably low when compared to the NACR data (mean age: 67, female: 29%) (NACR, 2019), which may have negatively influenced the study's representativeness. Furthermore, as there was insufficient data relating to the patients' history of depression, the authors recommend examining the impact of depression present before an acute heart event and incident depression, which could be precipitated by the cardiac event itself (Myers et al., 2012).

Gravely-Witte et al. (2009) conducted a study of 1489 CHD patients from Canada (mean age: 66.99±11.42, females: 28.6%), and found current or former smokers at baseline, as assessed by a self-answered questionnaire, had more depressive symptoms than non-smokers (OR: 1.04 $P<0.001$, OR: 1.02, $p<0.02$). However, the odds ratios were very close to 1, indicating no effect, questioning the value of this result. A limitation here was that this was a cross sectional study. The analysis associated with the follow up assessment could be beneficial, although this was not possible with this study (Gravely-Witte et al., 2009).

In contrast, four studies found smoking was a non-significant determinant (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Eastwood et al., 2012; Murphy et al., 2012). However, overall, the quality of the majority of these studies was poor (reported in Chapter 2) compared to other studies that found smoking to be a significant determinant. For example, there was a lower participation rate among eligible patients, and loss to follow up was higher than in the other studies, which may have influenced their results.

6.3.3.4 Physical activity status

The impact on depression of not meeting recommended physical activity levels was consistent in patients with a history of depression and those with new onset depressive symptoms. Physical inactivity (not meeting the recommended physical activity levels) at baseline was a statistically significant negative determinant of improvement following CR in both patients with a history of depression and those with new onset depressive symptoms. Patients with a history of depression were 30% less likely to reduce their depression levels following CR when they were physically inactive at baseline (OR: 0.707, 95%CI: 0.514 to 0.971); however, the effect size here was smaller in patients with new onset depressive symptoms and when baseline physical inactivity was associated with an 18% reduced likelihood of improvement in patients experiencing new onset depressive symptoms (OR: 0.822, 95%CI: 0.721 to 0.937). These findings reflect the evidence in the review chapter, which presented eight studies illustrating that physical inactivity is a significant determinant of depressive symptoms (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Ernstsen et al., 2016; Horne et al., 2013; Murphy et al., 2012; Myers et al., 2012; Pajak et al., 2012; Bonnet et al., 2005).

Ernstsen et al. (2016), a prospective Norwegian study, included 189 MI patients and investigated the association of physical activity with depression following a first MI. Post MI depressive symptoms, measured by HADS and a clinical cut off point of 8 is used in the analysis, and shows that 11% of patients had elevated depressive symptoms (HADS-D ≥ 8). In accordance with the studies referred to in the current

thesis, physical activity was found to be inversely associated with depressive symptoms. Patients who are persistently physically active were less likely to experience depressive symptoms than patients who are persistently inactive.

The results of an Australian cross sectional study also confirmed the current studies (Murphy et al., 2012). It recruited 275 patients (mean age: 59±9.1, female: 14%), admitted to hospital following MI or for PCI or GABG, and interviewed them six weeks following hospital discharge. However, the mean age of the participants was much younger, and the female percentage was much lower than in the routine clinical practice data provided by NACR; where the mean age was 67 and 29% were female (NACR, 2019). In addition, age and the female proportion in Murphy et al.'s (2012) study was also lower than in the studies included in the critical review (Chapter 2), which may influence the generalisability of the results to the wider population. The primary aim of the study was to investigate the relationship between health behaviours and depression in CVD patients. The HADS assessment tool was employed to assess participant's depressive symptoms. A HADS depression score ≥8 was used to classify patients as having elevated depressive symptoms, similar to the studies conducted in the current thesis, which found that 15.2% of the patients were residing in that level. The Active Australia Survey was used to measure patients with moderate activity and vigorous activity over the preceding two weeks based on self-reports, and referring to duration and frequency of walking. For the analysis, total physical activity in minutes per week was calculated for each patient, and was converted from 'minutes per week' to 'multiples of 10 minutes per week', as used in multivariate analysis. The study results showed that 10 minutes increased physical activity was associated with a 2% lower likelihood of having depressive symptoms (OR:0.976, p=0.010) (Murphy et al., 2012). However, this study was not inclusive of CR, despite it being an important intervention to enable secondary prevention for cardiac patients. However, the findings of the studies derived from the current thesis do show this association in CR patients,

and more specifically in populations of patients with history of depression and patients with new onset depressive symptoms.

Self-reported regular physical activity was also found to be associated with a reduced likelihood of experiencing depressive symptoms for MI patients assessed with Beck's Depression Inventory (BDI) at initial hospitalisation (Myers et al., 2012). The association of physical activity with reduced odds of experiencing depressive symptoms was also noted in studies conducted in Canada (Horne et al., 2013), France (Bonnet et al., 2005), China (Zhu et al., 2019), and Oman (Almamari, Muliira and Lazarus, 2019) among other countries (Pajak et al., 2012).

6.3.3.5 Total number of comorbidities

The total number of comorbidities was a negative determinant of improvement in both patients with a history of depression, and patients with new onset depressive symptoms. Having an increased total number of comorbidities at baseline was associated with 9% reduced odds of improvement in depression levels following CR in patients with a history of depression (OR:0.914, 95%CI: 0.854 to 0.979), and 7% lower odds of improvement in patients with new onset depressive symptoms (OR:0.932, 95%CI: 0.888 to 0.977). Overall, it can be concluded that total number of comorbidities has a similar influence on depression following CR in both patient populations. However, these results contradict two studies detailed in the critical review, which found that total number of comorbidities are viewed as a non-significant determinant (Eastwood et al., 2012; Gravely-Witte et al., 2009). In a study by Eastwood et al. (2012), the Charlson comorbidity index was used in the analysis; however, it was found to be a non-significant determinant of depressive symptoms. In Gravely-Witte et al.'s (2009) study, a broader binary variable was used, regardless of whether patients had any other comorbid condition or not. However, it was also found not to be a significant determinant. In addition, one study adjusted for comorbidities, but failed to report the results (Ernstsen et al., 2016).

6.3.3.6 Weight

With respect to weight, results were not consistent either among patients with a history of depression or those with new onset depressive symptoms. Weight was not a significant determinant of improvement in depressive symptoms following CR in patients with a history of depression (OR: 0.996, 95%CI: 0.988 to 1.004). However, it was found to be significant negative determinant of improvement in depressive symptoms following CR in patients with new onset depressive symptoms. The current thesis found, a one kilogram increase in weight was associated with 1% reduced odds of improvement in depression levels for patients with new onset depressive symptoms (OR:0.992, 95%CI: 0.989 to 0.996). These findings were partially consistent with previous studies, as reported in the review chapter. One cross sectional study, undertaken in 22 European countries found a positive association between BMI and depressive symptoms (Pajak et al., 2012). The multi-centre study included 8580 MI/PCI/CABG patients (mean age: male, 62.3 ± 9.5, female, 65.9 ± 8.9; gender/female%, 25%) assessed at least 6 months after hospitalisation following a cardiac event. However, four other studies found no significant association between BMI and depressive symptoms (Almamari, Muliira and Lazarus, 2019; Zhu et al., 2019; Stafford, Berk and Jackson, 2013; Eastwood et al., 2012). Although some other studies were adjusted for BMI, the results were not reported (Ernstsen et al., 2016; Bonnet et al., 2005).

6.3.3.7 Anxiety

The analysis found an increased HADS anxiety measurement was associated with a reduced likelihood of improvement in depression levels following CR, both in patients with a history of depression and new onset depressive symptoms. A one point score increase in HADS anxiety measurement was associated with a 12% reduced likelihood of improvement in depression levels for patients with a history of depression (OR: 0.883, 95%CI: 0.851 to 0.917). In addition, a one point score increase in HADS anxiety levels was associated with a 10% reduced likelihood of improvement in depression

levels in patients with new onset depressive symptoms (OR: 0.900, 95%CI: 0.885 to 0.915). This finding was supported in four studies that were included in the critical review, and showed a positive association between anxiety and depressive symptoms (Horne et al., 2013; Stafford, Berk and Jackson, 2013; Eastwood et al., 2012; Schrader et al., 2006).

Eastwood et al. (2012) conducted a retrospective observational study based in the USA, which recruited 622 HF patients (Mean age, 61±13; Female: 30%) to investigate the demographic, behavioural, clinical, and psychosocial factors associated with depressive symptoms in HF patients. The severity of depressive symptoms was assessed by a self-assessment questionnaire named the Patient Health Questionnaire (PHQ-9), with a cut-off point of ≥10 used to indicate the presence of depressive symptoms. The Brief Symptom Inventory (BSI) was another assessment tool employed to measure anxiety. There were 6 items in this scale, all of which were rated by patients; a score of 0 was an indicator of no stress, whereas 4 was an indicator of extreme stress. The findings from the multivariate analysis showed anxiety was a positive determinant of depressive symptoms.

Horne et al. (2013) conducted a prospective observational study based in Canada, and included 436 CABG patients. It found that post-operative stressful events were significantly associated with depressive symptoms, although the study mainly aimed to investigate the impact of physical activity on depressive symptoms. However, the nature of stressful events were not clearly described, nor were the variables used in the analysis. Furthermore, independent variables were used in the multivariable analysis, and the study results were not sufficiently or clearly reported.

One prospective Australian study of 1444 ACS/HF patients (Mean age: 62.2±12.4, Female: 32%) found that general anxiety disorder (GAD) was a significant determinant of depression, 3 months after discharge from hospital for an acute cardiac event (Stafford, Berk and Jackson, 2013). In this study, both GAD and depression were

assessed by employing the Mini International Neuropsychiatric Interview Version 5 (M.I.N.I.), which is a diagnostic structured interview, similar to the Structured Clinical Interview for DSM-IV.

6.3.3.8 Marital status

The association between marital status at baseline and improvement in patient's depression levels following CR was not consistent among patients with a history of depression and those with new onset depressive symptoms. Being single was not a significant determinant of improvement in participant's depression levels following CR in patients with a history of depression (OR: 0.916 95%CI: 0.677 to 1.240). However, single patients with new onset depressive symptoms were 24% less likely to experience improvement in their depression following CR (OR: 0.761 95%CI: 0.660 to 0.877). In general the critical review concluded that marital status was not a significant determinant in some studies (Stafford, Berk and Jackson, 2013; Eastwood et al., 2012; Murphy et al., 2012), despite being adjusted for in two studies (neither of which reported their results) (Zhu et al., 2019; Bonnet et al., 2005). Marital status was also categorised as either married or not married in one study (Stafford, Berk and Jackson, 2013), and in Eastwood et al.'s (2012) study, single, divorced, and widowed were categorised as single and the other category was married. Similarly, in the studies included in this thesis, patients who are married or in a permanent partnership were categorised as partnered, and those who are single, divorced, widowed or separated were categorised into not-partnered or single.

6.3.3.9 Other variables

To improve on the uniqueness of the study conducted in chapter 5 part 2, some comorbidities were tested in patients with new onset depressive symptoms, to investigate which might determine improvement in depressive symptoms following CR. The comorbidities of angina, diabetes, stroke, emphysema and chronic back problems were associated with a reduced likelihood of improvement after CR with 23%, 17%, 29%, 34%, and 19% respectively. IMD was also tested in chapter 5 part 2 to ascertain

whether it determined improvement in depression following CR in patients with new onset depressive symptoms. However, it was found not to be a significant determinant of depression outcome. In addition, patients with new onset depressive symptoms that had heart failure were 25% less likely to improve their depressive symptoms following CR (OR: 0.749, 95%CI: 0.610 to 0.919). Patients who receive CABG and other treatments reported 43% and 36% higher odds of having improved depressive symptoms (OR: 1.436 95%CI: 1.108 to 1.861 and OR: 1.367 95%CI 1.084 to 1.725, respectively). This was the first study providing these results for CR patients with new onset depressive symptoms.

6.3.4 Visual summary of synthesised determinants

To enable the reader to easily compare the findings from routine clinical practice data of NACR, and the findings from the critical review, and to identify any similarities and differences between them the following **table 6.2** was created, and it visually summarises this synthesis chapter. A total of four columns are presented in this table, where the first column represents the name of the determinants, and the second column displays the data source. Within the second column, NACR represents findings related to the studies in the current thesis, and represents the findings of the critical review. The third and fourth columns represent the determinants of depression outcome following CR in patients with a history of depression and patients with new onset depressive symptoms. Each row next to the NACR source shows two types of data, the first describing the effect size of that determinant and the second a coloured arrow. The arrow displays the role of the determinant, and the blue colour shows if the determinant is associated with a reduced likelihood of improvement in depression levels following CR, green colour means the determinant is associated with better improvement in depression, and red colour shows the determinants is not statistically significant.

Table 6.2: Visualisation of patient level determinants of depression

Variable	Source	Patients with a history of depression	Patients with new onset depressive symptoms
Older age	NACR		
	Critical Review	11 	
Gender (Male)	NACR	18% 	
	Critical Review	11 	
Smoking (Yes)	NACR	44% 	25% 
	Critical Review	10 	
150 min. a week physical activity (No)	NACR	30% 	18% 
	Critical Review	8 	
Higher Total Number of Comorbidities	NACR	9% 	7% 
	CRev	3 	
Weight	NACR		1% 
	Critical Review	7 	
Anxiety	NACR	12% 	10% 
	Critical review	4 	
Marital Status (Single)	NACR		24% 
	Critical Review	5 	

Key for table 6.2:

⇩ = reduced likelihood of improvement in depression; ⇧ = increased likelihood of improvement in depression; ⇔ = not significant; Critical review findings:  = proportion of studies; yellow colour represents that variable adjusted in the analysis but results not reported. NACR = findings of thesis studies using NACR data.

Turning to the critical review, the relevant rows show the total number of studies that examined the determinant, followed by a coloured doughnut chart denoting the proportion of studies that reported the determinant to have positive association with depression in blue colour, negative association with depression represented with green colour, not statistically significant with red colour, and finally yellow colour, denoting determinant adjusted in the analysis with results are not reported. The table shows only the variables reported in both NACR and critical review sources.

6.4 Limitations

There were some differences between the factors reported in the review chapter and the studies conducted in the current thesis using the audit data. The reason for this might be that in the critical review chapter, there were inconsistencies in the included studies that aimed to identify the determinants of depressive symptoms in terms of population characteristics, sample size, study designs, and statistical analyses were also varied among the different studies, and therefore, drawing definitive conclusions was not possible. In addition, there was a lack of studies specifically investigating patients' history of depression, which may explain some discrepancies in the results. A further consideration is that the studies included in the current thesis were more inclusive of the older multimorbid population and females than previous studies, which were mostly inclusive of males and a younger population with fewer comorbidities (Anderson et al., 2016; Brown et al., 2009; Witt et al., 2004).

6.5 Conclusion

This study is the first to synthesise determinants of improvement in depression following cardiac rehabilitation in patients with a history of depression and new onset depressive symptoms, using nationally representative data pertaining to CVD patients. The study also compared the synthesised findings in the current thesis to the results of previous studies included in the critical review. In addition, the study results contributed to the current literature by demonstrating the determinants of depressive symptoms among populations of patients with a history of depression and patients with new onset depressive symptoms, as well as merging evidence from routine clinical practice and previously conducted studies with different designs. The variables of smoking, physical inactivity, anxiety and a higher total number of comorbidities were statistically significant negative determinants of improvement in depressive symptoms following CR in both patients with history of depression and new onset depressive symptoms. Therefore, CR programmes might usefully target modifiable variables to benefit both populations.

Chapter 7: Conclusion

The final chapter of this thesis will summarise the key findings, their implications, their importance, and their relevance. After this a description of what these findings add to our understanding of the determinants of depression in CR patients, and the implications of these findings for clinical practice and future research is stated.

7.1 Key findings

This thesis is the first to investigate those patient characteristics associated with depressive symptoms at baseline, and determinants of depression outcome in patients with a history of depression following CR. Although few studies have investigated the determinants of depressive symptoms following a cardiac event, the current thesis is the first to investigate the patient characteristics associated with new onset post cardiac event depressive symptoms in the CR setting at baseline, or to examine the determinants of depression outcome following CR among this specific population. The results of the current thesis are:

- According to the critical review in chapter 2, there is a variation in the studies that aimed to identify determinants of depressive symptoms in CVD patients in terms of sample size, study designs, population characteristics and statistical analysis which do not allow the drawing of definitive conclusions. In addition, there are insufficient studies investigating patients with a history of depression.
- The current research in chapter 4 found that patients with a history of depression and high levels of depressive symptoms were typically younger, had increased weight, more comorbidities, greater anxiety, were physically inactive, more likely to be smokers and single than patients with low levels of depressive symptoms, at baseline CR assessment.
- Turning to the outcome of the analysis in chapter 4, the baseline characteristics of patients with a history of depression, such as having higher anxiety score, comorbidities, smoking, physical inactivity, and being male were found to be

significant determinants of reduced likelihood of improvement in HADS depression outcome following CR.

- In chapter 5 part 1, the analysis of patients with new onset depressive symptoms revealed that, at baseline CR assessment, determinants of new onset depressive symptoms were: comorbidities, high HADS anxiety score, increased weight, physical inactivity, being single etc., in the multivariate analysis.
- In chapter 5 part 2, an in depth investigation was conducted to establish the patient characteristics that determine outcomes in CR patients with new onset depressive symptoms. Based on the multiple regression findings, the baseline characteristics of patients with new onset post cardiac event depressive symptoms including comorbidities, were higher anxiety scores, physical inactivity, increased weight, and smoking. These were significant key determinants of a reduced likelihood of improvement in depression outcomes following CR.
- According to prospective survey results, there was a considerable variation among UK CR programmes in terms of the delivery of psychosocial health support; for example, in terms of the interventions being offered, external services that patients are referred to, and the health care professionals providing psychosocial support.
- According to the synthesised findings, the studies of the current thesis were that poor lifestyle choices, such as smoking and physical inactivity negatively impact depressive symptoms following CR, both in patients with a history of depression and those with new onset depressive symptoms.
- A high proportion of CR patients had elevated depressive symptoms, and this proportion was greater for patients with a history of depression than for those with new onset depressive symptoms.
- Patients with a history of depression and high levels of depressive symptoms scored five points higher on the HADS anxiety scale than patients with low

levels of depressive symptoms at baseline. This was also the case for patients with new onset acute depressive symptoms (HADS≥8) when compared to patients with new onset non-acute depressive symptoms (HADS<8). In addition, anxiety was a significant determinant of depression outcome following CR, both in patients with a history of depression and those with new onset depressive symptoms.

7.2 Strengths and Limitations

One of the main strengths of the current thesis is that it utilises a large data set based on routine clinical practice in UK CR programmes. The NACR is the largest database for CR patients in the UK (NACR, 2019). Although it is large, of high quality, intended for analysis, and implemented robust statistical techniques, the observational nature of the data might be subject to selection bias. Therefore, causal conclusions cannot be drawn. Moreover, the principal aim of the NACR data set was to monitor CR services in the UK, therefore, there might be some determinants that may have influence on depressive symptoms that are not included in the analysis because they are not being primarily collected in the data set. The data are entered manually by Caldicott Guardians to the NACR database for CR programmes; therefore, data entry error may be expected to influence the quality of the data and the results. However, in online NACR portal, there is automated data auditing in place which can improve the data quality (NACR, 2019).

The study samples were nationally representative of CR patients in the UK; however, it is important to report that not all CR programmes provide a full record of patients who complete CR. According to the NACR data set, 31% of patients do not access a follow up assessment, which might adversely influence the representativeness of the sample (NACR, 2019). Post CR assessments should be targeted by CR programmes, which is also one of the main standards included in recent BACPR guideline or referred to as a key performance indicator in the recent NACR report for the certification of CR

programmes (BACPR, 2017; NACR, 2019). One of the main recommendations in the NACR 2017 report relates to the assessment of patients who complete CR needing to be at 100% (NACR, 2017). Although this is deemed challenging in clinical practice, the recommendation continues to be of relevance. Once this is achieved by CR programmes, it will strengthen the quality of future studies. Despite the limitations, the current research was able to perform a large scale comprehensive investigation into depression in CR patients, as well as the factors determining outcomes following CR.

7.3 Implications

The findings from this research should be taken into consideration when implementing strategies to modify policies to improve outcomes for depressed CVD patients who undergo CR. There is range of clinical implications arising from the studies collated for the current thesis including:

- Patients with a history of depression who smoke, engage in little physical activity, have a higher total number of comorbidities, had a higher HADS anxiety score, and are male are at increased risk of remaining with high levels of depression and they are less likely to improve their depression levels. High risk patients might be more effectively identified if these factors were to be taken more widely into account. This might ultimately enable their further screening, and eventually, individualised intervention or treatment.
- The prevalence of high levels of depressive symptoms (HADS≥8) in patients attending CR was higher in patients with a history of depression than the general CVD population, whereas prevalence of new onset depressive symptoms was similar to that of the general CVD population. This might imply the necessity of routine assessment of patients with a history of depression, involving prioritising their CR assessments.
- The current research confirms that assessment of depressive symptoms at the start of CR, and following CR in patients with a history of depression and new

onset depressive symptoms is important to identify higher risk patients. Both patients with a history of depression, and those with new onset depressive symptoms require careful monitoring in core CR, considering their patient characteristics.

- Assessment of depressive symptoms at the end of a CR programme also helps identify patients at high risk of not improving their depression levels, as they may require further attention, such as a referral to psychosocial support services and long term monitoring.
- Furthermore, after CR, general practitioners and cardiologists need to be acknowledged of the higher risk status of these patients to provide long term monitoring of their conditions.
- Provision of more time devoted to depressed patients in core CR, and targeting identified risk factors in the current research is essential if the aim is to improve the depressive symptoms of patients with a history of depression and new onset depression. Overall, the findings of the current thesis indicate that patients with a history of depression and those with new onset depressive symptoms should be monitored carefully during core CR.
- Additionally, CR programmes should collaborate with patients' general practitioners, also during core CR, to inform them about the high risk status of these patients, so as to be able to offer them the required treatment when the capacity of CR programme is inadequate.
- Patients with a history of depression and new onset depressive symptoms, and those previously mentioned with characteristics associated with poor CR outcome (e.g. smoking, physical inactivity, higher total number of comorbidities), need to be identified by CR practitioners to ensure the capture of the most at risk patients. These patients require targeted and tailored CR interventions to benefit the most from CR.
- The current research has demonstrated that anxiety and depression are interrelated and co-exist. In addition, anxiety was found to be a significant

determinant of depression outcome in both patients with a history of depression and those with new onset depressive symptoms. Therefore, CR patients who are identified with depression should also be screened for anxiety, in line with the recommendations of the American Heart Association (AHA) (Lichtman et al., 2014).

- CR is a multicomponent comprehensive programme with specific guidelines, and key strategies to provide psychosocial support to CR patients and improve their psychosocial health are included in those guidelines (BACPR, 2017; SIGN, 2017). In addition, the guidelines recommend that the psychosocial needs of CR patients should be met. However, it is unclear how to successfully identify the subtypes of patients with depression and treat them. Therefore, future guidelines need to consider current research undertaken in this thesis and support the identification of patients with a history of depression and new onset depressive symptoms.

7.4 Recommendations

The recommendations derived from the results of the current thesis are below:

- It is essential to manage the depression levels of patients with a history of depression and new onset depressive symptoms. It is also necessary to reassess the plans for CR intervention for patients whose depressive symptoms are less likely to attenuate.
- In addition to CR programmes, patients with a history of depression or new onset depressive symptoms might be referred to outer services, such as general practitioners or IAPT services if the programme's capacity is not enough to deal with their condition (e.g. if they do not have any accredited staff to provide psychosocial support). Having diverse opportunities to capture patients with depression might enable patients to be identified and receive

appropriate interventions or treatments to improve their depression levels, augmenting their process of recovery.

- As CR is a comprehensive intervention, patients with a history of depression and new onset depressive symptoms represent potential areas of improvement for CR. The role of CR services should be strengthened to address depressed CVD patients via routine assessment of depressive symptoms, tailoring interventions within the programme, or referring patients to external services to provide optimal support when programmes lack capacity.
- CR programmes needs to be tailored around comorbidities, physical activity status, weight management, and smoking cessation in patients with depressive symptoms, as well as considering other the characteristics that inform depression outcomes.
- To be able to reduce inequalities among services and improve the psychosocial support delivered to patients, the recruitment of more psychologists into CR programmes can be beneficial, especially for services that do not provide any form of psychosocial support, which is an important area to look to improve when enough resources are available to invest by policymakers. Future policies might need to expand around improving the psychosocial support delivered by CR services.

7.5 Future research

Despite the studies in the current thesis contributing to the recent literature, there remain some gaps to be addressed by future research that is discussed below.

- In previous studies, CR programmes were not able to differentiate between patients with a history of depression and those with new onset depressive symptoms after their cardiac event. The findings of the current thesis need to be implemented in CR programmes, and future research needs to focus on interventions such as smoking cessation, weight management, promotion of

physical activity and the management of comorbidities to determine whether they contribute to improvement in depressive symptoms in CR patients. Furthermore, whether reduction in depression levels is associated with mortality and cardiac morbidity needs to be better explored in well-designed studies.

- Future CR studies should also take a more holistic approach, to improve both physical and psychosocial health in CR patients. In addition, studies should investigate psychosocial interventions targeting improvements in depression outcomes, specifically in patients with a history of depression and those with new onset depressive symptoms. This knowledge could enable the development of alternative interventions that fit individuals with a history of depression and new onset depressive symptoms. Identifying and treating patients with a history of depression and new onset depressive symptoms is an important goal for CR practice.
- As there are few psychologists engaged on current UK CR programmes, whether or not the inclusion of more psychologists on CR programmes influences depression outcomes can be studied in future research.

Appendices

Appendix - 1: Operational definitions

Cardiovascular disease (CVD):	CVD will be used as a general term for describing cardiac patients. However, while reporting some papers, the authors' choice of definition will be respected and used same as in the original paper.
Comorbidity depression:	The term "comorbid depression" will be used for patients with a history of depression prior to heart event. Comorbid depression is identified by case note review or asked in the NACR data with the question of "Have you ever been told by a doctor that you have definitely had or diagnosed with depression".
Depression:	The term "depression" will be used for whether patients presented depression symptoms before and after CR which has been measured by hospital anxiety and depression (HADS) measurement.

Appendix - 2

Search strategy for critical review in chapter 2

MEDLINE

Date searched: 22/12/2017

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

Search Strategy:

1	exp Myocardial Ischemia/ (440857)
2	exp Coronary Artery Bypass/ (54346)
3	((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (44985)
4	CORONARY.ti,ab. (363394)
5	exp Coronary Disease/ (225119)
6	Coronary disease*.tw. (14147)
7	exp Myocardial Revascularization/ (94647)
8	exp Myocardial Infarction/ (179277)
9	(HEART adj4 INFARCT$5).tw. (11210)
10	exp Cardiovascular diseases/ (2375565)
11	exp Heart diseases/ (1130910)
12	(cardiovascular adj4 (disorder*1 or disease*1)).tw. (149535)
13	(heart adj4 (disorder*1 or disease*1)).ti,ab. (165818)
14	(HEART adj4 INFARCT$5).tw. (11210)
15	exp Heart Failure/ (117472)
16	(HEART adj6 Failure).tw. (142089)
17	(Heart adj4 disease$2).tw. (163371)
18	MYOCARD$5.tw. (355856)

19 CARDIAC$2.tw. (534800)
20 CABG.tw. (15544)
21 (STENT$4 and HEART).tw. (4596)
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (2741998)
23 Depression/ (108691)
24 Depress$.ti,ab. (387739)
25 exp Depressive Disorder/ (106330)
26 23 or 24 or 25 (430876)
27 exp Exercise Therapy/ (45904)
28 rehabilitat*.tw. (130819)
29 (physical* adj5 (fit* or train* or therap* or activit*)).tw. (122067)
30 exp Exercise/ (178820)
31 (train* adj5 (strength* or aerobic* or exercise*)).tw. (30704)
32 ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (22173)
33 exp Rehabilitation/ (290407)
34 exp Cardiac Rehabilitation/ (1593)
35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (601197)
36 Predict*.tw. (1210762)
37 Determin*.tw. (2988099)
38 Characteristic*.tw. (1098484)
39 Social determinants of health/ (1527)
40 Risk factors/ (786774)

41 Risk factor*.tw. (469879)
42 risk/ (123705)
43 risk$.tw. (1771268)
44 related.tw. (1993170)
45 relationship.tw. (844210)
46 rates.tw. (869865)
47 difference$.tw. (2033933)
48 associated factors.tw. (12292)
49 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (8954881)
50 22 and 26 and 35 and 49 (4006)
****

PsycINFO

22/12/2017

Database: PsycINFO <1806 to December Week 2 2017>

Search Strategy:

1 ((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (1117)
2 CORONARY.ti,ab. (9380)
3 Coronary disease*.tw. (417)
4 (HEART adj4 INFARCT$5).tw. (319)
5 (cardiovascular adj4 (disorder*1 or disease*1)).tw. (11373)
6 (heart adj4 (disorder*1 or disease*1)).ti,ab. (9652)
7 (HEART adj4 INFARCT$5).tw. (319)

8	(HEART adj6 Failure).tw. (3420)
9	(Heart adj4 disease$2).tw. (9941)
10	MYOCARD$5.tw. (5431)
11	CARDIAC$2.tw. (16538)
12	CABG.tw. (414)
13	(STENT$4 and HEART).tw. (32)
14	Depression/ (24056)
15	Depress$.ti,ab. (265848)
16	rehabilitat*.tw. (56354)
17	(physical* adj5 (fit* or train* or therap* or activit*)).tw. (41134)
18	exp Exercise/ (23182)
19	(train* adj5 (strength* or aerobic* or exercise*)).tw. (5151)
20	((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (6129)
21	exp Rehabilitation/ (69575)
22	Predict*.tw. (396846)
23	Determin*.tw. (412149)
24	Characteristic*.tw. (292365)
25	Risk factors/ (68813)
26	Risk factor*.tw. (91142)
27	risk$.tw. (335652)
28	related.tw. (613919)
29	relationship.tw. (463033)
30	rates.tw. (138732)

31 difference$.tw. (610100)
32 associated factors.tw. (2383)
33 exp cardiovascular disorders/ (56278)
34 exp Myocardial Infarctions/ (2726)
35 exp Major Depression/ (115865)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 33 or 34 (78819)
37 14 or 15 or 35 (272263)
38 16 or 17 or 18 or 19 or 20 or 21 (150597)
39 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (2148019)
40 36 and 37 and 38 and 39 (1084)
41 **********

EMBASE

22/12/2017

Database: Embase <1974 to 2017 Week 51>

Search Strategy:

1 ((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (60285)
2 CORONARY.ti,ab. (497145)
3 Coronary disease*.tw. (18848)
4 (HEART adj4 INFARCT$5).tw. (16752)
5 (cardiovascular adj4 (disorder*1 or disease*1)).tw. (222112)
6 (heart adj4 (disorder*1 or disease*1)).ti,ab. (225162)
7 (HEART adj4 INFARCT$5).tw. (16752)

8	(HEART adj6 Failure).tw. (228364)
9	(Heart adj4 disease$2).tw. (221903)
10	MYOCARD$5.tw. (474153)
11	CARDIAC$2.tw. (746248)
12	CABG.tw. (27572)
13	(STENT$4 and HEART).tw. (10151)
14	Depression/ (318705)
15	Depress$.ti,ab. (526017)
16	rehabilitat*.tw. (197515)
17	(physical* adj5 (fit* or train* or therap* or activit*)).tw. (176143)
18	exp Exercise/ (290658)
19	(train* adj5 (strength* or aerobic* or exercise*)).tw. (42079)
20	((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (33312)
21	exp Rehabilitation/ (337589)
22	Predict*.tw. (1713253)
23	Determin*.tw. (3916957)
24	Characteristic*.tw. (1503046)
25	Risk factors/ (493779)
26	Risk factor*.tw. (699246)
27	risk$.tw. (2586446)
28	related.tw. (2648145)
29	relationship.tw. (1100620)
30	rates.tw. (1197896)

31 difference$.tw. (2772976)
32 associated factors.tw. (17805)
33 exp Major Depression/ (53192)
34 exp cardiovascular disease/ (3711772)
35 exp heart infarction/ (343693)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 34 or 35 (4084923)
37 14 or 15 or 33 (636207)
38 16 or 17 or 18 or 19 or 20 or 21 (831554)
39 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (11747405)
40 36 and 37 and 38 and 39 (8926)
41 **********

Cochrane Library

Search Name:

Date Run: 22/12/17 19:43:49.927

Description: Cochrane Library

ID Search Hits

(CORONARY or Coronary disease* or MYOCARD* or CARDIAC* or CABG or cardiovascular disease or myocardial infarction) and (depress* or major depression or depressive) and (rehabilitat* or exercise) and (Predict* or Determin* or Characteristic*or Risk factor* or risk* or relationship or associated factors) in Title Abstract Keyword - (Word variations have been searched) 611

CINAHL plus (EBSCO)

Friday, December 22, 2017 4:31:06 PM

S31 S13 AND S17 AND S22 AND S30 (1,268)

S30 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 (947,589)
S29 AB associated factors (44,645)
S28 AB relationship (191,940)
S27 AB risk* (395,686)
S26 AB Risk factor* (109,823)
S25 AB Characteristic* (152,789)
S24 AB Determin* (337,056)
S23 AB Predict* (201,048)
S22 S18 OR S19 OR S20 OR S21 (228,980)
S21 AB Physical* (147,474)
S20 AB Cardiac Rehabilitation (2,130)
S19 AB Exercise* (64,327)
S18 AB Rehabilitat* (51,760)
S17 S14 OR S15 OR S16 (83,252)
S16 AB Depress* (82,153)
S15 Depressive Disorder (8,512)
S14 AB Depression (67,906)
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 (148,481)
S12 AB CABG (2,597)
S11 AB CARDIAC* (64,063)
S10 AB MYOCARD* (34,511)
S9 AB Heart Failure (23,979)

S8	AB Heart diseases (24,497)
S7	AB Cardiovascular disease (29,693)
S6	AB Myocardial Infarction (22,682)
S5	AB Myocardial Revascularization (1,446)
S4	AB Coronary disease* (20,426)
S3	AB CORONARY (42,821)
S2	AB Coronary Artery Bypass (5,101)
S1	AB Myocardial Ischemia (2,623)

Appendix - 3

Updated search results

MEDLINE

27/02/2020

Database: Ovid MEDLINE(R) <1946 to February 27, 2020>

Search Strategy:

1	exp Myocardial Ischemia/ (424184)
2	exp Coronary Artery Bypass/ (52257)
3	((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (42607)
4	CORONARY.ti,ab. (352081)
5	exp Coronary Disease/ (214995)
6	Coronary disease*.tw. (13416)
7	exp Myocardial Revascularization/ (91025)
8	exp Myocardial Infarction/ (172777)
9	(HEART adj4 INFARCT$5).tw. (11051)
10	exp Cardiovascular diseases/ (2345457)
11	exp Heart diseases/ (1109135)
12	(cardiovascular adj4 (disorder*1 or disease*1)).tw. (156152)
13	(heart adj4 (disorder*1 or disease*1)).ti,ab. (161652)
14	(HEART adj4 INFARCT$5).tw. (11051)
15	exp Heart Failure/ (118630)
16	(HEART adj6 Failure).tw. (143838)
17	(Heart adj4 disease$2).tw. (159207)
18	MYOCARD$5.tw. (342658)

19 CARDIAC$2.tw. (527882)
20 CABG.tw. (15440)
21 (STENT$4 and HEART).tw. (4622)
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (2707477)
23 Depression/ (115162)
24 Depress$.ti,ab. (390851)
25 exp Depressive Disorder/ (106974)
26 23 or 24 or 25 (433147)
27 exp Exercise Therapy/ (49161)
28 rehabilitat*.tw. (137981)
29 (physical* adj5 (fit* or train* or therap* or activit*)).tw. (129371)
30 exp Exercise/ (189555)
31 (train* adj5 (strength* or aerobic* or exercise*)).tw. (31513)
32 ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (23393)
33 exp Rehabilitation/ (298633)
34 exp Cardiac Rehabilitation/ (2213)
35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (621027)
36 Predict*.tw. (1262521)
37 Determin*.tw. (2990510)
38 Characteristic*.tw. (1129726)
39 Social determinants of health/ (2724)
40 Risk factors/ (805296)

41 Risk factor*.tw. (489273)
42 risk/ (120971)
43 risk$.tw. (1851946)
44 related.tw. (2055235)
45 relationship.tw. (855435)
46 rates.tw. (889416)
47 difference$.tw. (2059761)
48 associated factors.tw. (14919)
49 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (9093476)
50 22 and 26 and 35 and 49 (4174)
51 2018$.ed. (900095)
52 2019$.ed. (971109)
53 2020$.ed. (153497)
54 201712$.ed. (74313)
55 51 or 52 or 53 or 54 (2099014)
56 50 and 55 (629)
****

PsycINFO

27/02/2020

Database: PsycINFO <1806 to February Week 4 2020>

Search Strategy:

1 ((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (1195)

2	CORONARY.ti,ab. (9935)
3	Coronary disease*.tw. (435)
4	(HEART adj4 INFARCT$5).tw. (346)
5	(cardiovascular adj4 (disorder*1 or disease*1)).tw. (12842)
6	(heart adj4 (disorder*1 or disease*1)).ti,ab. (10411)
7	(HEART adj4 INFARCT$5).tw. (346)
8	(HEART adj6 Failure).tw. (3861)
9	(Heart adj4 disease$2).tw. (10730)
10	MYOCARD$5.tw. (5773)
11	CARDIAC$2.tw. (17819)
12	CABG.tw. (435)
13	(STENT$4 and HEART).tw. (36)
14	Depression/ (25359)
15	Depress$.ti,ab. (294825)
16	rehabilitat*.tw. (61637)
17	(physical* adj5 (fit* or train* or therap* or activit*)).tw. (47581)
18	exp Exercise/ (25779)
19	(train* adj5 (strength* or aerobic* or exercise*)).tw. (5847)
20	((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (7029)
21	exp Rehabilitation/ (47222)
22	Predict*.tw. (445761)
23	Determin*.tw. (451148)
24	Characteristic*.tw. (318453)

25 Risk factors/ (77976)
26 Risk factor*.tw. (103526)
27 risk$.tw. (383374)
28 related.tw. (686461)
29 relationship.tw. (510918)
30 rates.tw. (155028)
31 difference$.tw. (667033)
32 associated factors.tw. (2975)
33 exp cardiovascular disorders/ (61017)
34 exp Myocardial Infarctions/ (2849)
35 exp Major Depression/ (128080)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 33 or 34 (85754)
37 14 or 15 or 35 (301736)
38 16 or 17 or 18 or 19 or 20 or 21 (142402)
39 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (2363433)
40 36 and 37 and 38 and 39 (1246)
41 2020*.up. (25690)
42 2019*.up. (155398)
43 2018*.up. (155121)
44 201712*.up. (18831)
45 41 or 42 or 43 or 44 (355040)
46 40 and 45 (164)

****

EMBASE

27/02/2020

Database: Embase <1974 to 2020 February 27>

Search Strategy:

1 ((ISCHAEMI$2 or ISCHEMI$2) adj4 HEART).tw. (66326)
2 CORONARY.ti,ab. (545241)
3 Coronary disease*.tw. (19684)
4 (HEART adj4 INFARCT$5).tw. (19047)
5 (cardiovascular adj4 (disorder*1 or disease*1)).tw. (265220)
6 (heart adj4 (disorder*1 or disease*1)).ti,ab. (248850)
7 (HEART adj4 INFARCT$5).tw. (19047)
8 (HEART adj6 Failure).tw. (272227)
9 (Heart adj4 disease$2).tw. (245218)
10 MYOCARD$5.tw. (512986)
11 CARDIAC$2.tw. (836826)
12 CABG.tw. (31676)
13 (STENT$4 and HEART).tw. (12125)
14 Depression/ (355082)
15 Depress$.ti,ab. (595563)
16 rehabilitat*.tw. (225604)
17 (physical* adj5 (fit* or train* or therap* or activit*)).tw. (212539)
18 exp Exercise/ (329684)

19 (train* adj5 (strength* or aerobic* or exercise*)).tw. (50465)
20 ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw. (40788)
21 exp Rehabilitation/ (378808)
22 Predict*.tw. (2058512)
23 Determin*.tw. (4391246)
24 Characteristic*.tw. (1761086)
25 Risk factors/ (618472)
26 Risk factor*.tw. (840437)
27 risk$.tw. (3116665)
28 related.tw. (3106466)
29 relationship.tw. (1254238)
30 rates.tw. (1411156)
31 difference$.tw. (3220653)
32 associated factors.tw. (24181)
33 exp Major Depression/ (62289)
34 exp cardiovascular disease/ (3957852)
35 exp heart infarction/ (369376)
36 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 34 or 35 (4363508)
37 14 or 15 or 33 (712872)
38 16 or 17 or 18 or 19 or 20 or 21 (944675)
39 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (13497796)
40 36 and 37 and 38 and 39 (10676)

41	2018$.ew. (1669452)
42	2019$.ew. (2710237)
43	2020$.ew. (628925)
44	41 or 42 or 43 (5008614)
45	40 and 44 (2450)
**********	

Cochrane Library

Date Run: 27/Feb/2020

Description: Cochrane Library

ID Search Hits

(CORONARY or Coronary disease* or MYOCARD* or CARDIAC* or CABG or cardiovascular disease or myocardial infarction) and (depress* or major depression or depressive) and (rehabilitat* or exercise) and (Predict* or Determin* or Characteristic*or Risk factor* or risk* or relationship or associated factors) in Title Abstract Keyword - (Word variations have been searched) 1013

CINAHL plus (EBSCO)

Friday, February 28, 2020 3:59:49 PM

S37	S31 AND S36 (337)
S36	S32 OR S33 OR S34 OR S35 (991,512)
S35	EM 201712* (32,924)
S34	EM 2018* (549,305)
S33	EM 2019* (349,870)
S32	EM 2020* (59,413)
S31	S13 AND S17 AND S22 AND S30 (1,641)

S30 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 (1,296,050)
S29 AB associated factors (63,952)
S28 AB relationship (259,551)
S27 AB risk* (547,676)
S26 AB Risk factor* (150,563)
S25 AB Characteristic* (213,392)
S24 AB Determin* (452,396)
S23 AB Predict* (277,509)
S22 S18 OR S19 OR S20 OR S21 (301,293)
S21 AB Physical* (196,868)
S20 AB Cardiac Rehabilitation (2,652)
S19 AB Exercise* (83,171)
S18 AB Rehabilitat* (65,517)
S17 S14 OR S15 OR S16 (113,273)
S16 AB Depress* (112,029)
S15 Depressive Disorder (11,230)
S14 AB Depression (92,472)
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 (199,810)
S12 AB CABG (3,402)
S11 AB CARDIAC* (87,317)
S10 AB MYOCARD* (46,602)
S9 AB Heart Failure (32,762)

S8	AB Heart diseases (31,359)
S7	AB Cardiovascular disease (40,873)
S6	AB Myocardial Infarction (28,945)
S5	AB Myocardial Revascularization (1,968)
S4	AB Coronary disease* (26,558)
S3	AB CORONARY (56,810)
S2	AB Coronary Artery Bypass (6,751)
S1	AB Myocardial Ischemia (3,560)

Appendix - 4

National Audit of Cardiac Rehabilitation Questionnaire

The National Database for Cardiac Rehabilitation

QUESTIONNAIRE MASTERS
Assessment 1

CONTENTS

THE QUESTIONNAIRES AND THE NATIONAL AUDIT OF CARDIAC REHABILITATION

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

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

WHAT HAPPENS TO THE INFORMATION?

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

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

WHO SEES MY INFORMATION?

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

DO I HAVE TO TAKE PART

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

QUESTIONS?

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

THANK YOU FOR YOUR HELP

ABOUT YOU

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

Date: .....

Gender (please tick)

Male	☐1	Female	☐2

Marital Status (please tick)

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

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

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

2

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 cilexetil (*Amias*)
irbesartan (*Aprovel*)
olmesartan (*Olmetec*)
cilazapril (*Vascase*)
fosinopril (*Staril*)
lisinopril (*Carace, Zestril*)
perindopril (*Coversyl Plus*)
ramipril (*Tritace*)
valsartan (*Diovan*)
eprosartan (*Teveten*)
losartan (*Cozaar*)
telmisartan (*Amias*)

3. Beta Blocker No ☐ Yes ☐

Examples include:

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

4. Cholesterol pills (Statins) No ☐ Yes ☐

Examples include:

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

5. Omega 3 No ☐ Yes ☐

Examples include:

omacor

SMOKING

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

Weight (kg) and Height (m):

Weight ☐ kg or ☐ st ☐ lbs

Height ☐ m or ☐ ft ☐ inches

Waist Circumference ☐ cm or ☐ inches

5

HAD Scale

Name: Date:

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

Tick only one box in each section

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Do not write below this line

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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

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

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 - 5

Psychosocial Health Online Survey

Psychosocial Health in CR

*1. Please give your contact/programme details

Primary Contact Name:

Programme Name:

City/Town:

Postcode:

Primary Contact Email Address:

*2. Does your CR programme offer support for patients with their psychosocial health?

Yes, referred internally

Yes, referred out externally

Both internally and referred out

No

Referred internally within the programme

3. How does the patient receive psychosocial support within your programme?

One to one sessions

Group sessions

Mixture of one to one and group sessions

Other

4. Who delivers the psychosocial support within your programme? (you can select more than one)

CR team (eg. Nurse of OT)

Qualified Clinical Psychologist

Health Psychologist

Other (please specify)

5. Which health professional prescribes the psychosocial support medication within your programme? (you can select more than one)

CR team (eg. Nurse or OT prescribers)

Qualified Clinical Psychologist

GP

Other (please specify)

6. Which interventions are offered for psychosocial support within your programme? (you can select more than one)

Behavioural therapies (eg. CBT or behavioural activation)

Anxiety/Stress Management (eg. Relaxation Therapy)

Other (please specify)

Referred out externally

3. What external services are the patients referred to? (you can select more than one)

GP appointment

Psychologist

IAPT (Improving Access to Psychological Therapies)

Other (please specify)

4. What is the patient's referral based on?

Hospital Anxiety and Depression Scale (HADS)

General Anxiety Disorder Assessment and Patient Health Questionnaire (GAD7/PHQ9)

Beck’s Depression Inventory

Other

Yes, both internally and referred out

3. How does the patient receive psychosocial support within your programme?

One to one sessions

Group sessions

Mixture of one to one and group sessions

Other

4. Who delivers the psychosocial support within your programme? (you can select more than one)

CR team (eg. Nurse of OT)

Qualified Clinical Psychologist

Health Psychologist

Other (please specify)

5. Which health professional prescribes the psychosocial support medication within your programme? (you can select more than one)

CR team (eg. Nurse or OT prescribers)

Qualified Clinical Psychologist

GP

Other (please specify)

6. Which interventions are offered for psychosocial support within your programme? (you can select more than one)

Behavioural therapies (eg. CBT or behavioural activation)

Anxiety / Stress Management (eg. Relaxation Therapy)

Other (please specify)

7. What external services are the patients referred to? (you can select more than one)

GP appointment

Psychologist

IAPT (Improving Access to Psychological Therapies)

Other (please specify)

8. What is the patient's referral based on?

Hospital Anxiety and Depression Scale (HADS)

General Anxiety Disorder Assessment and Patient Health Questionnaire (GAD7/PHQ9)

Beck’s Depression Inventory

Other

9. What would inform the decision whether a patient receives the CR programme psychosocial intervention or is referred out? (you can select more than one)

Programme availability

Patient preference

Not having enough funding

Severity of patient's condition (eg. clinically anxious or depressed)

Other (please specify)

NO

3. Please explain the reasons for not offering support for psychosocial health. (you can select more than one)

Funding constraints

No psychologist available

Provided in other services

Other (please specify)

Appendix - 6

Published Papers

Paper 1

Sever et al. BMC Cardiovascular Disorders (2018) 18:230
https://doi.org/10.1186/s12872-018-0974-2

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Factors associated with acute depressive symptoms in patients with comorbid depression attending cardiac rehabilitation

Serdar Sever*, Su Golder and Patrick Doherty

Abstract

Background: The literature suggests that comorbid depression, defined in this paper as a history of depression prior to a cardiovascular event, has an impact on later onset depression as well as constituting increased risk of mortality and adverse cardiac events. However, which factors are associated with depression, specifically in patients with comorbid depression, is unclear. Therefore, this paper investigates the factors associated with depression in patients with comorbid depression attending cardiac rehabilitation (CR).

Methods: This observational study used routinely collected data from the British Heart Foundation National Audit of Cardiac Rehabilitation for the time period between April 2012 and March 2017. CR participants with comorbid depression were selected as the study population. An independent t-test and chi-square test were used to compare the association between acute depression symptoms and baseline characteristics in this population.

Results: A total of 2715 CR patients with comorbid depression were analysed. Characteristics associated with acute depressive symptoms in patients with comorbid depression were found to be: young age (MD: 2.71, 95% CI 1.91, 3.50), increased number of comorbidities (MD: -0.50, 95% CI -0.66, – 0.34), increased weight (MD: -1.94, 95% CI -3.35, – 0.52), high BMI (MD: -1.94, 95% CI -3.35, – 0.52), HADS anxiety (MD: -5.17, 95% CI -5.47, – 4.87), comorbid anxiety (52.4%, $p < 0.001$), physical inactivity (150 min moderate physical activity a week and 75 min vigorous exercise a week; 27.5%, $p < 0.001$; 5.6%, $p < 0.001$ respectively), smoking (12.7%, $p < 0.001$), and being less likely to be partnered (63.6%, $p < 0.001$).

Conclusion: The study demonstrated the association between a variety of clinical and socio-demographic factors and depression. The findings of the research indicated that, at CR baseline assessment, caution must be taken with patients with comorbid depression, specifically those with higher level depressive symptoms at the start of rehabilitation. Furthermore, their multi-comorbid condition must also be taken into account. Patients with higher depression symptoms and comorbid depression scored five points higher on the HADS anxiety scale in comparison to patients with lower level depression symptoms at the start of CR, which demonstrated that anxiety and depression are interrelated and present together.

Keywords: Cardiovascular disease, Cardiac rehabilitation, Depression, Depressive symptoms, History of depression, Comorbid depression, Observational study

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Open access Cardiac risk factors and prevention

openheart

Determinants of depression in patients with comorbid depression following cardiac rehabilitation

Serdar Sever, Alexander Stephen Harrison, Su Golder, Patrick Doherty

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ABSTRACT

Background A prior history of depression, at the point patients start cardiac rehabilitation (CR), is associated with poor outcomes; however, little is known about which factors play a part in determining the extent of benefit following CR. Therefore, we aim to identify and evaluate determinants of CR depression outcomes in patients with comorbid depression.

Methods An observational study of routine practice using the British Heart Foundation National Audit of Cardiac Rehabilitation data between April 2012 and March 2017. Baseline characteristics were examined with independent samples t-test and χ^2 test. A binary logistic regression was used to predict change in depression outcome following CR.

Results The analysis included 2715 CR participants with depression history. The determinants of Hospital Anxiety and Depression Scale (HADS) depression measurement post-CR were higher total number of comorbidities (OR 0.914, 95% CI 0.854 to 0.979), a higher HADS anxiety score (OR 0.883, 95% CI 0.851 to 0.917), physical inactivity (OR 0.707, 95% CI 0.514 to 0.971), not-smoking at baseline (OR 1.774, 95% CI 1.086 to 2.898) and male gender (OR 0.721, 95% CI 0.523 to 0.992).

Conclusion Baseline characteristics of patients with comorbid depression such as higher anxiety, higher total number of comorbidities, smoking, physical inactivity and male gender were predictors of their depression levels following CR. CR programmes need to be aware of comorbid depression and these related patient characteristics associated with better CR outcomes.

Key questions

What is already known about this subject?

- A prior history of depression is associated with poor cardiac rehabilitation outcomes; however, little is known about which factors play a part in determining the extent of benefit after cardiac rehabilitation in patients with history of depression.

What does this study add?

- This study is the first to identify and evaluate the factors that determine cardiac rehabilitation depression outcomes in patients with prior history of depression and inform future cardiac rehabilitation practice.

How might this impact on clinical practice?

- Cardiac rehabilitation programmes need to be aware of patients with history of depression and their modifiable baseline patient characteristics such as anxiety, smoking and physical inactivity associated with outcomes to ensure patients with history of depression gain the most from CR programmes and improve their depression levels after cardiac rehabilitation.

INTRODUCTION

Cardiovascular disease (CVD) constitutes the highest mortality rate among all causes of death and is responsible for 17.9 million deaths around the world in 2016[1] and approximately 152 500 deaths in the UK in 2016.[2] Additionally, 83.5 million people in European Society of Cardiology member countries continue to live with CVD.[3] Due to increased survival rates in CVD and an ageing population, there has been an increase in the number of comorbidities present with CVD which further complicates the management of a patient's condition and service delivery options.[4] Depression is reported to be a prevalent comorbidity in cardiac patients; the prevalence of depression ranges from 15%–20% to nearly 50% depending on the assessment measurement ranging from structured interviews applied for clinical diagnosis to self-answered survey questions, respectively.[5] Furthermore, several systematic reviews have shown that depression is an independent risk factor for cardiac mortality[6] as well as all-cause mortality.[7 8] In addition, the evidence suggests that when depression and CVD present together, they have a significant influence on both medical costs and service delivery.[9]

Cardiac rehabilitation (CR) is a multicomponent intervention that incorporates secondary prevention for CVD.[10 11] Recent systematic reviews have shown that CR is an effective intervention[12 13] and reduces depressive symptoms.[14] Two cohort studies have also shown the impact of CR on reducing

Paper 3

Sever et al. BMC Cardiovascular Disorders (2019) 19:256
https://doi.org/10.1186/s12872-019-1245-6

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

To what extent is multi-morbidity associated with new onset depression in patients attending cardiac rehabilitation?

Serdar Sever[1*], Patrick Doherty[2], Alexander Stephen Harrison[2] and Su Golder[2]

Abstract

Background: Depression is associated with increased mortality and poor prognosis in patients with cardiovascular disease (CVD). However, little is known about the patient characteristics associated with new onset post heart event depressive symptoms, specifically medical comorbidities, among cardiac rehabilitation (CR) participants. Therefore, this paper examines the comorbidity profile and characteristics associated with new onset depressive symptoms in patients attending CR.

Methods: An observational study using the routine practice data of British Heart Foundation National Audit of Cardiac Rehabilitation (NACR) from the last six years between April 2012 and March 2018. Patients with new onset post heart event depression and no previous documented history of depression were selected as the study population. An independent samples t-test and chi square tests were used to compare the association between new onset depressive symptoms and patient variables including demographics, clinical measures and comorbidities. A binary logistic regression was conducted to investigate the predictors of new onset depressive symptoms employing log-likelihood ratio statistic.

Results: The analyses included 109,055 CR patients with new onset depression measured by Hospital Anxiety and Depression Scale (HADS). At baseline assessment, comorbidity measures associated with new onset depressive symptoms were increased total number of comorbidities and a range of comorbidities - including diabetes, angina, arthritis, chronic back problems, asthma, stroke, anxiety, rheumatism, claudication, osteoporosis, chronic bronchitis and emphysema. After multivariate adjustments were done, at the start of CR, the significant predictors of new onset depressive symptoms were physical inactivity, high HADS anxiety score measurement, increased weight, total number of comorbidities, diabetes, stroke, chronic back problems, being from areas with higher levels of social deprivation, being single, and male.

Conclusion: The research findings establish new insights into the association between patient demographic and clinical variables across a range of comorbidities in patients with new onset post heart event depressive symptoms. At the start of CR, patients with new onset depressive symptoms need to be assessed skilfully as they tend to have a complex multi-morbid presentation linked to psychosocial risk factors known to hinder CR engagement.

Keywords: Cardiovascular disease, Cardiac rehabilitation, Depression, New onset depressive symptoms, Comorbidities, Observational study

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Abbreviations

AHA	American Heart Association
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
BHF	British Heart Foundation
BDI	Beck Depression Inventory
CABG	Coronary Artery Bypass Graft (Surgery)
CHD	Coronary Heart Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
CVD	Cardiovascular Disease
HADS	Hospital Anxiety and Depression Scale
ESC	European Society of Cardiology
HF	Heart Failure
ICD-10	International Classification of Diseases
IMD	Indices of Multiple Deprivation
MI	Myocardial Infarction
NACR	National Audit of Cardiac Rehabilitation
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PHQ-9	Patient Health Questionnaire
RCT	Randomised Controlled Trial
SIGN	Scottish Intercollegiate Guidelines Network
WHO	Word Health Organisation

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