Psychological and biological determinants of emotional adaptation and recovery after cardiac surgery

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I, Lydia Poole, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in this thesis.

Signature:…… Date:…….

Abstract

How and why depression confers greater risk of impaired adaptation following coronary artery bypass graft (CABG) surgery is not well understood. This PhD aimed to address these issues by: developing and piloting a longitudinal study (the ARCS study) in order to track the recovery of patients undergoing CABG surgery; and conducting an extended version of the ARCS study on which to test the association between pre-operative depression and post-operative recovery and the underlying social-behavioural, cognitive and biological pathways. Outcomes were studied in the early and short term, namely three to five days (216 participants) and two months (154 participants) following surgery. The results indicated that greater pre-operative depression symptoms were predictive of poorer recovery, including longer in-hospital stays, greater emotional distress, physical symptoms and pain in the early term, and greater emotional distress, physical symptoms and pain and impaired health status in the short term, independent of demographic and disease severity factors (all p <0.05). Some associations were limited to subtypes of depression symptoms. Specifically, somatic/affective, but not total or cognitive/affective, depression symptoms were predictive of short-term outcomes. Mediators of the depression-recovery relationship were tested. Social support and behavioural factors were not shown to be mediators, but instead physical activity, body mass index and smoking status all had independent effects on recovery. Cognitive mediation was shown, with greater pre-operative negative illness perceptions mediating the relationship between pre-operative depression symptoms and post-operative anxiety and physical symptoms in the early term, and affective pain and physical symptoms in the short term. Biological mediation was not shown: although depression symptoms were related to neuroendocrine and inflammatory patterns suggestive of poorer physical functioning, these patterns did not consistently relate to recovery. Further work is needed to translate these findings into new ways to approach the measurement, diagnosis and treatment of depressed cardiac surgery patients.

Contents

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List of publications

Some of the research described in this thesis has been published and other sections have been submitted for publication. In addition, some of the research has been presented in international conferences.

Peer reviewed journal articles:

Poole, L., Kidd, T., Jahangiri, M., Steptoe, A. (Manuscript prepared). Pre-operative sleep disturbance is associated with physical and emotional recovery in the days and months following cardiac surgery.

Poole, L., Dickens, C., and Steptoe, A. (2011). The puzzle of depression and acute coronary syndrome: reviewing the role of acute inflammation. *Journal of Psychosomatic Research,* 71: 61-68.

Poole, L., Steptoe, S., Wawrzyniak, A. J., Bostock, S., Mitchell, E. S. (2011). Associations of objectively measured physical activity with daily mood ratings and psychophysiological stress responses in women. *Psychophysiology,* 48: 1165-1172.

Poole, L., Hamer, M., Wawrzyniak, A. J., Steptoe, A. (2011). The effects of exercise withdrawal on mood and inflammatory cytokine responses in humans. *Stress,* 14: 439-447.

Book chapters:

Hamer, M., Endrighi, R., **Poole, L.** (2012). Physical Activity, Stress Reduction and Mood: Insight into Immunological Mechanisms. In: Yan Q (Ed). *Psychoneuroimmunology: Methods and Protocols*. New York: Springer.

Conferences:

International Congress of Behavioural Medicine, Budapest, Hungary, 2012. 'Pre-operative sleep disturbance is associated with physical and emotional recovery in the days and months following cardiac surgery.' [Oral presentation].

American Psychosomatic Society Annual Conference, Texas, USA 2011. 'Pre-operative illness perceptions are associated with health status following cardiac surgery.' [Poster presentation].

Dedication

In memory of

Raphaella Poppy Moggridge (3.1.2012 to 8.9.2012),

who battled so bravely against cancer throughout my thesis write-up.

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List of abbreviations

ACS: Acute Coronary Syndrome

ACE: Angiotensin Converting Enzyme

ARCS: Adjustment and Recovery after Cardiac Surgery

AS: Professor Andrew Steptoe

AUC: Area Under the Curve

BMI: Body Mass Index

BDI: Beck Depression Inventory

BIPQ: Brief Illness Perception Questionnaire

CABG: Coronary Artery Bypass Graft

CAR: Cortisol Awakening Response

CHD: Coronary Heart Disease

CI: Confidence Interval

CREATE: Canadian Cardiac Randomised Evaluation of Antidepressant and Psychotherapy Efficacy

CROQ: Coronary Revascularisation Outcome Questionnaire

CRH: Corticotrophin Releasing Hormone

CRP: C-Reactive Protein

CVD: Cardiovascular Disease

DALYs: Disability Adjusted Life Years

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th Edition

EL: Miss Elizabeth Leigh

ENRICHD: Enhancing Recovery In Coronary Heart Disease

ESSI: ENRICHD Social Support Inventory

EUROASPIRE III: European Action on Secondary and Primary Prevention by Intervention to Reduce Events III

euroSCORE: European System for Cardiac Operative Risk Evaluation

GAD: Generalised Anxiety Disorder

GP: General Practitioner

GRACE: Global Registry of Acute Coronary Events

HADS: Hospital Anxiety Depression Scale

HPA: Hypothalamic Pituitary Adrenal

HR: Hazard Ratio

HRV: Heart Rate Variability

hs: high sensitivity

ICD-10: International Statistical Classification of Diseases and Related Health Problems - 10th Revision

ICU: Intensive Care Unit

IL: Interleukin

INF: Interferon

IPAQ: International Physical Activity Questionnaire

LP: Lydia Poole

LVEF: Left Ventricular Ejection Fraction

MARS: Medication Adherence Report Scale

MI: Myocardial Infarction

MIND-IT: Myocardial Infarction and Depression Intervention Trial

MINI: Mini International Neuropsychiatric Interview

MJ: Professor Marjan Jahangiri

MoCA: Montreal Cognitive Assessment

MPQ-SF: McGill Pain Questionnaire- Short Form

NHS: National Health Service

NICE: National Institute of Clinical Excellence

PAR: Population Attributable Risk

P-ARCS: Pilot Study - Adjustment and Recovery after Cardiac Surgery

Ra: Receptor antagonist

sACC: subgenual Anterior Cingulate Gyrus

SADHART: Setraline Antidepressant Heart Attack Randomised Trial

SAQ: Seattle Angina Questionnaire

SF-12/36: Short Form Health Survey – 12/36 Item

SSRI: Selective Serotonin Reuptake Inhibitor

STOFHLA: Short Test of Functional Health Literacy in Adults

T1/2/3/4: Time point 1/2/3/4

TK: Dr Tara Kidd

TNF: Tumour Necrosis Factor

UCL: University College London

WHO: World Health Organisation

YCBQ: York Cardiac Beliefs Questionnaire

Chapter 1. Literature review (I): Coronary heart disease and depression

1.1 Introduction

This chapter will describe the literature relating to the diagnosis and treatment of coronary heart disease (CHD) and depression, as separate and co-morbid disease states. The literature showing a relationship between depression and poor cardiac outcomes will be described, in relation to two patient groups: myocardial infarction (MI) and coronary artery bypass graft (CABG) surgery patients.

An electronic search of the literature was conducted in four online databases: PubMed, PsycINFO, EMBASE and SCOPUS, and a bibliography search was conducted to identify any previously missed papers. Much of the literature discussed in this chapter can be found in our review (Poole, Dickens, & Steptoe, 2011).

1.2 Coronary heart disease

1.2.1 Pathogenesis

Cardiovascular disease (CVD) is an umbrella term, referring to all diseases affecting the circulatory system, the most prevalent of which is CHD, also known as ischaemic heart disease or coronary artery disease. Atherosclerosis is the primary pathological process which underlies CHD and is a life-long process by which fatty deposits (atheroma) lead to the narrowing of the coronary arteries. Atherosclerosis begins in childhood, with changes gradually occurring throughout adolescence and young adulthood (Berenson et al., 1989) due to the cumulative effect of several known risk factors (Craig & Mindell, 2008; Williams, 2008). These risk factors can be divided into behavioural factors such as physical inactivity, tobacco use, excessive alcohol consumption and poor diet, biological factors such as male gender, older age and genetic predisposition, clinical factors including hypertension, diabetes, obesity and hyperlipidaemia, social factors including low educational status and low socioeconomic status, and psychological factors such as depression. The majority of people will remain in an asymptomatic disease state for many years.

Atherosclerosis was once thought to be a cholesterol storage disease but is now understood to be an inflammatory disorder capable of affecting all medium- and large-sized blood vessels in the cardiovascular system (Libby, Ridker, & Hansson, 2011; Libby, Ridker, & Maseri, 2002). Appendix 1 shows the cell structure of a human artery. In response to certain biological catalysts such as, among others, bacterial products, dyslipidaemia, and pro-inflammatory cytokines associated with excess adiposity, the expression of adhesion molecules

that promote the sticking of blood leukocytes to the inner surface of the endothelium is increased. Once these cells have migrated to the arterial intima, an immune and inflammatory response is initiated leading to migration of smooth muscle cells (the endogenous cells of the arterial wall) from the tunica media into the intima. These cells proliferate, forming a complex extracellular matrix which, principally via the action of proteoglycans, can bind lipoproteins, prolong their residence in the intima and make them susceptible to modification via oxidation and glycation. These changes to lipoproteins sustain the inflammatory response and as a result they are engulfed by monocytes. The oxidised-low density lipoproteins accumulate in the macrophages, creating 'foam cells'. Foam cells form the fatty streaks of atheroma in the intima. As the lesion progresses a fibrous cap forms, consisting primarily of smooth muscle cells and collagen. Simultaneously, underneath this cap, the macrophages die, resulting in the lipid-rich necrotic core of the atherosclerotic plaque. As cells and lipids continue to accumulate in the lesion, the plaque enlarges, bulging into the artery lumen. Over time, the fibrous cap begins to thin and fissures may appear on the surface of the plaque. If the plaque ruptures, the lipid fragments and cellular debris leak through into the lumen triggering the formation of a thrombus. For an up to date review of atherosclerosis pathogenesis see Weber & Noels (2011).

The clinical manifestations of CHD as a result of atherogenesis include: ACS, namely MI and unstable angina, and angina pectoris. MI refers to the occlusion of one of the coronary arteries by a thrombus following the rupture of an atherosclerotic plaque; the resulting oxygen shortage can lead to damage or death of heart tissue. Angina pectoris is a chronic condition characterised by chest pain on exertion caused by a lack of oxygen supply to the heart muscle due to stenosis (i.e. narrow atherosclerotic arteries). Unstable angina is distinct from angina pectoris in that symptoms occur more frequently and for a longer duration; aetiologically, unstable angina is different as it is caused by a thrombus resulting in partial occlusion of a coronary artery.

1.2.2 Prevalence

CVD represents a major public health challenge both globally and nationally. Recently, the World Health Organisation (WHO) published an update on the global status of CVD (Mendis, Puska, & Norrving, 2011). This report stated that worldwide, in 2008, CVD accounted for 30% of deaths from all causes (i.e. 17.3 million deaths), equivalent to the death rate from communicable, nutritional and maternal and perinatal conditions combined. Moreover, CVD is not just a disease of the very old, being the leading cause of death, globally, for persons less than 70 years of age. In terms of the global disease burden (DALYs[1]), 10% is attributable to

[1] DALYs: Disability Adjusted Life Years. The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.

CVD. Furthermore, projections of global CVD mortality rates are set to rise by 17% between 2006 and 2015 (WHO, 2005).

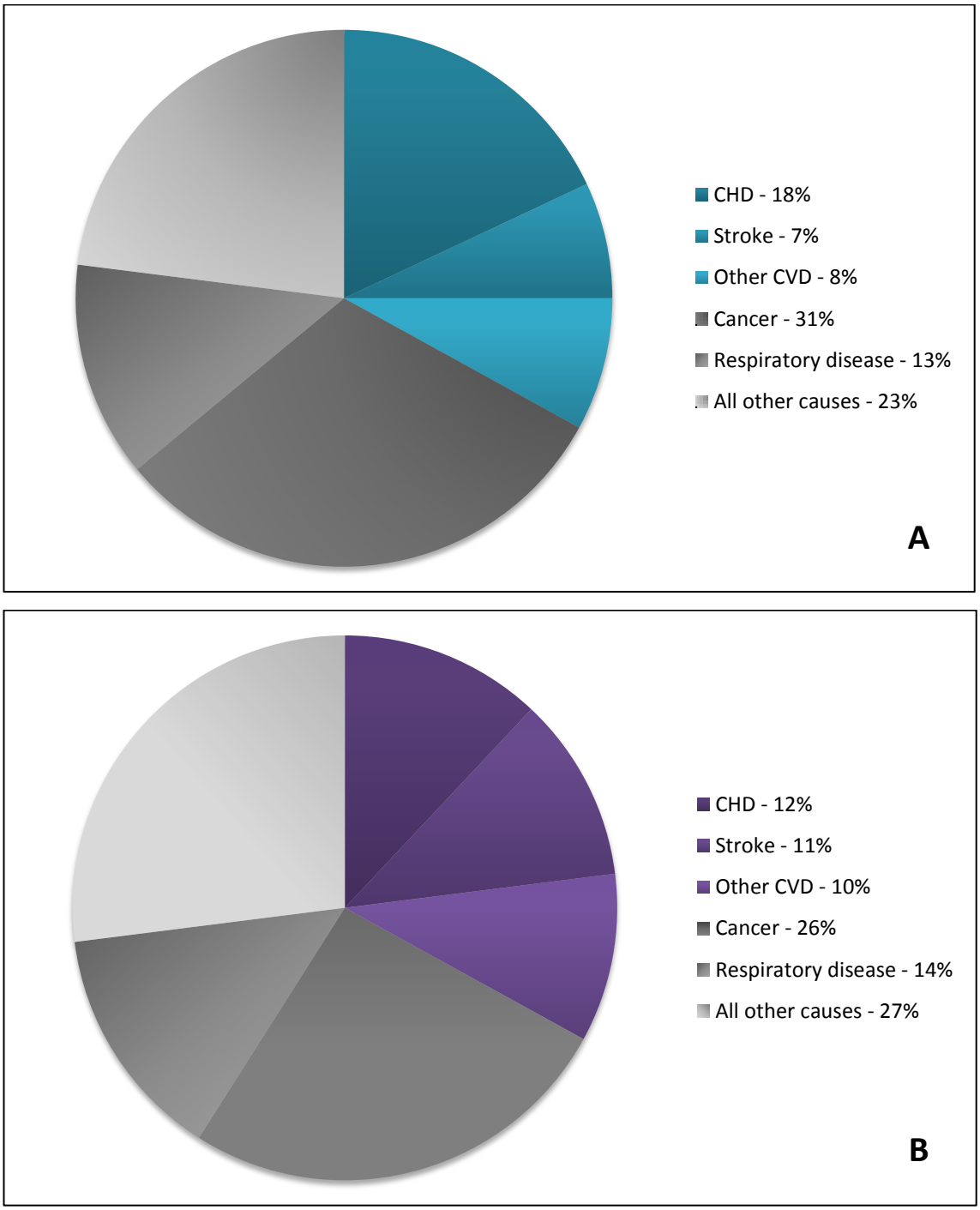

FIGURE 1.1: DEATHS BY CAUSE (A) MEN AND (B) WOMEN, 2009, UK

Despite downward trends in mortality rates over the past 50 years, CVD remains the biggest killer in the UK, accounting for almost 180,000 deaths in 2009, nearly half of which were due to CHD (Scarborough, Wickramasinghe, Bhatnager, & Rayner, 2011). This makes CHD the biggest single cause of death in the UK, accounting for approximately one-fifth of all deaths

in men and one eighth of all deaths in women (Figure 1.1). CHD is also the leading cause of premature death, accounting for just over 26,000 deaths of persons below the age of 75 years in 2009 (*ibid*).

The economic implications of CHD are high. In 2006, CHD cost the UK health care system £3.2 billion, 73% of which was spent on hospital care (Scarborough et al., 2010). However, the true economic costs are thought to be much higher. When loss of production due to work absenteeism was considered, the UK spent a further £3.9 billion in 2006; in the same year the cost of providing informal care to CHD patients cost the UK £1.8 billion (*ibid*).

1.2.3 Treatment

Various treatment options exist for patients with CHD, including behaviour modification, prescription drugs and surgery. The UK National Institute of Clinical Excellence (NICE) provides a secondary prevention care plan for those patients with known CHD (Cooper et al., 2008). The first step in this plan recommends lifestyle advice to be given, where appropriate, to all patients regarding smoking cessation, diet and weight control, physical activity and alcohol reduction. The efficacy of non-pharmaceutical methods of CHD secondary prevention has been subject to recent review (Müller-Riemenschneider et al., 2010). Evidence suggests that increasing physical activity levels can be effective at reducing mortality, but there is a scarcity of high-quality research investigating the effect of smoking cessation and diet modification programmes on mortality reduction in CHD patients. A recent longitudinal examination of smoking status in over 4500 post-ACS patients has begun to address this issue (Boggon et al., in press). These authors reported that smoking cessation advice, while advocated by NICE, was only provided by general practitioners (GPs) to 24% of patients after ACS. Moreover, those patients who did quit conferred benefits in terms of both reduced mortality risk and reduced risk of major adverse cardiac events. More high quality research is needed to further enhance our understanding of the effect of behavioural modification on cardiac risk.

The second step in the NICE care plan is to discuss with patients their CVD risk (i.e. the risk of a cardiovascular event occurring) and management options through the use of drugs. Since the 1980s there has been a marked increase in the number of medicines prescribed for the management of CHD in the UK. In 2008 alone, there were 266 million prescriptions for CVD treatments (Scarborough et al., 2010). The NICE guidelines outline medication options to include statins, antihypertensives and antiplatelet agents, and for those patients post-MI, beta-blockers and angiotensin converting enzyme (ACE) inhibitors.

The UK Department of Health published a National Service Framework for CHD in 2000, with the aim to modernise CHD services over a 10-year period. One of the standards presented in this report was to address the problem of under-provision of revascularisation in

the UK (Department of Health, 2000). According to these guidelines, revascularisation should be considered for those individuals with angina pectoris, unstable angina or those who have survived an MI, who meet the criteria for angiography based on evidence of persisting extensive ischaemia and/or angina that is unresponsive to optimal drug therapy and lifestyle advice. If angiogram shows significant narrowing of the left main coronary artery, three coronary arteries, or two coronary arteries including the proximal left anterior descending coronary artery, and the benefits of surgery outweigh the risks, then CABG surgery is recommended. Percutaneous coronary intervention (also called coronary angioplasty) with or without stenting, is the alternative revascularisation procedure offered to those patients who have an operable narrowing of one or two coronary arteries without significant narrowing of the left main stem.

A large scale survey of cardiovascular prevention in Europe, EUROASPIRE III (European Action on Secondary and Primary Prevention by Intervention to Reduce Events III), collected data from 76 centres across 22 countries in Europe in 2006-7 regarding the lifestyle, risk factor and therapeutic management of CHD patients (Kotseva et al., 2009). Patients were identified retrospectively, following hospital admission for elective or emergency CABG or percutaneous transluminal coronary angioplasty, acute MI or acute myocardial ischaemia without infarction. In the UK, over 600 participants had their medical notes reviewed, 399 of whom underwent a physical examination and interview at least six months after their coronary event. At interview, 20.1% of UK participants were smokers, 75.6% were overweight (body mass index [BMI] ≥ 25kg/m^2) and 47.4% had elevated blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg). These results show that despite the NICE guidelines, a large number of CHD patients do not achieve therapeutic targets for secondary prevention.

1.3 Depression

1.3.1 Diagnosis and pathogenesis

Depression is not an illness with discrete boundaries, encompassing an array of symptoms and having a heterogeneous diagnosis. Indeed there is little consensus amongst clinicians and researchers about how best to categorise depressive disorders (Wakefield, 2011). Two main classification systems are used to diagnose depressive disorders: the International Statistical Classification of Diseases and Related Health Problems - 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV); this latter system terms the disorder 'major depression' (see Table 1.1 for a list of the DSM-IV diagnostic criteria). Both systems require a series of symptoms to be present most days for at least two weeks and at least one of these symptoms must include low mood or loss of interest and

pleasure; the ICD-10 also includes loss of energy as one of the key diagnostic symptoms. Further symptoms also need to be reported, such as feelings of guilt/worthlessness, appetitive changes, sleep disruption, suicidal ideation, loss of concentration and psychomotor agitation or retardation. The ICD-10 requires at least four out of ten symptoms and the DSM-IV requires at least five out of nine symptoms to be present to meet a diagnosis.

TABLE 1.1: DSM-IV-TR CRITERIA FOR MAJOR DEPRESSIVE EPISODE

(Adapted from: American Psychiatric Association, 2000)

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) Depressed mood most of the day, nearly every day.

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

(3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day.

(6) Fatigue of loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day.

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than two months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Conceptual problems with the nosology of depression become apparent when one considers that depression can present different symptom clusters in different individuals (e.g. somatic or cognitive symptom preponderance), it can manifest itself either as an excess or insufficiency of certain behaviours (e.g. hypersomnia or insomnia, weight gain or weight loss),

and symptoms of major depression overlap with other disorders including dysthymia, adjustment disorders and bipolar depression. Moreover, recent critiques of depression have focussed on whether discrete subtypes of depression exist based on symptom patterns (Lichtenberg & Belmaker, 2010; Lux & Kendler, 2010).

Severity of the depressive disorder is based both on the number and severity of an individual's symptoms and the level of distress and impairment in normal functioning. However, it is now considered more appropriate to conceptualise depression as occurring along a continuum of severity, without discrete cut-offs for mild-moderate-severe (Lewinsohn, Solomon, Seeley, & Zeiss, 2000). Indeed, the NICE guidelines recognise the importance of sub-clinical depression for causing considerable distress and disability. Sub-clinical depression refers to the presence of at least one key depressive symptom, but insufficient other symptoms to meet the full criteria for depression (National Collaborating Centre for Mental Health, 2010a).

The aetiology of depression is as varied and multifactorial as the diagnosis, and is thought to originate from the interaction between genetic and environmental vulnerabilities including the experience of stressful life events, physical inactivity, obesity, female sex, smoking, alcohol consumption and low socioeconomic status. We still lack a clear understanding regarding the pathogenesis of depression, with several competing hypotheses currently under investigation (Ebmeier, Donaghey, & Steele, 2006; Nestler et al., 2002). There is the so-called monoamine hypothesis, which is based on deficiency in the biogenic amine system, principally serotonin and noradrenalin (Ressler & Nemeroff, 2000). Also, there is the hypothalamic pituitary adrenal (HPA) axis dysfunction theory, based on dysregulation of this system resulting in excess glucocorticoid production (Dinan, 1994; Pariante & Lightman, 2008). Other theories include the cognitive model centred on the role of dysfunctional self-schema (Clark & Beck, 2010), the neurogenesis hypothesis which posits that depression is precipitated by stress induced decreases in neurogenesis in the hippocampus (Jacobs, Van Praag, & Gage, 2000), the inflammatory theory which emphasises the role of pro-inflammatory cytokines (Miller, Maletic, & Raison, 2009), the neurotrophic theory which implicates the role of growth factors such as brain derived neurotrophic factor (Altar, 1999), and the neurodegenerative hypothesis which recognises evidence of structural and volumetric changes to the hippocampus, amygdala, prefrontal cortex, anterior cingulate and basal ganglia in the brains of depressed patients (Maes et al., 2009). In order to better understand the neurobiology of depression, researchers are now beginning to look for similarities across the models to create one unifying theory. In particular, is the role of glucocorticoids, which are central to the HPA axis dysfunction, inflammatory and neurodegenerative theories (Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011).

1.3.2 Prevalence

Mental illness is now firmly on the world health agenda, with estimates suggesting that it accounted for approximately 11% of the global burden of disease in 1990, a figure which is predicted to rise to 15% by 2020 (WHO, 2001). Mood disorders are the most prevalent mental illness, of which the most common is major depressive disorder. Depression made the fourth largest contribution to the total global disease burden in 1990 and is predicted to become the second largest after CHD by 2020 (*ibid*). A systematic review of depression prevalence reported a one-year pooled prevalence of 4.1% and a lifetime prevalence of 6.7% for major depression (Waraich, Goldner, Somers, & Hsu, 2004).

Depression is also a growing challenge for UK health services. In 2000, the Office for National Statistics conducted a survey of UK households on behalf of the Department of Health estimating that the point prevalence for a depressive episode among those aged 16 to 74 years was 2.3% for men and 2.8% for women (pooled point prevalence 2.6%) (Singleton, Bumpstead, O'Brien, Lee, & Meltzer, 2003).

The consequences for the UK economy are high. In 2000, it was estimated that the cost of adult depression was more than £9 billion, £370 million of which was spent on treatment costs. An additional £8 billion was attributed to loss of earnings due to absenteeism, while loss of future earnings due to death by suicide was estimated at £562 million (Thomas & Morris, 2003). Another recent review was published by the King's Fund to look at projected costs of depression expenditure within the UK from 2006 to 2026 (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008). This review predicted the number of people with depression to rise by 17% by 2026, to 1.45 million, leading to a concomitant rise in the cost of services and lost employment over the same period from £7.5 billion to £12.2 billion. Similar across both the Thomas and Morris and King's Fund publications is that the health service costs are relatively minor in comparison to the indirect costs of depression.

1.3.3 Treatment

One of the main problems with treating depression is the poor identification of depression cases in primary care. This is in part accounted for by the failure of the individual to consult with their GP about mood symptoms (Meltzer et al., 2003) and in part explained by a failure of GPs to identify symptoms of depression, particularly among those presenting with mild symptoms (Goldberg, Privett, Ustun, Simon, & Linden, 1998; Thompson, Ostler, Peveler, Baker, & Kinmonth, 2001). The NICE guidelines for depression (National Collaborating Centre for Mental Health, 2010a) recognise that some cases of depression will remit spontaneously without treatment, while other cases will recur and take a more chronic course; for a review of this literature see Richards (2011).

The current UK guidelines for treating depression follow a stepped care plan, in which treatment recommendations are based on the severity and chronicity of the depressive episode. For mild cases, watchful waiting is often prescribed in which patients are asked to return after two weeks for symptoms to be re-assessed. For more severe cases, possible treatment options include pharmacological interventions and psychological treatment, including cognitive behavioural therapy and counselling. Pharmacological treatments include use of tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs), which work on the premise of monoamine neurotransmission deficiency causing depression. However, these drugs are only modestly efficacious, with effect sizes reported to be 0.31 (95% confidence interval [CI], 0.27 to 0.35) for both published and unpublished trials (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Despite the treatment options available in primary care, some patients fail to respond to antidepressant treatment entirely, so-called 'treatment resistant' depression (Vieta & Colom, 2011). Poor treatment response is further compounded by poor adherence to antidepressant medication, with estimates of non-adherence ranging from 10% to 60% (Lingam & Scott, 2002).

Treatment of depression can be improved by using cognitive behavioural strategies as an adjunct to pharmacotherapy (Thase et al., 1997). Counselling or psychotherapy, where stress-management techniques and sometimes exercise are involved, tend to be less frequently prescribed than antidepressant drugs; however there is a growing body of evidence finding in support of their efficacy (Bower, Knowles, Coventry, & Rowland, 2011). Moreover, some authors suggest that such treatment strategies would actually be preferred by patients (Dwight-Johnson, Sherbourne, Liao, & Wells, 2000). In addition, there has been recent interest in the use of physical exercise as a treatment for mental illness (Blumenthal, 2011; Phillips, Kiernan, & King, 2003). Support for the mood-enhancing benefits of physical activity, both in terms of reducing negative mood symptoms (Poole, Hamer, Wawrzyniak, & Steptoe, 2011) and promoting positive wellbeing (Poole, Steptoe, et al., 2011), have been demonstrated recently in our own empirical studies and review (Hamer, Endrighi, & Poole, 2012).

1.3.4 Depression in physical illness

The full health implications of depressive disorders have only emerged in recent years and depression is now recognised as contributing to the onset and progression of physical illness (Steptoe, 2007). Moreover 'mood disorder due to a general medical condition' is a recognised subtype of depressive disorder within DSM-IV, in which major depressive disorder onsets as a direct physiological consequence of a physical illness; it is not merely a failure to adapt to the emotional burden of medical illness. In the UK, NICE also recognises co-morbid depression in physical illness and has clinical management guidelines in place to improve treatment of these

patients (National Collaborating Centre for Mental Health, 2010b). However, NICE points out that depression in these patients is not a separate disorder with different symptoms or treatment requirements, but rather reflects the different contexts in which depression can manifest itself.

Depression in physical illness is highly prevalent. The WHO World Health Survey (Moussavi et al., 2007) sampled just fewer than 245.5 thousand participants from across 60 countries, covering all regions of the world. They used the ICD-10 classification system to estimate depressive episode prevalence alone and in conjunction with four physical illnesses: diabetes, arthritis, angina, and asthma. They found that the one-year prevalence of a depressive episode co-morbid with diabetes was 9.3% (95% CI 7.3–11.3), for those with arthritis it was 10.7% (95% CI 9.1–12.3), for those with angina it was 15.0% (95% CI 12.9–17.2), and for those with asthma it was 18.1% (95% CI 15.9–20.3). In comparison, the healthy comparison group had a one-year prevalence of a depressive episode at just 3.2% (95% CI 3.0–3.5). Moreover, a dose-response relationship seems to exist, whereby those participants with two or more physical illnesses had even greater risk, with nearly a quarter also having co-morbid depression. With an ageing population and an ever-increasing rise in the prevalence of chronic illness, a concomitant rise in the diagnosis of co-morbid depression is expected (Moussavi et al., 2007).

Several good quality reviews have now been published in this area, showing that depression can lead to physical illness onset. For example, a meta-analysis of longitudinal studies showed depressed individuals to be at 60% greater risk of developing type II diabetes than those without depression (Mezuk, Eaton, Albrecht, & Golden, 2008). Depression has also been implicated as a risk factor in cancer, with another recent meta-analysis of prospective studies revealing depression morbidity predicted a 29% increase in cancer incidence (Chida, Hamer, Wardle, & Steptoe, 2008). In addition, a systematic review of prospective cohort studies (Kuper, Marmot, & Hemingway, 2002) demonstrated that in individuals free from disease at baseline, the presence of depression symptoms was related to an increased risk of future cardiac events, both fatal and non-fatal, up to 40 years later (c.f. Ford et al., 1998). Moreover, depression has also been associated with an increase in disease progression in HIV patients (Leserman, 2008) and a greater risk of mortality in cancer (Satin, Linden, & Phillips, 2009) and stroke (Ellis, Zhao, & Egede, 2010) patients. The subjective experience of disease burden is also different in depressed patients, with depressed patients experiencing more symptoms of their physical illness compared to their non-depressed counterparts (Katon, Lin, & Kroenke, 2007).

Creed and Dickens note that methodological issues arise from the assessment of depression in those with a physical illness, primarily due to measurement problems caused by

the commonality of somatic symptoms in both depression and physical illness, for example sleep, fatigue and appetite changes (Creed & Dickens, 2007). Therefore, care must be taken when interpreting the results of these studies, taking into account this conceptual overlap.

1.4 Depression and coronary heart disease

1.4.1 Depression in acute coronary syndrome

Co-morbid depression is commonly observed in patients suffering from CHD (Blumenthal, 2008; Lett et al., 2004; Steptoe, 2007), and has been most widely studied in patients suffering from acute MI. A comprehensive literature review of hospitalised post-MI patients estimates the prevalence rate to be nearly 20% for major depression as measured using clinical interviews (Thombs et al., 2006). Prevalence varied from 7.3% (Hospital and Anxiety Depression Scale score [HADS] ≥11) to 31.1% (Beck Depression Inventory [BDI] score ≥10) when using standardised questionnaires measuring elevated depression symptomatology. Similar estimates have been reported more recently for both major and minor depression, again in post-MI patients (Carney & Freedland, 2008; Frasure-Smith & Lespérance, 2010). The association between depression and cardiovascular morbidity following ACS was first identified in the literature more than 15 years ago; Frasure-Smith and colleagues (Frasure-Smith, Lespérance, & Talajic, 1993) showed that major depression in patients recently admitted to hospital for MI was an independent risk factor for mortality at six months. This association has since been replicated in several studies (Brown, Stewart, Stump, & Callahan, 2011; Meijer et al., 2011, 2011; Nabi et al., 2010; van Melle et al., 2004). The association with recurrent cardiac disease is apparent not only for clinical depression, but for subclinical dysphoria and elevated symptoms of depression within the normal range (Bush et al., 2001; Lespérance, Frasure-Smith, Talajic, & Bourassa, 2002).

Depression in CHD patients is associated with poorer quality of life after MI (Lane, Carroll, Ring, Beevers, & Lip, 2001), longer hospital stays and greater cardiac-related readmissions after MI (Frasure-Smith et al., 2000; Myers, Gerber, Benyamini, Goldbourt, & Drory, 2012), greater disease progression such as atherosclerosis in CABG patients (Wellenius, Mukamal, Kulshreshtha, Asonganyi, & Mittleman, 2008), and increased use of urgent and unscheduled care (Frasure-Smith et al., 2000; Kurdyak, Gnam, Goering, Chong, & Alter, 2008; Lauzon et al., 2003). Indeed in recognition of the prevalence and negative sequelae of depression in CHD, the American Heart Association now recommends routine screening for depression in all heart disease patients (Bigger & Glassman, 2010; Lichtman et al., 2008), but such guidelines have yet to be introduced in the UK. However, screening has yet to be shown to impact patient outcomes (Thombs et al., 2008).

There are several features of depression in CHD patients which add additional layers of complexity to our understanding of the relationship (Poole, Dickens, et al., 2011). The first unusual feature of the relationship between depression and CHD is that there appears to be a difference between those patients who are depressed before the occurrence of an ACS and those who develop depressive symptoms following the cardiac event. Several subtypes of depression in response to an ACS have been reported, differentiating patients according to the timing and recurrence of a depressive episode. Recent evidence indicates there is a stronger association with mortality and recurrent cardiac events in patients with new onset depression (post-ACS depressed with no prior history of depression; also called 'incident' depression). For example, in a prospective cohort study of 588 patients admitted to hospital with MI, Dickens and colleagues (Dickens et al., 2007, 2008) observed 167 cases of depression of which 96 had depression before their MI and 71 developed depression during the 12 months following their MI. Kaplan-Meier survival analysis showed that depression symptomatology from the week preceding MI did not confer risk of cardiac mortality, but new onset depression did (hazard ratio [HR] = 2.33, p = 0.038), even after controlling for a range of risk factors including age, history of angina prior to MI, Killip class, beta-blocker use on discharge, left ventricular ejection fraction (LVEF), use of antidepressant medication at baseline and serious cardiac events during 12-month follow-up. Other studies have supported these findings (Carney et al., 2009; de Jonge, van den Brink, Spijkerman, & Ormel, 2006; Grace et al., 2005; Lespérance, Frasure-Smith, & Talajic, 1996; Parker et al., 2008). By contrast, recent findings from the Sertraline Antidepressant Heart Attack Randomised Trial (SADHART) found that although major depression following hospital admission predicted mortality over the next seven years, timing of depression onset and a history of major depression did not (Glassman, Bigger, & Gaffney, 2009).

One explanation for this pattern of findings proposed by Spijkerman and colleagues (Spijkerman et al., 2005) and later Goodman and colleagues (Goodman, Shimbo, Haas, Davidson, & Rieckmann, 2008) is that new onset depression is associated with more severe coronary artery disease than is recurrent depression; however, the studies reported above (de Jonge et al., 2006; Dickens et al., 2007; Parker et al., 2008) all controlled for cardiac risk factors. It has been suggested that new onset depression has different risk factors to recurrent depression (Dickens et al., 2004), further indicating that it may be a distinct phenomenon. In particular, negative perceptions regarding one's heart condition in the days following an MI (Dickens et al., 2008b) were associated with increased risk of developing depression. Other analyses have shown the greater cardiac risk associated with post-ACS depression may be in large part attributable to an increase in depressive symptoms following MI, rather than the prolongation of recurrent depressive symptoms from before the MI (Zuidersma, Ormel,

Conradi, & de Jonge, 2012). In particular these authors reported that each new depression symptom experienced post-MI carried an increased risk of new cardiac events of 15%, remaining significant even after adjusting for baseline disease severity and demographic confounders. This study did not distinguish new onset depression cases, but rather analysed the absolute number of depression symptoms experienced pre- and post-MI. A systematic review by the same research group suggested that due to the small number of studies published and the inconsistent findings, firm conclusions are difficult to draw about the risk of new onset depression cases over and above recurrent episodes (Zuidersma et al., 2011). Moreover, care needs to be taken when interpreting the literature in this area due to concerns over the measurement of incident depression. While a first-ever ACS can be established from medical notes, establishing a first-ever depressive episode is likely to be subject to recall bias and may not be objectively verifiable since some episodes may have escaped medical attention. In addition, it is not clear to what extent depression that onsets after an ACS differs from depression that onsets after a first-ever manifestation of CHD, such as angina. This distinction would have implications for understanding the direction of the causal direction, but has yet to be addressed in the literature. However, it seems the weight of evidence points towards new onset cases of depression carry at least as much, if not more, risk as chronic, recurrent depression.

The second intriguing feature of the depression-CHD relationship concerns the symptom profile of patients with post-ACS depression who are at risk of future cardiac events. Some types of symptoms appear to be more "cardiotoxic" than others, with somatic symptoms being particularly damaging. Analyses performed on two large datasets comprising more than 2000 patients compared three dimensions of depression symptoms derived from the BDI in relation to cardiovascular risk markers, mortality and readmissions over an average of 2.5 years after ACS (De Jonge, Ormel, et al., 2006). Cox regression analyses found somatic/affective symptoms (e.g. fatigue, pessimism) to predict cardiovascular events and mortality, even after controlling for cardiac risk factors (LVEF, Killip class, and previous myocardial infarction), while cognitive/affective (e.g. social withdrawal, work difficulty) and appetitive symptoms (e.g. loss of appetite, weight loss) did not. Other studies have reported similar findings (Doyle, Conroy, McGee, & Delaney, 2010; Hoen et al., 2010; Linke et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; McGowan et al., 2004) and this observation has been subject to recent discussion (Carney & Freedland, 2012; Ormel & de Jonge, 2011). Somatic depression symptoms have also been shown to be positively correlated to intima-media thickness of the carotid artery, a marker of atherosclerotic disease progression (Bus et al., 2011).

It should be noted that not all evidence supports this association. For example, an early study by Lespérance and colleagues (Lespérance et al., 1996) found that by removing appetite and sleep disturbance symptoms from analyses, depression was better able to predict mortality at six months. However, a key limitation of this study is its small sample size, with only 42 depressed patients being followed up at six months. It is also interesting that somatic symptoms of depression overlap with the concept of vital exhaustion, which is commonly defined as symptoms of excessive tiredness, increased irritability and a sense of demoralisation (Appels, Höppener, & Mulder, 1987). Vital exhaustion has been shown to be predictive of cardiac prognosis in MI and heart failure patients (Smith, Kupper, Denollet, & De Jonge, 2010). Although depression and vital exhaustion are generally understood to be separate constructs (Kopp, Falger, Appels, & Szedmak, 1998), in a recent study this was only observed in men and not women (Lindeberg, Rosvall, & Östergren, 2012). Another study used principal component analyses on questionnaire responses of 528 MI patients on the BDI and Maastricht Questionnaire (a measure of vital exhaustion) (Vroege, Zuidersma, & De Jonge, 2012). These authors showed strong conceptual overlap between the two scales, with all but two items from the Maastricht Questionnaire loading on the somatic/affective dimension of the BDI. Moreover, this somatic/affective dimension was able to predict recurrent events, but the cognitive/affective dimension was not. Due to these disparate findings, more research is needed to delineate the independent effect of vital exhaustion over and above depression, on the prognosis of ACS patients.

A third feature is that depression following ACS responds relatively poorly to standard treatment. The Enhancing Recovery In Coronary Heart Disease (ENRICHD) randomised controlled trial of cognitive-behavioural treatment versus usual case for depressed MI patients (Berkman et al., 2003), showed only a modest and poorly sustained difference in depression following treatment between the two groups. Although statistically significant, the improvement observed was only between 1.5 and 2.8 points depending on the scale used, which is of questionable clinical significance. Other randomised trials, such as SADHART, CREATE (Canadian Cardiac Randomised Evaluation of Antidepressant and Psychotherapy Efficacy) and MIND-IT (Myocardial Infarction and Depression Intervention Trial), have reported similarly modest treatment effects (SADHART: Glassman et al., (2002); CREATE: Lespérance et al., (2007); MIND-IT: van Melle et al., (2007)). Interestingly, in subgroup analyses in two of these trials (SADHART and CREATE), new onset depression showed poorer treatment response than recurrent depression (Glassman, Bigger, Gaffney, Shapiro, & Swenson, 2006; Habra et al., 2010), which is in line with the evidence discussed earlier that timing of depression is key to cardiac outcomes. In a systematic review, Thombs and colleagues (Thombs et al., 2008) demonstrated only modest benefits to antidepressant treatment in cardiac patients with

hedges' *g* effect sizes ranging from 0.20 to 0.38. High rates of placebo response as opposed to low treatment responses may in large part explain these results. Evidence also suggests that treatment resistant depression is linked to cardiac mortality (Carney & Freedland, 2009; de Jonge et al., 2007; Scherrer et al., 2012).

However, these findings should be interpreted in light of evidence from non-cardiac populations. Turner and colleagues (Turner et al., 2008) conducted a literature search of both published and unpublished data on antidepressant efficacy in psychiatric populations finding effect sizes that are comparable to the ENRICHD and SADHART results. This suggests both non-cardiac and cardiac patients often respond poorly to standard treatment. One of the difficulties in determining whether cardiac patients respond less well to treatment is that many cases of depression resolve in the weeks following the event, making a treatment effect hard to demonstrate. The literature is suggestive of a reduced response to pharmacological and cognitive behavioural treatments following ACS, but further systematic studies are required to fully resolve this issue.

It can be argued that the form of depression in ACS that is particularly cardiotoxic is a distinct disorder from psychiatric depression. It comprises the three elements described, namely new onset, somatic/affective symptoms and limited responsiveness to treatment. This model presents one way in which we can interpret the differences in presentation of depression in ACS patients compared with their psychiatric counterparts. One important point to be borne in mind when summarising the literature in this field, relates to the issue of publication bias and the large number of papers published with positive findings. This is a consideration raised in a recent critique of the cancer prognosis literature (Kyzas, Denaxa-Kyza, & Ioannidis, 2007) in which 95.8% of 1575 original articles were found to report positive significant findings. This highlights the need for careful interpretation of published findings, so as not to overestimate the effect of prognostic markers. Several methods to examine publication bias exist, including the use of statistical techniques such as Egger's method. Alternatively, meta-analyses could include published as well as unpublished datasets to estimate accurate effect sizes. While recent meta-analyses have made use of statistical techniques to demonstrate that publication bias is likely to be an issue in the depression-CHD literature (e.g. Nicholson, Kuper, & Hemingway, 2006), to date no meta-analyses have systematically studied the impact of including unpublished trials on effect estimates.

Nevertheless, despite this controversy, research has continued to explore the depression-CHD relationship. It can be argued that by drawing on a greater range of cardiac populations we would be better able to understand the patterns of depression incidence in this patient group. Therefore, recent research has also begun to investigate these issues in cardiac surgery patients as well.

1.4.2 Depression in cardiac surgery

1.4.2.1 Estimating depression prevalence

CABG surgery is one of the most common revascularisation procedures used for CHD patients in the UK (Scarborough et al., 2010) and the USA (Lloyd-Jones et al., 2010) and is the treatment of choice for patients over 65 years of age and for patients with co-morbid conditions such as diabetes (Hlatky et al., 2009) and with multivessel disease (Biryukova et al., 2010; Mokadam et al., 2011). It is primarily used in patients for whom, due to the number, location and extent of coronary artery occlusions, MI is a significant risk. In addition, CABG may be used during or immediately following an MI in order to minimise damage to heart muscle. As such it is used both for the relief of symptoms and the improvement of life expectancy in patients suffering from CHD; it is not a cure for CHD (Van Domburg, Kappetein, & Bogers, 2009). CABG patients differ from an ACS population in that many patients requiring CABG have not had a prior MI but rather suffer from stable angina; some others will have no cardiac symptoms at all but may have another form of CVD such as cerebrovascular disease or peripheral arterial disease. Short-term survival rates following CABG are high; according to the Healthcare Commission, 98.4% of first-time patients in the UK were successfully discharged from hospital in 2009 (Care Quality Commission, 2010).

Two different surgical techniques can be used in CABG surgery: either on-pump or off-pump. On-pump surgery involves cardioplegic arrest, using a cardiopulmonary bypass machine to keep blood flowing round the body. On the other hand, off-pump surgery is performed without cardiopulmonary bypass, mechanically stabilising the heart and using drugs to slow the patient's heart rate. A systematic review of randomised controlled trials comparing on-pump and off-pump CABG surgery techniques concluded that in the majority of studies, patients generally show improved health-related quality of life after CABG, irrespective of the surgery type (Jokinen, Hippeläinen, Turpeinen, Pitkänen, & Hartikainen, 2010). However, the reason why some patients fail to show these improvements is not clear and has yet to be fully accounted for in the literature. For example, Hawkes and Mortensen (Hawkes & Mortensen, 2006) reported cross-cultural data showing that 27% of cardiac surgery patients have a clinically significant decline in quality of life at six-month follow-up compared to pre-surgery levels and this has been supported by others (Covinsky et al., 2008). Moreover, the impact of CABG on patients' emotional adjustment is often less positive than might be expected for a surgery which aims to remove symptoms and promote wellbeing.

TABLE 1.2: PREVALENCE OF DEPRESSION BEFORE AND AFTER CABG SURGERY

BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Studies Depression scale; DASS-D: Depression Anxiety Stress Scales- Depression subscale; DISH: Depression Interview and Structured Hamilton; HADS: Hospital and Anxiety Depression Scale; MINI: Mini International Neuropsychiatric Interview; PHQ-9: Patient Health Questionnaire- 9 item; SCL-90-R: Symptom Checklist- 90 items- Revised.

Reference	*Sample size*	*Surgical procedure*	*Excluded those currently treated for depression?*	*Design*	*Depression measure*	*Time in relation to CABG*	*Prevalence*
			Pre-CABG depression				
Baker et al. (2001)	158 (118 male, 40 female)	Urgent and elective, CABG +/- valve replacement	No	Cross-sectional	DASS-D	1 day pre-CABG	15.2% depressed (DASS-D≥10)
Beresnevaitė et al. (2010)	109 male	CABG in isolation	No	Cross-sectional	SCL-90-R	1 day pre-CABG	23% depressed (SCL-90R≥71)
Blumenthal et al. (2003)	817 (596 male, 221 female)	Elective CABG in isolation	Yes	Prospective	CES-D	1 day pre-CABG	26% mild depression (CES-D 16–26) 12% moderate to severe depression (CES-D ≥27)
Borowicz et al. (2002) (follow-up study of McKhann et al. (1997) dataset)	172 (134 male, 38 female)	Elective first-time or re-do CABG in isolation	No	Prospective	CES-D	≥1 day pre-CABG	32% depressed (CES-D≥16)
Burg, Benedetto, Rosenberg, et al. (2003)	89 male	Urgent and elective, first-time or re-do, CABG in isolation	No	Prospective	BDI	≤1 week pre-CABG	28.1% depressed (BDI≥10)
Dunkel et al. (2009)	1238	CABG	No	Cross-sectional	PHQ-9	1-3 days pre-CABG	21.6% depressed (PHQ-9≥10)
Krannich et al. (2007)	142	Elective CABG	No	Prospective	HADS	2 days pre-CABG	25.8% depressed (HADS≥8)
Langeluddecke, Fulcher, Baird, Hughes, & Tennant (1989)	89	Elective, first-time CABG	No	Prospective	CES-D	2 days pre-CABG	36% depressed (CES-D>15)
McKhann, Borowicz, Goldsborough, Enger, & Selnes (1997)	124 (100 male, 27 female)	Elective first-time or re-do CABG in isolation	No	Prospective	CES-D	≥1 day pre-CABG	27.4% depressed (CES-D≥16)
Mitchell et al. (2005)	123	Elective CABG in isolation	No	Prospective	MINI BDI	≤28 days pre-CABG	28.2% depressed 39% depressed (BDI≥10)

Oxlad & Wade (2006)	119 (100 male, 19 female)	Elective CABG +/- valve replacement	No	Cross-sectional	DASS-D	90% between 2-112 days pre-CABG	14.3% depressed (DASS-D≥10)
Phillips-Bute et al. (2008) (sub-study of Blumenthal et al. (2003) cohort)	427 (299 male, 128 female)	Elective on-pump CABG in isolation	Yes	Prospective	CES-D	1 day pre-CABG	36.8% depressed (CES-D>16)
Pirraglia, Peterson, Williams-Russo, Gorkin, & Charlson (1999)	237	Elective CABG	No	Prospective	CES-D	1 day - 1 week pre-CABG	43.1% depressed
Timberlake et al. (1997)	121 (109 male, 12 female)	Elective CABG	No	Prospective	BDI	Pre-CABG (no time frame defined)	37% depressed (BDI≥9)
Tully, Baker, & Knight (2008)	440 (360 male, 90 female)	Elective, first-time, on-pump CABG +/- valve replacement	No	Cross-sectional	DASS-D	1 day - 1 week pre-CABG	20% depressed (DASS-D≥10)
Yang et al. (2012)	232	Elective, first time CABG	No	Prospective	PHQ-9	≥3 days pre-CABG	18.1% depressed (PHQ-9≥10)
			Post-CABG depression				
Blumenthal et al. (2003)	555	Elective CABG in isolation	Yes	Prospective	CES-D	6 months post-CABG	20.5% depressed (CES-D≥16)
Borowicz et al. (2002) (follow-up study of McKhann et al. (1997) dataset)	147 128 117	First-time or re-do CABG in isolation	No	Prospective	CES-D	1 month post-CABG 1 year post-CABG 5 years post-CABG	28% depressed (CES-D≥16) 21% depressed (CES-D≥16) 16% depressed (CES-D≥16)
Burg, Benedetto, Rosenberg, et al. (2003)	89 male	Urgent and elective, first-time or re-do, CABG in isolation	No	Prospective	BDI	6 months post-CABG	13.5% depressed (BDI>10)
Connerney, Shapiro, McLaughlin, Bagiella, & Sloan (2001)	309 (207 male, 102 female)	Urgent and elective, first-time or re-do, CABG +/- valve replacement	No	Cross-sectional	Clinical interview (modified DSM-IV criteria) BDI	4-10 days post-CABG	20.4% depressed 28% depressed (BDI≥10)

Doering et al. (2006)	75 female 55 female	First-time CABG	No	Prospective	DISH	Prior to discharge post-CABG 2-4 weeks post-discharge 6 months post-discharge	36% depressed 16.4% depressed 12.8% depressed
Krannich et al. (2007)	132	Elective CABG	No	Prospective	HADS	10 days post-CABG	17.5% depressed (HADS≥8)
Kustrzycki et al. (2012)	37	Elective on-pump CABG	No	Prospective	BDI	8 years post-CABG	37.8% depressed (BDI>13)
Langeluddecke, Fulcher, Baird, Hughes, & Tennant (1989)	89	Elective, first-time CABG	No	Prospective	CES-D	6 months post-CABG 1 year post-CABG	26% depressed (CES-D>15) 22% depressed (CES-D>15)
McKhann, Borowicz, Goldsborough, Enger, & Selnes (1997)	124 (100 male, 27 female)	Elective first-time or re-do CABG in isolation	No	Prospective	CES-D	1 month post-CABG 1 year post CABG	24.2% depressed (CES-D≥16) 19.4% depressed (CES-D≥16)
Mitchell et al. (2005)	120	Elective CABG in isolation	No	Prospective	MINI BDI	6-12 weeks post-CABG	16.4% depressed 30% depressed (BDI≥10)
Phillips-Bute et al. (2008) (sub-study of Blumenthal et al. (2003) cohort)	420 411	Elective on-pump CABG in isolation	Yes	Prospective	CES-D	6 months post-CABG 1 year post CABG	17% male, 33% female depressed (CES-D>16) 17% male, 32% female depressed (CES-D>16)
Pirraglia, Peterson, Williams-Russo, Gorkin, & Charlson (1999)	219	Elective CABG	No	Prospective	CES-D	6 months post-CABG	23.4% depressed (CES-D≥16)
Timberlake et al. (1997)	121 (109 male, 12 female)	Elective CABG	No	Prospective	BDI	8 days post-CABG 8 weeks post-CABG 1 year post-CABG	50% depressed (BDI≥9) 24% depressed (BDI≥9) 23% depressed (BDI≥9)
Yang et al. (2012)	232	Elective, first time CABG	No	Prospective	PHQ-9	6 months post-CABG	18.1% depressed (PHQ-9≥10)

CABG has been shown to have negative emotional effects, and both severe depression in the clinical range and subclinical milder depression are common sequelae (Pignay-Demaria, Lespérance, Demaria, Frasure-Smith, & Perrault, 2003). Prevalence of depression has been found to vary widely both before and after CABG surgery; Table 1.2 summarises these studies. Before CABG the prevalence of depression has been shown to be between 14.3% and 43.1%, while after surgery estimates are between 12.8% and 50%. These prevalence data were used to calculate weighted means: on average 28.22% of patients were depressed pre-surgery and post-surgery 28.17% of patients were depressed. Therefore, overall estimates suggest similar prevalence rates both pre- and post-operatively; however, assessment timing is likely to influence the rate of post-operative depression, with the prevalence rate tending to peak shortly after surgery and declining in the succeeding months. There may be several reasons for the variability across studies, namely issues with: measurement, study design and inclusion and exclusion criteria.

The choice of measurement tool (e.g. questionnaire, clinical interview) presents several issues. The cut-off implemented by researchers to determine caseness varies greatly between studies, even among those using the same instrument. In particular, the study by Timberlake and colleagues (Timberlake et al., 1997) used a cut-off of ≥9 on the BDI, which may in large part account for their finding of 50% depression cases in the days following surgery. This is a much higher estimate than others who also used the BDI found. Also related to measurement is the fact that the criteria for the different instruments vary, so prevalence may not be consistent, especially given the overlap between somatic depression symptoms and illness symptoms.

The second broad issue with the prevalence data concerns the study design, which varies across studies. While the majority of studies cited have the advantage of using a prospective design, tracking patient's depression symptoms from pre- to post-operative stages, several studies only report cross-sectional data (Baker, Schrader, & Knight, 2001; Beresnevaitė et al., 2010; Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Dunkel et al., 2009; Oxlad & Wade, 2006; Tully, Baker, & Knight, 2008). One of the principal issues surrounding cross-sectional data in cardiac patients is that little can be discovered about how depression progresses, for example whether it persists or resolves following surgery. Another issue with the study design is the timing of assessments. While the majority of studies assessed depression the day prior to surgery, the post-operative assessment point varies widely across studies, with some studies using assessments just days after surgery (Connerney et al., 2001; Doering, Magsarili, Howitt, & Cowan, 2006; Krannich et al., 2007; Timberlake et al., 1997) while others had much longer follow-ups of five (Borowicz et al., 2002) and eight (Kustrzycki et al., 2012) years. This makes it difficult to directly compare the results across the different studies.

It is important to note that this latter study (Kustrzycki et al., 2012) had a small sample of only 37 participants, which limits the conclusions to be drawn from the data due to potential bias and risk of committing a type I or II error.

The third general issue surrounds the use of study inclusion and exclusion criteria, namely the surgical procedure, the sex of participants and current treatment for depression. CABG surgery is often broadly defined in research studies to include elective and emergency cases, CABG in isolation or in conjunction with another procedure, first-time and re-do cases, and on-pump and off-pump. In reviewing the literature it is notable how ill-defined and unspecific the phrase 'CABG surgery patients' is used; few studies provided full details on the type of CABG surgery participants underwent. In addition, even if participants were characterised as, for example, elective cases, more detailed information is not provided, such as length of time spent on the waiting-list. Nor is it clear how long after a patient's first manifestation of CHD the surgery was performed, which would provide an indication of the chronicity of the underlying cardiac disease. This information is necessary to make direct comparisons in prevalence rates since the sample demographic is likely to vary according to the type of procedure performed. Another inclusion criteria that varies across studies is the sex of participants, with some studies including only men (Beresnevaitė et al., 2010; Burg, Benedetto, Rosenberg, et al., 2003), one study including only women (Doering et al., 2006) and the remainder using mixed sex samples. Depression has been shown to be more common in female than male CABG surgery patients (Phillips-Bute et al., 2008), but some studies report mixed findings (Mitchell et al., 2005) and most studies report prevalence rates irrespective of sex, making it hard to disentangle the relationship entirely. Psychiatric history and current use of depression treatment is also inconsistently taken into account across studies, with only the studies by Blumenthal and colleagues (Blumenthal et al., 2003) and Phillips-Bute and colleagues (Phillips-Bute et al., 2008) excluding those participants being treated for depression at study entry, which may otherwise mask depression symptoms. Despite the methodological limitations making it difficult to draw robust conclusions, it seems clear that depression is commonly experienced by cardiac patients both before and after CABG surgery.

1.4.2.2 Depression and cardiac morbidity

Depressive symptoms after CABG have been shown to significantly increase the risk of graft disease progression (Wellenius et al., 2008) and hospital readmissions (Tully, Baker, Turnbull, & Winefield, 2008). In addition, depression has been associated with poorer functional recovery such as shorter walking distances (Doering, Moser, Lemankiewicz, Luper, & Khan, 2005) and poorer physical recovery including more infections and impaired wound healing (Doering, Martínez-Maza, Vredevoe, & Cowan, 2008; Doering et al., 2005; Kendel et al., 2010).

In another study, Burg and colleagues (Burg, Benedetto, Rosenberg, & Soufer, 2003) found that patients who were depressed pre-surgery had higher levels of medical complications during the six months following surgery, and were more likely to report poor quality of life and worse recovery. Moreover, two years after surgery pre-surgery depression was linked to greater risk of death (Burg, Benedetto, & Soufer, 2003).

Two landmark studies in the *Lancet* documented the impact of depression on survival following CABG. Blumenthal and colleagues (Blumenthal et al., 2003) studied 817 patients awaiting CABG for an average follow-up of 5.2 years. In models adjusting for age, sex, number of grafts, diabetes, smoking, LVEF, and previous MI, patients with pre-CABG depression had increased risk of death from all causes compared to those without depression. Specifically, these authors also reported a dose-response relationship such that severity of depression was predictive of mortality, with moderate to severe depression (n = 97) significantly increasing risk of all-cause mortality (HR 2.37, 95% CI 1.40-4.00, p = 0.001) while mild depression (n = 213) did not (HR 1.08, 95% CI 0.70-1.67, p = 0.723). In secondary analyses, event rates were analysed comparing the mortality rates between those patients who had pre-CABG depression but had remitted at six-month follow-up (10% of whom died), those who were never depressed (10% of whom died), those with new onset depression post-CABG (14% of whom died), and those who were persistently depressed (19% of whom died), indicating that there was a trend towards those with more severe depression (either persistent or new onset) being at greatest risk. However, due to the small event rate, further studies are required before firm conclusions can be drawn. Another limitation of this study includes the reliance on a questionnaire measure of depression, with no clinical diagnostic tool being used. The second study published was by Connerney and colleagues (Connerney et al., 2001) who used standard diagnostic interviews in 309 patients in the days following CABG assessing for both current and history of depression. Patients were followed up at six and 12 months. They found that post-CABG depression was an independent risk factor for cardiac events after controlling for other risk factors including disease severity. However, they did not distinguish between those with recurrent as opposed to new onset depression. In addition, this study only measured depression post-operatively and therefore the progression of depression symptoms over time was not able to be studied objectively.

While there is extensive research using ACS patients, there is a distinct lack of research investigating depression to the same level of detail in CABG patients. For example, does depression with onset pre-CABG and post-CABG follow similar patterns to that observed in MI patients? Are some types of depression symptoms more cardiotoxic than others in CABG patients? Can depression in CABG patients be effectively treated? Taken together, these questions again ask whether depression in cardiac patients can be seen as distinct from that

observed in psychiatric populations. Depression in CABG patients remains relatively underexplored, indeed one of the few studies to date which has begun to address these issues has been published recently (Connerney, Sloan, Shapiro, Bagiella, & Seckman, 2010). In particular, these authors were interested in unpicking the relevance of depression symptom subtypes and depression onset in predicting cardiac mortality after CABG.

In order, to distinguish between the different depression onset subtypes, a recent paper by Zuidersma and colleagues (Zuidersma et al., 2011, p.228) devised a schematic representation to neatly depict the different depression onset subtypes, which is displayed in Figure 1.2. This figure shows how we can distinguish between first-ever depression as opposed to recurrent depression, post-CABG onset depression as compared to pre-CABG onset depression and incident (or new onset) depression versus non-incident depression. Depression as a consequence of a cardiac event refers to post-CABG onset and could be either first-ever (i.e. incident) or recurrent.

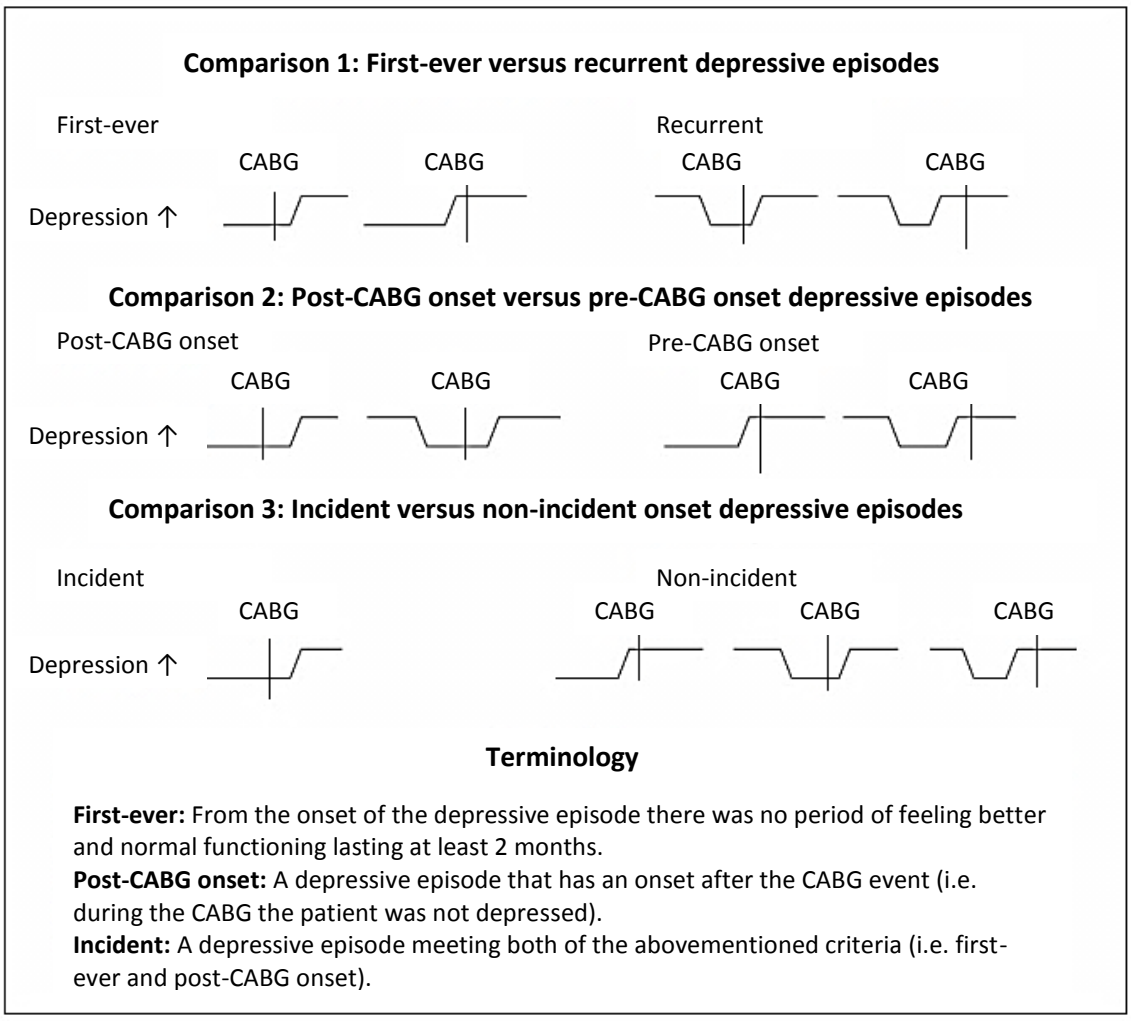

FIGURE 1.2: MODELS OF DEPRESSION IN CABG

(Adapted from: Zuidersma et al., 2011, p.228)

In a 10-year follow-up study of the original cohort (Connerney et al., 2001), these authors found post-CABG depression was significantly associated with elevated cardiac mortality. Importantly, these authors further explored the relevance of depression onset for prognosis. In models adjusted for sex, age, ejection fraction and diabetes, those patients with new onset depression (*n* = 39) (HR 2.12, 95% CI 1.09-4.15, *p* = 0.03) had twice the risk of cardiac mortality compared with those patients who had never been depressed (*n* = 198). Recurrent depression (*n* = 24) was not significantly different to the never depressed group (HR 1.72, 95% CI 0.78-3.80, *p* = 0.18). These authors also compared depression symptoms, finding cognitive/affective but not somatic symptoms to be predictive of cardiac mortality in models adjusted for confounders. These results have been supported by another recent study of morbidity and mortality in CABG patients, which also found cognitive depressive symptoms to be particularly damaging (Tully, Winefield, Baker, Turnbull, & De Jonge, 2011). These findings are contradictory to findings from MI patients and need to be corroborated by future research. It is also important to note that not all studies have supported the association between depression and increased mortality following CABG (Borowicz et al., 2002; Peterson et al., 2002). However, these studies may have been under powered to find a significant effect. The study by Borowicz and colleagues studied the association between depression one month following CABG surgery and cardiac morbidity and mortality up to five years following surgery; however there were only 41 cases of depression, which may explain the null findings. The study by Peterson and colleagues investigated the effect of new onset depression cases at six months post-CABG on mortality at three-year follow-up, producing results of borderline significance (*p* = 0.054); these results may similarly be explained by the small number of depression cases (*n* = 12). In addition, a recent study has also noted the high prevalence of complicated grief in depressed CABG patients (Ghesquiere et al., 2011). Complicated grief is classified in the DSM-IV as a bereavement-related adjustment disorder, characterised by an inability to accept the death of a loved one, extreme feelings of sorrow and emotional pain, and a lack of future planning in one's own life. The conceptual overlap that complicated grief has with depression demands awareness so that patients are not misdiagnosed in research studies.

Interventions designed to improve emotional wellbeing after CABG have shown mixed results. Positive results were found by Freedland and colleagues (Freedland et al., 2009) who conducted a 12-week randomised controlled trial to assess the efficacy of two different types of non-pharmacological treatment for depression after CABG, in comparison to usual care controls. Results showed significantly higher rates of remission in depressed patients who received cognitive behavioural therapy (*n* = 41) or supportive stress-management (*n* = 42) compared to usual care controls (*n* = 40), at three- and nine-month follow-up. A more recent

intervention study, the Bypassing the Blues trial, investigated the impact of a telephone delivered collaborative care intervention in post-CABG depressed patients (*n* = 150), compared to usual care depressed controls (*n* = 150) and non-depressed controls (*n* = 150). The primary aim of this study was to improve health-related quality of life, with secondary aims to improve mood, cardiovascular morbidity, employment, health service use and treatment costs. The intervention group received a tailored nurse-led telephone delivered programme for up to eight months following CABG. Specifically, they provided both written and oral educational materials and offered a variety of treatment options including initiation and adjustment of antidepressant medications, referral to community mental health services and, where appropriate, watchful waiting. Results showed significant improvements in health-related quality of life and mood in the intervention group compared to usual care controls, however the effect was stronger for men than women (Rollman & Herbeck Belnap, 2011; Rollman et al., 2009). Other studies have produced less convincing results. For example, the results of a home-based psychological and informational intervention programme by Lie and colleagues (Lie, Arnesen, Sandvik, Hamilton, & Bunch, 2007) reported mixed results, finding that while significant improvements in depression symptoms over the six-month follow-up period were observed, there were no significant differences between the intervention and control arms of the study. An intervention administered prior to surgery was able to reduce depression compared to usual care, but these effects were not maintained in the post-operative period (Furze et al., 2009). Another study reported damaging results of a behavioural risk modification programme, with usual care controls improving significantly more than the intervention group (Sebregts, Falger, Appels, Kester, & Bär, 2005). In conclusion, there is some evidence to suggest that depression may be amenable to change in these patients, but more work is needed to explore the best treatment methods. Research exploring the mechanisms underpinning the relationship between depression and poor cardiac outcomes would also likely aid these interventions, providing a theoretical framework for treatment strategy.

1.5 Anxiety, negative affect and coronary heart disease

The depression literature by far outweighs studies of other psychological disorders in relation to poor cardiac outcomes. However, recent attention has also highlighted the role of anxiety and its prevalence in CHD patients. Some authors propose that depression and anxiety should be conceptualised as a single state of negative affectivity. These arguments are outlined below.

1.5.1 Anxiety

Anxiety disorders refer to a collection of different diagnoses, including generalised anxiety disorder (GAD), panic disorder, phobic disorder and post-traumatic stress disorder, among others. Common to all anxiety disorders are intense and excessive feelings of fear and worry that impact on an individual's ability to function as usual in everyday life. According to the DSM-IV, GAD refers to chronic feelings of anxiety and worry that are not specific to a single object or situation, that are difficult to control, and that persist on more days than not for at least six months. At least three accompanying symptoms must also be present, to include: feelings of restlessness or being 'on edge', fatigue, difficulty in concentrating, irritability, muscle tension and sleep disturbance. In panic disorder, an individual suffers from a discrete period of intense fear or discomfort that arises quickly and peaks within about 10 minutes of onset. Such episodes or 'panic attacks' are accompanied by at least four somatic (e.g. palpitations, shortness of breath) or cognitive symptoms (e.g. derealisation or depersonalisation, fear of dying).

There is growing evidence surrounding the role of anxiety in predicting poorer prognosis in those patients with CHD (Player & Peterson, 2011). For example, in patients with stable heart disease, anxiety was able to predict increased risk of cardiac events in two large-scale prospective studies (Martens, de Jonge, et al., 2010; Moser et al., 2011). Moreover in ACS patients, a recent meta-analysis concluded that anxiety following MI is associated with a 36% increased risk of adverse cardiac outcomes (Roest, Martens, Denollet, & de Jonge, 2010). These observations in MI patients were recently confirmed in a 10-year follow-up study of 438 MI patients showing that three months after MI, those patients with GAD (n = 24) were almost twice as likely to experience adverse events (mortality or cardiac-related hospital readmissions) than those without GAD, even after controlling for baseline disease severity, demographic and depression variables (Roest, Zuidersma, & de Jonge, 2012). Similar observations have also been reported in CABG patients. Tully and colleagues (Tully, Baker, & Knight, 2008) found that those patients with higher levels of pre-operative anxiety were at greater risk of mortality (HR 1.88, 95% CI 1.12–3.17, p = 0.02). Another study has also confirmed the effect of anxiety on mortality in patients who had previously undergone CABG surgery (Rosenbloom, Wellenius, Mukamal, & Mittleman, 2009). Oxlad and colleagues showed anxiety in the immediate post-operative period was associated with greater hospital readmissions six months after CABG (Oxlad, Stubberfield, Stuklis, Edwards, & Wade, 2006). It is not yet clear to what extent anxiety predicts cardiac morbidity and mortality over and above depression and to what extent they can be considered overlapping disorders.

1.5.2 Negative affectivity: unifying psychological constructs

Depression and anxiety often present as co-morbid conditions, which may partly be explained by the common symptom criteria for both disorders. Theories have been proposed in which anxiety and depressive disorders should be viewed collectively as part of a higher-order diagnosis of negative affectivity, characterised by heightened levels of distress, negative emotionality and neuroticism (Andrews et al., 2009; Brown & Barlow, 2009; Prenoveau et al., 2010; Watson, 2009). Symptom clusters within negative affectivity have been identified and have been described as 'anxious-misery', including DSM-IV diagnoses of major depression, dysthymia, GAD and post-traumatic stress disorder, and 'visceral fear' including panic and phobic anxiety disorders (Krueger, 1999). Another method of grouping disorders does not look for symptom clusters, but instead identifies unique phenotypic[2] variance that best represents each disorder. For example, low positive affect has been shown to be characteristic of depression, whereas somatic hyperarousal is a key trait in panic disorder (Prenoveau et al., 2010; Watson, 2009).

These issues have recently been investigated in 158 CHD patients prior to undergoing CABG surgery (Tully & Penninx, in press). Findings showed that symptom scores for somatic anxiety and low positive affect scores were able to detect cases of panic disorder and depression respectively. These authors did not find trait negative affect, anxious-misery or visceral fear to be an optimal screen for any emotional disorder. However, it is not clear to what extent such classifications can predict cardiac outcomes over and above the current depression and anxiety definitions. As such, more work is needed to explore the differential effects of anxiety and depression in greater detail, as it is unclear whether negative affectivity is more important than either depression or anxiety alone.

1.6 Chapter summary

Depression and CHD are common co-morbidities which present a challenge to researchers to understand why depression in combination with CHD increases morbidity and mortality in both ACS and CABG patients. Methodological issues arise in terms of how best to operationalise depression and in understanding to what extent depression presents a unique predictor of cardiac prognosis over and above other psychological disorders, including depression, vital exhaustion, complicated grief and anxiety. These problems all need to be kept in mind when interpreting the literature in this area.

To understand the interaction between depression and CHD not only requires understanding of the direction of any causal relationship, but also the underlying mechanisms

[2] Phenotype refers to observable characteristics or traits.

and pathways involved. Only by doing this are we able to devise targeted and efficient interventions to tackle morbidity and mortality in these patients. These issues will be explored in the next chapter.

Chapter 2. Literature review (II): Understanding causal mechanisms

2.1 Introduction

Both antecedent and consequence models have been investigated, such that depression has been shown to be both a precursor to and consequence of CHD; these models are depicted in Figure 2.1. The literature relevant to both these models will be described below discussing whether there is consistent and reliable evidence in favour of depression causing both clinical and subclinical manifestations of CHD, or whether it is instead better to view depression as a consequence of underlying CHD disease processes (for a review see Steptoe, 2007; Williams & Steptoe, 2007). Methodological considerations will also be highlighted, in particular the timing of depression assessment. In addition, depression will be described as a prognostic factor, explaining the association between CHD and poor cardiac outcomes in some patients. Finally, cardiac surgery will be described as a model in which we can better elucidate the causal and mechanistic pathways linking depression and poor cardiac outcomes.

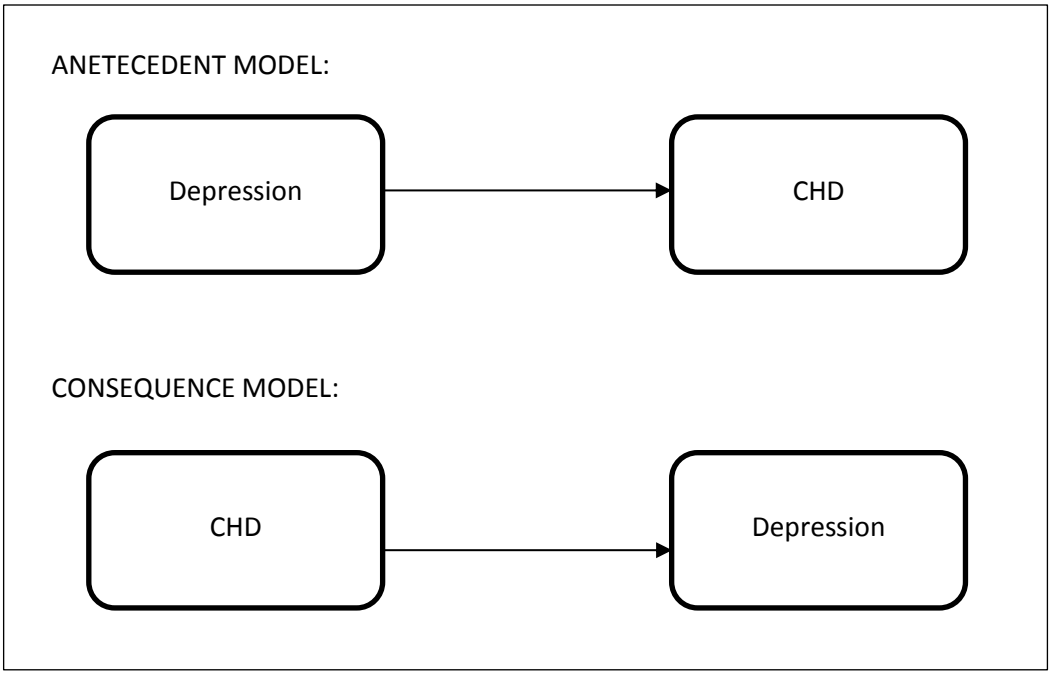

FIGURE 2.1: ANTECEDENT AND CONSEQUENCE CAUSAL MODELS OF DEPRESSION AND CHD

2.2 Determining causality

Depression as an aetiological factor in the development of CHD has been subject to much interest and debate. Causality can be investigated using different research methods to establish whether those who are depressed or who have elevated depression symptoms are at increased risk of cardiac events in the future. The studies discussed here all used a clinical measure of CHD, with objectively verifiable outcomes such as MI, in order to transcend issues surrounding self-report data and recall bias. The earliest studies to suggest a link between psychological attributes and cardiac health were cross-sectional, showing depression to be more common in CHD patients compared to healthy controls. For example, the Interheart study used a case-control design with data from across 52 countries and over 12 thousand first-time MI patients and matched controls. Results showed a 9% population attributable risk (PAR)[3] of depression symptoms being associated with MI (Rosengren et al., 2004). However, studies of this type are limited since they are unable to determine the temporal relationship, that is whether depression precedes CHD onset or vice versa.

Other studies have made use of longitudinal designs, following a cohort of participants over time to determine the onset of depression in relation to the onset of cardiac symptoms. One such study showing a prospective association between depression and risk of future cardiac events was by Anda and colleagues (Anda et al., 1993), who used USA data from 2832 participants in the National Health and Nutrition Examination Survey cohort. They followed individuals free from cardiac and other chronic illnesses at baseline for an average of 12.4 years, finding that depression symptoms were associated with a 50% increased risk of cardiac mortality compared to those who were not depressed (relative risk 1.5, 95% CI 1.0-2.3). UK data have also replicated these findings (Surtees et al., 2008), showing in individuals free from CHD at baseline, elevated depressive symptoms in the year preceding baseline assessment was associated with greater risk of cardiac mortality over a median follow-up period of 8.5 years. These results have also been supported more recently (Brown et al., 2011) and have been subjected to systematic review (Kuper et al., 2002; Wulsin & Singal, 2003) and meta-analysis (Nicholson, Kuper, & Hemingway, 2006; Rugulies, 2002; Van der Kooy et al., 2007), also finding in favour of this association, independent of possible confounders. Indeed, the systematic review of prospective cohort studies by Kuper and colleagues (Kuper et al., 2002) demonstrated that in individuals free from disease at baseline, the presence of depression symptoms was related to an increased risk of future cardiac events, both fatal and non-fatal, up to 40 years later (c.f. Ford et al., 1998). However, these authors have also cautioned that careful interpretation of the literature is required, and while results from their horizontal

[3] PAR can be defined as the proportion of all cases attributable to the given factor, if causality was proven.

systematic review show a relative risk of 1.9 for CHD in depressed patients, they discuss how the European guidelines for CHD prevention (De Backer et al., 2003) prioritise depression over and above other important risk markers such as the inflammatory marker, C-reactive protein (CRP) (Kuper et al., 2009). Inflammatory processes are discussed in this literature review in Section 2.6.4.

Other authors have also argued that care must be taken when considering these results, as heterogeneity between studies exists. For example, some studies have found that major depression carries more risk than minor depression (Penninx et al., 2001), and clinical depression diagnosed by interview has been reported to be a better predictor than depressive symptoms as measured using standardised questionnaires (Rugulies, 2002). Moreover, the review by Kuper and colleagues (Kuper et al., 2009) pointed to problems with reverse causality and publication bias in the depression-CHD field. Other methodological issues also exist in this literature, as discussed in a review by Frasure-Smith and Lespérance (Frasure-Smith & Lespérance, 2005). These authors argue that despite the large number of empirical studies and reviews showing in favour of depression as a risk factor for future cardiac mortality, cardiologists have yet to seriously take note because of issues surrounding low sample sizes, the heterogeneity of depression measures, frequent repeat publications using the same data, as well as inconsistencies in the control of covariates. Consequently, researchers need to pay greater attention to standardising their approach to this issue. Regardless, the weight of evidence does conclude in favour of depression preceding the onset of cardiac events. However, the relationship becomes less clear-cut when the aetiology of CHD is considered as a process which begins in childhood.

Studies have sought to investigate whether depression is involved in the long term evolution of cardiac disease as well as being related to its clinical manifestations. These studies have become possible in recent years with the advent of non-invasive methods of measuring atherosclerosis, including measures of intima-media thickness using ultrasonography techniques and measures of coronary artery calcification using computed tomography. Research of this type has been able to add to our understanding of the temporal relationship between depression and CHD. Atherosclerosis is a progressive disease, and post-mortem evidence of young (aged 15-34 years) victims of accidental or violent death has shown the extent of stenosis to be associated with risk factors such as smoking and high serum cholesterol (Zieske, Malcom, & Strong, 2002). This means it is difficult to establish that depression precedes the development of atherosclerotic disease underlying CHD, even in a prospective study that involves participants who are apparently healthy at baseline. For example, it could be argued that subclinical CHD causes biological changes, which in some susceptible individuals can cause depression. In this scenario, depression would then act to

compound these biological changes, perhaps also causing unhealthier lifestyle choices and eventually leading to clinical manifestations of the disease in these vulnerable individuals.

However, this debate is largely hypothetical and has not been supported in a recent large-scale cohort study which tracked the progression of subclinical atherosclerosis on incident (i.e. new onset) depression risk in 3564 community-dwelling older adults over a six-year follow-up (Newson et al., 2010). This study found no evidence to suggest that underlying subclinical atherosclerosis increased the risk of incident depression onset, concluding that depression either contributes to vascular burden or that both are caused by a third, unmeasured, biological process. It is important to note that this study used measures of extracoronary atherosclerosis as a proxy measure of coronary atherosclerosis. Another prospective study has supported the association between higher baseline levels of depression with greater subclinical atherosclerosis at three-year follow-up, using a measure of carotid intima-media thickness in 324 healthy, community dwelling men and women (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007). Others studies have used cross-sectional designs, with mixed results. For example, one study found depressed patients to be at greater risk of subclinical heart disease, as measured by carotid intima-media thickness, compared to healthy controls (Seldenrijk et al., 2010), while others have not supported the association using measures of coronary calcification (Diez Roux et al., 2006; Matthews, Owens, Edmundowicz, Lee, & Kuller, 2006). It is not clear to what extent the different measurement techniques explain the disparate findings. Moreover, single assessments of depression may raise problems regarding reliability and validity, since mood is likely to be affected by environmental and situational factors, and previous research has shown multiple assessments of depression, but not single assessments, to be associated with the extent of coronary artery calcification (Hamer, Kivimaki, Lahiri, Marmot, & Steptoe, 2010). Future work is needed to address these methodological issues, however it seems plausible from these initial studies that depression contributes not only to the clinical manifestations of CHD, but also to the underlying disease pathology.

Another methodological concern is with regards to the timing of depression in relation to the cardiac event (Steptoe, 2007). This is relevant since depression that is particularly cardiotoxic may have certain features that distinguish it from other, less cardiotoxic, forms. For example, it has been thought that depression may be causally related to acute coronary events only in those with advanced disease. However, the prospective cohort study by Anda and colleagues (Anda et al., 1993) accounted for this by excluding those who had died within two years of the psychological assessment, finding the relationship between depression and future cardiac mortality remained. As such it is thought that depression is an important predictor of cardiac endpoints even for those with less advanced disease. Moreover, the problem of

singular assessment points is also relevant here, since it is possible that depression that varies according to its transience and severity may have differential effects on CHD outcomes. Penninx and colleagues (Penninx et al., 1998) analysed CHD events in a sample of 3701 older adults with repeated measurements of depression symptoms over a six-year period. These authors were able to show that CHD risk was greatest for newly depressed participants as opposed to those with a more chronic course of depression symptoms. This supports the earlier discussion (Section 1.4.1) that depression with new onset may be particularly damaging. Indeed, another possibility is that the onset of a depressive episode could actually act as a trigger for an ACS; a trigger being an external stimuli, emotional state, or other activity that provokes an acute pathophysiological change directly causing the start of a coronary event (Strike & Steptoe, 2005). Steptoe's group found that in 295 men and women admitted to hospital for ACS, who were interviewed regarding their emotional state in the two hour period prior to symptom onset, that 18.2% had experienced depressed mood in this hazard period (Steptoe, Strike, Perkins-Porras, McEwan, & Whitehead, 2006). This highlights the fact that depression may not only have accumulative effects but may also have an acute effect in vulnerable individuals. Taking all these issues into account, it seems that methodological issues surrounding the measurement of depression are key to understanding its causal relationship with CHD.

The difficulty arises when one attempts to reconcile our understanding that depression leads to greater cardiac risk, with the literature previously described in Chapter 1, in which an ACS and CABG surgery have both been found to be capable of triggering a first-time depressive episode (see Section 1.4). In a systematic review, incident (i.e. new onset) depressive episode patients were shown to have a less severe course and were less likely to have a previous history of MI, than non-incident depressed ACS patients (Zuidersma et al., 2011). The reasons for this are not clear, but as alluded to earlier, it could be that new onset/incident depression is distinct from, or a unique subtype of, psychiatric depression in cardiac patients. These issues are part of an on-going debate within the literature (Bech, 2010; Ormel & de Jonge, 2011; Poole, Dickens, et al., 2011). The issue of causality has yet to be fully resolved, and research has meanwhile focussed on depression as a prognostic marker in CHD.

2.3 Depression as a prognostic factor in CHD

Depression has been described as a prognostic factor contributing to, or directly causing, poor cardiac outcomes in CHD patients. Opponents to this hypothesis would argue that a direct relationship between CHD and poor cardiac outcomes exists, such that the relationship between CHD and recurrent cardiac events is due to underlying coronary artery disease severity. Recurrent cardiac events and mortality are predicted by the extent of coronary

stenosis and by features of the ACS such as impaired left ventricular function. In a meta-analysis of depression as a prognostic risk factor in CHD (all-cause mortality or fatal CHD), it was found that control of underlying heart disease is salient but inconsistently taken into account in studies of this type (Nicholson et al., 2006). These authors reported that, although the mortality risk is still present, it is reduced by 48% when LVEF is included in analyses. Surprisingly, only eight studies out of the 34 included in this meta-analysis actually reported LVEF adjusted analyses, highlighting the need for careful interpretation of the work in this area.

A number of composite measures of risk have also been developed such as the Global Registry of Acute Events (GRACE) index that uses nine variables to predict survival, namely older age, history of MI, history of heart failure, increased pulse rate at presentation, lower systolic blood pressure at presentation, elevated initial serum creatinine level, elevated initial serum cardiac biomarker levels, ST-segment depression on presenting electrocardiogram, and not having a percutaneous coronary intervention performed in hospital (Eagle et al., 2004). The predictive value of the index for short- and longer-term morbidity has been confirmed in independent studies (Bradshaw, Ko, Newman, Donovan, & Tu, 2006; Tang, Wong, & Herbison, 2007). Lett and colleagues (Lett, Ali, & Whooley, 2008) found no relationship between depression and disease severity in a sample of over 1000 outpatients with stable CHD. A more recent study of 457 patients with ACS showed that that even after adjusting for GRACE scores, the relationship between depression and future cardiac morbidity remained significant (Kronish, Rieckmann, Schwartz, Schwartz, & Davidson, 2009). Meurs and colleagues (Meurs, Zuidersma, Dickens, & de Jonge, in press) used data from 494 MI patients and studied associations of somatic/affective and cognitive/affective depression with recurrent cardiac events, before and after controlling for GRACE scores. Findings showed controlling for GRACE score did not affect the relationship of total depression score nor cognitive/affective depression on prognosis and only partly attenuated the risk of somatic/affective depression on prognosis. Consequently, depression can be considered a causal factor in cardiac prognosis, and a number of different mechanistic pathways have been proposed (see Sections 2.5 and 2.6). We can gain a better understanding of these pathways by investigating these issues in different cardiac patient groups. In the following section, the case of cardiac surgery will be described.

2.4 Depression and cardiac prognosis: The case of cardiac surgery

The relative dearth of literature using CABG patients to explore the CHD-depression relationship is surprising considering the several advantages that a CABG population offers over MI patients. One difficulty in interpreting findings from ACS patients is that mental health

before the cardiac event is assessed retrospectively. Although this criticism could also be levelled at the Connerney studies (Connerney et al., 2001; Connerney et al., 2010), this problem has the potential to be overcome in studies of CABG patients, since measures of mood can be taken beforehand. Another problem is that the temporal relationship of depression and CHD is not clear and it is difficult to assess in ACS patients because of problems with defining the direction of the causal pathway: does depression cause CHD or vice versa? Since we can get true baseline measures of depression and disease severity (including measures of non-coronary disease) and because CABG actually physically manipulates the level of coronary stenosis, by studying CABG patients we are able to tease out the long-term effects of disease severity on depression and are more able to elucidate causal pathways. It is not clear why some patients who have CABG develop new onset depression: if it is due to underlying disease severity we would expect alleviation of the physical burden of the disease to lead all patients to show at least some improvements after surgery. Since this is not the case, other processes must be at play and potential mechanisms include demographic, clinical, behavioural, social, cognitive and biological factors. These factors have not been fully investigated in CABG patients, with pre-operative levels not adequately measured and perioperative factors rarely considered. The existing literature will be discussed in the following sections.

However, throughout the subsequent discussion, several caveats need to be borne in mind. First, even though we can measure depression pre-operatively, this does not mean patients are being tested in a disease-free state. CABG surgery patients often have multivessel disease and many will have experienced an MI prior to revascularisation; therefore it is possible for pre-CABG depressed patients to also be classified as post-ACS depressed. Disentangling the relative risk associated with post-CABG depression over and above post-ACS depression thus becomes more complex in these patients. Moreover, even in those patients who have not experienced an MI, depression has been associated with greater subclinical disease (e.g. Stewart et al., 2007). Therefore, care needs to be taken to characterise depressed CABG patients as a heterogeneous group and the effects of depression need to be fully explored in relation to all these contributing factors.

Second, although post-ACS depression provides a useful model on which we can base our research rationale and hypotheses, this does not amount to post-ACS and post-CABG depression being one in the same, even in new onset cases. While both ACS and CABG surgery provide a huge assault to the body's resources, the psychological environment is likely to differ between the two scenarios. In particular, fear of dying in patients who have experienced an MI is thought to be an important factor in post-ACS depression (Steptoe et al., 2011; Whitehead, Strike, Perkins-Porras, & Steptoe, 2005) and ACS is now considered as a potential trigger for

the development of post-traumatic stress disorder (Wikman et al., 2011); however it is unclear whether CABG surgery provides the same stimulus. While there are likely to be similarities between the two patient groups, it is important to not interpret findings from CABG patients as being 'true' simply because they are in line with ACS patient findings, just as it is important not to discount incongruous findings.

The final caution is that it is not yet clear whether CABG surgery patients tell us anything over and above patients undergoing other major surgery. For example, depression has been shown to increase the risk of mortality in patients undergoing orthopaedic surgery (Guerini, Morghen, Lucchi, Bellelli, & Trabucchi, 2010), organ transplant surgery including kidney, liver and heart (Corruble, Barry, Varescon, Durrbach, et al., 2011; Corruble, Barry, Varescon, Falissard, et al., 2011; Havik et al., 2007), as well as a myriad of other surgical procedures (Abrams, Vaughan-Sarrazin, & Rosenthal, 2010). Nor is it clear to what extent CABG surgery differs from other types of cardiac surgery. While the majority of work has focussed on depression in CABG surgery patients, recent evidence suggests similar effects of depression on mortality in percutaneous coronary intervention patients too (Damen et al., in press). Regardless of this, a CABG population presents a useful model in which we can unpick some of the mechanistic pathways linking depression with future morbidity and mortality in the physically ill, and is made more relevant since cardiac disease and revascularisation treatment is so common. Moreover, from a pragmatic perspective, since CABG surgery offers a population at high risk of depression, it presents a good opportunity to recruit enough cases to demonstrate an effect, which can contribute to the cardiac literature as well as the dialogue on the commonality of disease processes (Field, 2001; Southerland, Taylor, Moss, Beck, & Offenbacher, 2006).

2.4.1 Demographic risk factors

Gender and age have been recently reviewed as risk factors for post-operative depression in CABG patients, with results proving inconclusive (McKenzie, Simpson, & Stewart, 2010). Gender has been shown to be a risk factor in CABG patients, with women thought to be at greatest risk of experiencing depressive symptoms both pre-operatively (Dunkel et al., 2009) and post-operatively (Doering et al., 2006). However, not all studies have supported this post-operative association; for example Mitchell and colleagues (Mitchell et al., 2005), found no gender effect, with women showing a significant improvement in depression symptoms from pre- to post-CABG time points compared to men. Moreover, negative sequelae of depression in CABG patients have been shown for both women (Phillips Bute et al., 2003) and men (Burg, Benedetto, Rosenberg, et al., 2003; Burg, Benedetto, & Soufer, 2003) and Connerney and colleagues (Connerney et al., 2010) found no effect of gender on either cardiac or all-cause

mortality in CABG surgery patients. Younger age has also been highlighted as a risk factor for depression in CABG patients (Mallik et al., 2005), although some authors have not reported this effect (Burg, Benedetto, Rosenberg, et al., 2003; Pirraglia et al., 1999) and still others have found the relationship to be inconsistent (Timberlake et al., 1997).

Socioeconomic position has also been implicated in the link between depression and CHD. Data from the Whitehall II epidemiological study of UK civil servants, have shown that employment grade is prospectively associated with mental health in patients with known CHD, such that those with lower employment grade showed greater deterioration in mental health functioning during the 12-year follow-up than those in the highest grades (Sacker, Head, & Bartley, 2008). In a sample of 298 men and women admitted to hospital with ACS, it has been reported that low household income was associated with elevated depression symptoms on the BDI at three weeks, six months and one year following ACS and this effect was independent of other demographic and clinical risk factors as well as history of depression (Steptoe et al., 2011). The same effect on depression was not observed for another marker of socioeconomic position, education. Other studies have also found education to be inconsistently associated with depression in ACS patients. For example, Frasure-Smith and colleagues (Frasure-Smith et al., 1993) found no difference in in-hospital depression between those with low and high levels of education, and Martens and colleagues (Martens, Smith, Winter, Denollet, & Pedersen, 2008) found a similarly null effect of education on persistent depression over the 12 months following ACS. However, another study did find a difference by education levels, finding new onset and recurrent depressed patients to be more likely to have less than 12 years of education than their non-depressed counterparts (Carney et al., 2009).

When socioeconomic status has been taken into account in relation to depression in CABG patients, results are mixed. For example, some have shown that low education is associated with greater risk of pre-operative depression (Dunkel et al., 2009; Pirraglia et al., 1999), but not others (Burg, Benedetto, Rosenberg, et al., 2003). In terms of post-operative depression, Connerney and colleagues (Connerney et al., 2001) reported no difference in education levels between depressed and non-depressed CABG patients and this has been found by others (Pirraglia et al., 1999). The mixed results may be a result of education being a weak marker of socioeconomic position in this patient group, since most will have completed formal education several decades prior to the onset of cardiac disease (Steptoe et al., 2011). More studies are needed to determine to what extent socioeconomic position mediates or moderates the effect of depression on cardiac prognosis.

2.4.2 Clinical risk factors

Depression has been shown to be associated with traditional cardiac risk factors including smoking, diabetes mellitus and hypertension (Carney, Freedland, Miller, & Jaffe, 2002) and also cardiac medications such as statins and beta-blockers. Statins have actually been shown to have a protective effect for depression, with several longitudinal studies finding use of statins to confer a risk reduction for depression onset in CHD patients (Otte, Zhao, & Whooley, 2012; Stafford & Berk, 2011). In contrast, the literature on beta-blockers and depression is less clear, with some early evidence suggesting they may be capable of inducing mood disturbance (Greenblatt & Koch-Weser, 1974). More recently, evidence from systematic reviews has not substantiated this link, although the popular misconception persists in prescription practice (Ko et al., 2002). Nevertheless, these clinical risk factors need to be considered when investigating the association between depression and cardiac outcomes.

In the CABG literature, pre-surgical clinical factors such as co-morbidities and pre-existing cerebrovascular disease, aspects of the surgical procedure itself, and sequelae such as inflammatory responses and cardiac arrhythmia, may contribute to impairment after surgery (Karimi et al., 2008; Murphy, Ascione, Caputo, & Angelini, 2003; Newman et al., 2006; Sadeghi, Sadeghi, Mood, & Karimi, 2002). Despite the importance of these factors, their relationship with emotional adjustment has been variable. For example, Dunkel and colleagues (Dunkel et al., 2009) studied 1238 MI patients awaiting CABG surgery, finding clinical factors to be predictive of pre-operative depression status. These authors reported that dyspnoea (shortness of breath) on exertion and at rest, history of previous MI, co-morbidities and use of tranquilisers, were all significantly associated with pre-operative depression risk. Wellenius and colleagues (Wellenius et al., 2008) reported depression to be independently associated with graft disease progression after controlling for previous medical history, blood pressure and renal function. However, the effect was attenuated when aggressive lipid lowering medication was taken into account. Another study reported no quality of life differences after surgery when comparing on-pump and off-pump CABG patients (Motallebzadeh, Bland, Markus, Kaski, & Jahangiri, 2006). This suggests that surgical technique may not be predictive of emotional adaptation following surgery. Another clinical risk factor that may be relevant is metabolic syndrome, which refers to a combination of symptoms including diabetes or insulin resistance, hypertension, dyslipidaemia and obesity (for a review of different classification systems see Beilby, 2004). Metabolic syndrome has been shown to partly mediate the link between depression and subclinical atherosclerosis (Hamer, Malan, Harvey, & Malan, 2011) and depression and clinical disease (Vaccarino et al., 2008), but has yet to be studied in CABG patients. In summary, it is not clear to what extent clinical risk factors impact on patient quality

of life and emotional responses following CABG surgery and whether such factors are best conceptualised as confounders or mechanisms in this relationship.

2.5 Depression and cardiac prognosis: Non-biological mechanisms

The definition of mechanisms as mediators described by Skala and colleagues (Skala, Freedland, & Carney, 2006) will be used here. They describe a mechanism to be a variable on the causal pathway between depression and cardiac prognosis (illustrated in Figure 2.2, showing the direct and indirect pathways). Such mechanisms are usually identified since they are either predictive of cardiac outcomes or are aetiologically involved in them. However, to be a valid mechanism, mediation must also be upheld such that depression precedes the candidate mechanism, and in turn the mechanism precedes the cardiac outcome. In statistical analysis, partial mediation occurs when the addition of the mechanism to the model attenuates the association between depression and the cardiac outcome, whereas full mediation entirely removes this association. Since the majority of studies only report partial mediation, other mechanisms are usually also implicated in the causal pathway. As such it is important to consider how individual mechanisms may be interrelated. The following section will describe potential mechanisms and their possible linkages. Principally under discussion is the literature in CABG patients, but where evidence is scarce, work on ACS patients will also be drawn upon to add to the discussion.

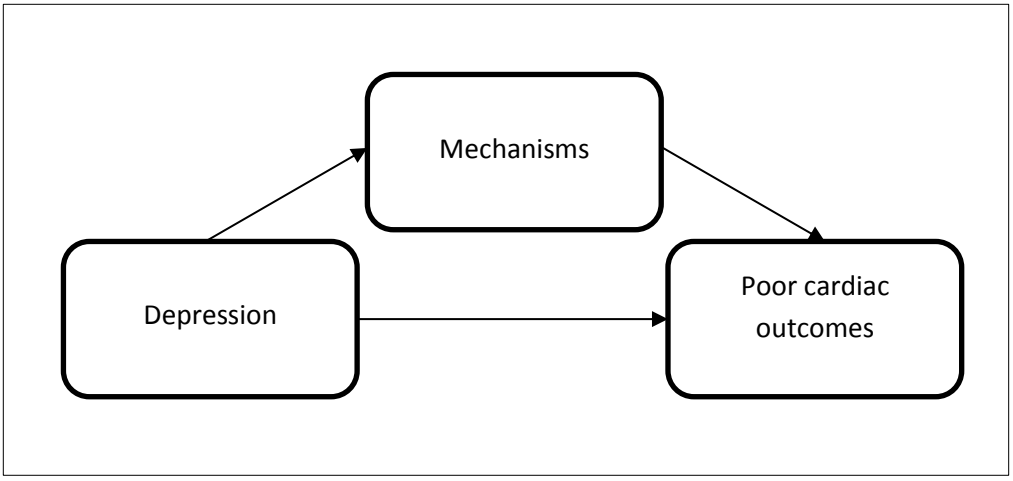

FIGURE 2.2: MEDIATION MODEL OF DEPRESSION AND POOR CARDIAC PROGNOSIS

2.5.1 Behavioural and social factors

Candidate mechanisms linking depression to cardiac prognosis are likely to include behavioural and social factors. Physical activity has been shown to be an important component of cardiac rehabilitation, being associated with reduced total and cardiovascular mortality and hospital

readmission (Heran et al., 2011). A recent study showed that the relationship between depressive symptoms and future cardiac events in patients with CHD was largely accounted for by poor health behaviours, particularly physical inactivity (Whooley et al., 2008). Few studies have investigated these effects in CABG patients, although physical activity is thought to have important protective effects in these patients (Nery & Barbisan, 2010). The effect of other health behaviours, such as smoking, is less clear. For example, smokers were found to be at greater risk of pulmonary complication following CABG surgery, but not of in-hospital mortality (Al-Sarraf et al., 2008). In an eight-year follow-up study, smokers were found to be at lower risk of arrhythmia than non-smokers (Al-Sarraf et al., 2010). Smoking has long been associated with depression (Fergusson, Goodwin, & Horwood, 2003; Glassman et al., 1990), although the causal relationship is unclear (Kendler et al., 1993). The study by Whooley and colleagues (Whooley et al., 2008) did show current smoking to partially mediate the association between depression and future cardiac events in patients with stable CHD, but this has yet to be tested in CABG patients. Obesity is another cardiac risk factor that has also been associated with depression (Luppino et al., 2010) and although many studies using CABG patients do not report body mass index (BMI) statistics, the few that have do not show BMI or obesity to be associated with depression (Blumenthal et al., 2003; Burg, Benedetto, Rosenberg, et al., 2003; Dunkel et al., 2009). Therefore, at present it is not clear whether obesity plays a role in the relationship between depression and cardiac prognosis.

Poor adherence to medical and lifestyle advice has been documented in CABG patients (Kulik, Shrank, Levin, & Choudhry, 2011; Yam et al., 2006). Studies of patients following acute MI indicate that patients who become depressed are less adherent to medication (Rieckmann, Gerin, et al., 2006; Rieckmann, Kronish, et al., 2006) and secondary prevention advice such as quitting smoking and attending cardiac rehabilitation programmes (Kronish et al., 2006). Furthermore, non-adherence may partly explain the increased risk of a major adverse cardiac event in depressed patients, up to one-year following ACS (Rieckmann et al., 2011). The personal, social and economic costs of non-adherence are profound for many patients with CHD (Ho et al., 2004), therefore it is important to better understand the mediatory role of non-adherence for long-term outcomes in CABG patients.

Another behaviour which has recently emerged in the literature as an important factor is sleep. Sleep duration and quality have been associated with both cardiovascular disease and events (Leineweber, Kecklund, Janszky, Akerstedt, & Orth-Gomér, 2003; Sabanayagam & Shankar, 2010; Schwartz et al., 1998). A recent meta-analysis of prospective studies found that both short and long sleep duration was associated with increased risk of developing or dying from CHD and stroke (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011). Poor sleep is also thought to have negative consequences for emotional wellbeing and research has shown an

association between poor sleep quality and depression (Almeida, Alfonso, Yeap, Hankey, & Flicker, 2011; Benca, Obermeyer, Thisted, & Gillin, 1992). While evidence for the direction of this relationship is limited, studies tend to suggest poor sleep contributes to depression onset (Baglioni et al., 2011; Cho et al., 2008; Ford & Kamerow, 1989; Roberts, Shema, Kaplan, & Strawbridge, 2000). Although sleep is recognised to be an important issue in post-CABG recovery (Jenkins, Jono, & Stanton, 1996; Redeker & Hedges, 2002), very few studies have investigated the impact of poor sleep on physical and emotional adaptation and recovery following cardiac surgery.

Hunt and colleagues (Hunt, Hendrata, & Myles, 2000) assessed 108 CABG patients 12-months after surgery and used cross-sectional analyses to test for associations between poor self-reported sleep quality and poor quality of life. They assessed sleep quality using a one-item measure devised by the authors to assess how often participants felt they slept well; quality of life was measured using the short form health survey (SF)-36. These authors found patients reporting poor sleep were 4.8 times more likely to also report poor quality of life (95% CI, 1.66-14.0, p = 0.002). Redeker and colleagues (Redeker, Ruggiero, & Hedges, 2004) studied 72 cardiac surgery patients in a study which implemented both self-report (Pittsburgh Sleep Quality Index) and objective (wrist actigraphy) measures of sleep on quality of life after surgery. They reported cross-sectional associations between poor sleep and worsened physical and emotional health status at four and eight weeks after surgery, showing that in regression models entering both the self-report measure of sleep quality and the objective measure of sleep efficiency in the same step, poor sleep accounted for 16% of variance in physical functioning at four weeks post-CABG and 8% at eight weeks post-CABG, and 13% of variance in emotional functioning at four weeks post-CABG and 16% at eight weeks post-CABG. However, these authors only controlled for age and sex in their models. Lastly, a study which recruited 38 males prior to CABG surgery used prospective analyses to show that the pre-surgery sleep symptom of feeling unrefreshed on awakening explained 44.5% of variance in quality of life scores, as measured using the Nottingham Health Profile questionnaire, six months after surgery (Edéll-Gustafsson & Hetta, 1999). These authors also reported that having a sad or depressed mood reaction to sleep loss was predictive of sleep problems, suggesting the problem may be self-perpetuating. The studies in this area highlight sleep as important factor in the prediction of mental and physical adaptation following CABG, but issues surrounding study quality, such as use of cross-sectional analyses and small sample sizes, limit the inferences that can be drawn. Moreover, it is not clear to what extent sleep is a cause or consequence of depressed mood in CABG patients and whether it affects cardiac prognosis following surgery; this is an important area for further work given that sleep disturbance is in itself a symptom of depression.

The role of social processes is less clear, although social support and social networks or connectivity are likely to be important (Lett et al., 2005). Steptoe's group has shown that social networks, practical social support, marital status and stress within social relationships affect adherence to medication and lifestyle advice following acute MI (Molloy, Perkins-Porras, Bhattacharyya, Strike, & Steptoe, 2008; Molloy, Perkins-Porras, Strike, & Steptoe, 2008; Molloy, Stamatakis, Randall, & Hamer, 2009). There is a small research base examining the role of social support in recovery and quality of life after CABG, but these studies report mixed findings. For example, Okkonen and colleagues found that lower perceived family support prior to surgery was associated with greater depression symptoms, feelings of hopelessness and anxiety (Okkonen & Vanhanen, 2006). Another study found that instrumental social support was associated with positive improvements in mental health but not physical functioning at six months following CABG (Barry, Kasl, Lichtman, Vaccarino, & Krumholz, 2006). Husak and colleagues (Husak et al., 2004) found that low social support was not able to predict cardiac rehabilitation attendance in CABG patients after adjusting for confounders. There is a need, therefore, to clarify the role of social support in emotional adaptation and quality of life following CABG. In summary, low social support may mediate the relationship between depression and cardiac outcomes by affecting a patient's ability to perform health behaviours; this hypothesis has yet to be empirically tested.

Psychological factors are also relevant. Indeed, there is evidence that hostility is associated with poor outcomes (Chida & Steptoe, 2009a), while optimistic dispositions appear to be protective (Scheier et al., 1989) and may improve treatment response in depressed cardiac patients (Tindle et al., 2012). However, it is not yet clear whether these factors are mediators in the relationship between depression and cardiac outcomes.

2.5.2 Cognitive factors

Cognitions, including illness perceptions, may well be implicated in linking depression to poor cardiac prognosis. The illness perception perspective emphasises the importance of patients' beliefs about their treatment and the course of their illness. The relevance of these cognitions will be influenced by the extent to which patients' expectations are fulfilled, and unanticipated patterns of symptom recovery and healing may undermine belief structures. The majority of the work in this area has used MI patients, and negative illness perceptions (e.g. *my illness will last a long time* and *my illness will not be cured*) have been associated with an array of poorer outcomes for this population, including greater illness related disability at home and at work (Petrie, Weinman, Sharpe, & Buckley, 1996), reduced quality of life (French, Lewin, Watson, & Thompson, 2005; Stafford, Berk, & Jackson, 2009), later return to work (Maeland & Havik, 1987; Petrie et al., 1996), increased fatigue (Alsén, Brink, Persson, Brändström, & Karlson,

2010), and greater risk of in-hospital complications (Cherrington, Moser, Lennie, & Kennedy, 2004). This work is made more relevant since research has shown that illness perceptions are amenable to change in several intervention studies, with results of one trial showing improvements in functional recovery, i.e. faster return to work, as a result of a brief in-hospital intervention to challenge and replace negative illness perceptions in MI patients (Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009). In addition, more negative illness perceptions have been related to poorer emotional responses to ACS, such as greater depression symptoms (Grace, Krepostman, et al., 2005; Stafford et al., 2009). In a study which assessed illness perceptions in the days following hospital admission for MI, more negative beliefs were associated with the development of new onset depression in particular (Dickens et al., 2008b).

The notion that illness perceptions are causally related to depression in MI patients is consistent with the cognitive vulnerability theory of depression in which negative cognitive appraisals, or negative schemas[4], are thought to be triggered during stressful situations and consequently are then capable of leading to depression onset, maintenance and relapse/recurrence (Scher, Ingram, & Segal, 2005). However, more recent evidence has proposed a mediation model in which negative illness perceptions mediate the relationship between depression and cardiac outcomes. Such a model suggests that depression leads to negative illness perceptions, which in turn are capable of affecting health outcomes. For example, in a study of 201 (25 depression cases) stable CHD outpatients who completed baseline and six-month follow-up assessments, the negative illness perceptions of consequences, identity, illness concern and emotional representation were shown to partly mediate the prospective, negative, relationship between baseline depression and follow-up health-related quality of life (Dickens, Cherrington, & McGowan, 2011). Only two studies to date have examined these effects in cardiac surgery patients, the first of these studies showed pre-surgical negative illness perceptions predicted depression three months after surgery (Juergens, Seekatz, Moosdorf, Petrie, & Rief, 2010). The second study reported associations between negative illness perceptions and greater psychological distress in patients before CABG (Hermele, Olivo, Namerow, & Oz, 2007). In summary, patients with a clinical manifestation of CHD (either ACS or CABG) may be more prone to depression if they have a more negative view of their illness. However, it is not clear to what extent negative illness perceptions may actually mediate the relationship between depression and poor cardiac prognosis; further work is needed to explore this in greater detail.

[4] Negative schemas refer to: "negatively toned representations of self-referent knowledge and information that guide appraisal and interact with information to influence selective attention, memory search, and cognitions" (Scher, Ingram, & Segal, 2005, p.489).

Other cognitive factors have also been implicated as mechanisms. For example, there has been marked interest and debate in the evidence suggesting a deterioration in various neurocognitive processes following CABG, such as memory loss and difficulties with concentration and problem-solving. Both short- and long-term deficits in neurocognition have been observed in CABG patients. In a systematic review of studies using CABG patients, van Dijk and colleagues (van Dijk et al., 2000) reported pooled estimates showing on average, 22.5% of CABG patients had a cognitive deficit two months following surgery. Longer-term effects have also been observed, with a study of 261 (171 available at five years) CABG patients by Newman and colleagues (Newman et al., 2001) reporting cognitive decline in 42% of patients at five-year follow-up.

Some research has suggested that the type of CABG surgical procedure used may affect neurocognitive risk, with on-pump patients thought to be particularly vulnerable (Stroobant, Van Nooten, Van Belleghem, & Vingerhoets, 2005; Zamvar et al., 2002). However, this has not been replicated in the majority of studies. The Octopus study is a large-scale prospective randomised controlled trial comparing cognitive decline in on-pump and off-pump CABG patients in the Netherlands (van Dijk et al., 2007; van Dijk et al., 2002). Two hundred and eighty one participants were randomised to receive either an on-pump or off-pump CABG procedure and were assessed one day prior to surgery and initially followed-up three and 12 months after surgery. Findings showed that the off-pump patients had significantly better cognitive function at three months after CABG than on-pump patients, but this effect had disappeared by 12 months (van Dijk et al., 2002); nor was it evident in recently published data from the five-year follow-up (van Dijk et al., 2007). This has also been supported by others (Hernandez et al., 2007; Stroobant, van Nooten, De Bacquer, Van Belleghem, & Vingerhoets, 2008) and confirmed in a recent systematic review which concluded that there is insufficient evidence that brain damage in cardiac surgery patients is attributable to the use of cardiopulmonary bypass (Alston, 2011).

Other studies using control groups are beginning to question whether CABG surgery *per se* confers risk of cognitive deterioration or whether it is more general to CHD patients or surgical patients at large. One study which tried to address this recruited 140 CABG patients and 92 matched non-surgical CHD controls, finding that at 12-month follow-up there was no difference between the groups in an array of neurocognitive tests (Selnes et al., 2003); these results have been supported by others (McKhann et al., 2005; Sweet et al., 2008) and have been replicated at three-year follow-up (Selnes et al., 2007). The problem of using an adequate control group has also been highlighted by recent analyses performed on the Octopus dataset, which was reanalysed and compared to neuropsychological test scores of 112 healthy controls at baseline, three and 12-month follow-up (Keizer, Hijman, Kalkman, Kahn, & Van Dijk, 2005).

Interestingly, by their three month assessment, between 14% and 28% of controls were classified as having cognitive decline, which is similar to the CABG patient group, in which 25% were classed as having cognitive decline. This highlights the need for conservative cut-offs which taken into account the natural variability in test scores over repeated assessments. When the Octopus cohort was re-analysed according to the new cut-offs, only 7.7% were defined as suffering from cognitive decline. Such results reinforce the need for careful interpretation of the literature in this area. As mentioned, it is also not clear to what extent CABG surgery patients are at greater risk than other surgical patients, who are also at risk of cognitive decline: a phenomenon termed post-operative cognitive dysfunction (for a review see Reichenberg, Dahlman, Mosovich, & Silverstein, 2007).

Regardless of this on-going debate, cognitive function is a potential mediator between depression and cardiac outcomes. Low levels of cognitive function have long been associated with greater all-cause (Bosworth & Siegler, 2002) and cardiac mortality (Batterham, Mackinnon, & Christensen, 2012). This latter study followed-up 592 community-dwelling participants for up to 17 years, and showed that while initial cognitive function was the better predictor, deterioration in cognition function over time was also predictive of future mortality, after adjustment for demographic, physical functioning and depression and anxiety scores. Cognitive difficulties are also well-established in depression, among the geriatric depressed (Butters et al., 2004; Rapp et al., 2005) and also younger adults (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Herrmann, Goodwin, & Ebmeier, 2007; Thomas et al., 2009). However, McKhann and colleagues (McKhann et al., 1997) found no association between depression and cognitive decline in a one-year follow-up study of 124 CABG patients. A more recent study has shown cross-sectional associations between depression and cognitive function at six months and five years following CABG surgery, though the effects were only small and explained no more than 7.2% of variance in any of the cognitive domains (Tully, Baker, Knight, Turnbull, & Winefield, 2009). Other studies have also found mixed results (Andrew, Baker, Kneebone, & Knight, 2000; Tsushima, Johnson, Lee, Matsukawa, & Fast, 2005), with further high-quality work needed. In summary, it is not yet clear to what extent CABG patients are at increased risk of cognitive deterioration following surgery, or whether any observed deterioration mediates the association between depression and cardiac outcomes. Further work is needed to test this hypothesis in greater detail.

Another cognitive factor that may be important is the concept of health literacy. Health literacy describes the degree to which individuals have the capacity to obtain, process, and understand the basic health information and services needed to make appropriate health decisions (Von Wagner, Steptoe, Wolf, & Wardle, 2009). Poor health literacy has been associated with failure to follow medical advice in many clinical groups (Herndon, Chaney, &

Carden, 2010; Ngoh, 2009), and may be important in CABG patients (Conlin & Schumann, 2002). Therefore, in people with depression, poor health literacy may act to compound non-adaptive health behaviours, particularly adherence to medication, because of an inability to comprehend medical advice; this has yet to be tested empirically.

2.6 Depression and cardiac prognosis: Biological mechanisms

Emotional distress and depression are associated with a number of biological processes in patients with CHD, which may contribute to poor health outcomes, including autonomic dysfunction, platelet reactivity, heightened neuroendocrine responses and inflammation, among others (Carney et al., 2002; de Jonge et al., 2010; Nemeroff & Goldschmidt-Clermont, 2012; Skala et al., 2006; Steptoe, 2007). An overview of these processes will be provided in the following sections. As with the previous mechanisms described, the CABG literature is of primary importance here, but where studies are scarce work in ACS patients will be drawn upon. However, drawing direct comparisons between ACS and CABG patients must be conducted with care since there are obvious differences between the two groups in terms of the cause of the physiological trauma: ACS being the result of internal pathophysiology whereas CABG is an external assault.

2.6.1 Autonomic dysfunction

Autonomic balance is essential for health and on the contrary, imbalance, characterised typically by hyperactive sympathetic nervous system activity and hypoactive parasympathetic activity, is associated with several cardiac pathologies (Sztajzel, 2004). Heart rate variability (HRV) refers to beat to beat changes in heart rate in reaction to internal and external stimuli and it can be used as a marker of cardiac autonomic control and the sympathetic/ parasympathetic balance; for a thorough discussion of this methodology see Thayer, Hansen, & Johnson (2010). In essence, low HRV is associated with poorer health outcomes, including increased risk of mortality, than high HRV. Indeed, low HRV has been shown to predict the occurrence of potentially fatal arrhythmias in MI patients (La Rovere et al., 2001) and mortality following MI (Bigger et al., 1992; Kleiger, Miller, Bigger, & Moss, 1987). Moreover, HRV has been shown to be lower in depressed patients than their non-depressed counterparts in stable CHD populations (Carney et al., 1995; Krittayaphong et al., 1997; Stein et al., 2000) and in MI patients (Carney et al., 2001). However, it should be noted that not all studies have reported this association (Gehi, Mangano, Pipkin, Browner, & Whooley, 2005) and HRV may be differentially associated with somatic and cognitive depression symptoms (De Jonge, Mangano, & Whooley, 2007). A review by Carney and Freedland (Carney & Freedland, 2009b) concluded that HRV may partly mediate the association between depression and poor cardiac

outcomes. Autonomic dysregulation has also been associated with depressed mood following CABG surgery (Hallas, Thornton, Fabri, Fox, & Jackson, 2003) and may partly explain why depressed patients have poorer outcomes following CABG (Dao et al., 2010). However, little is known about the impact of these autonomic changes on long-term recovery following CABG.

2.6.2 Platelet reactivity

Platelets are circulating cells that play a key role in haemostasis and in the repair and healing of vascular damage. Platelet aggregation plays an essential role in the pathophysiology of atherosclerosis and acute coronary events (Lefkovits, Plow, & Topol, 1995; Markovitz & Matthews, 1991). These latter authors were the first to describe that abnormal platelet function can be increased by psychological stress and circulating catecholamines. Moreover, a case-control study showed that mental stress in male CHD outpatients stimulated sustained platelet activation compared to healthy controls (Strike et al., 2004). Several authors have supported the association between depression and increased platelet activation (Musselman et al., 1996; Nemeroff & Musselman, 2000). However, only limited evidence exists for this effect in depressed CHD patients (Laghrissi-Thode, Wagner, Pollock, Johnson, & Finkel, 1997; Serebruany et al., 2003). More recently, a critical review deemed the findings to be inconclusive, with most studies not reporting increased platelet aggregation in depressed patients. However, these authors did find evidence in favour of the platelet hypothesis being more evident in those with CHD than those without; they concluded that further large-scale studies are needed (Von Känel, 2004). These effects have yet to be tested in depressed CABG patients.

2.6.3 Neuroendocrine dysfunction

Another biological factor thought to play a mediatory role is the neuroendocrine hormone, cortisol. On perception of a stressor, the HPA axis is activated (see Figure 2.3 (Glaser & Kiecolt-Glaser, 2005, p.245)) and, via release of corticotrophin releasing hormone (CRH), the corticosteroid cortisol is secreted. Cortisol is vital to life, being involved in glucose production and metabolism as well as regulating the immune system. However, chronic over-activity of the HPA axis can lead to dysregulation of cortisol output and since cortisol is essential for homeostasis, any deviation from the optimal range is thought to have deleterious effects. For example, in the cardiac literature, elevated cortisol has been linked to cardiac risk factors such as hypercholesterolemia, abdominal obesity and hypertension, by some (Brown, Varghese, & McEwen, 2004), but not all (Otte et al., 2004), authors. Cortisol dysregulation may contribute to cardiovascular risk not only through effects on metabolic processes (Chandola, Brunner, & Marmot, 2006) but also via atherosclerosis (Whitworth, Williamson, Mangos, & Kelly, 2005). In

addition, flatter cortisol rhythms across the day have been linked with the progression of coronary calcification (Matthews, Schwartz, Cohen, & Seeman, 2006).

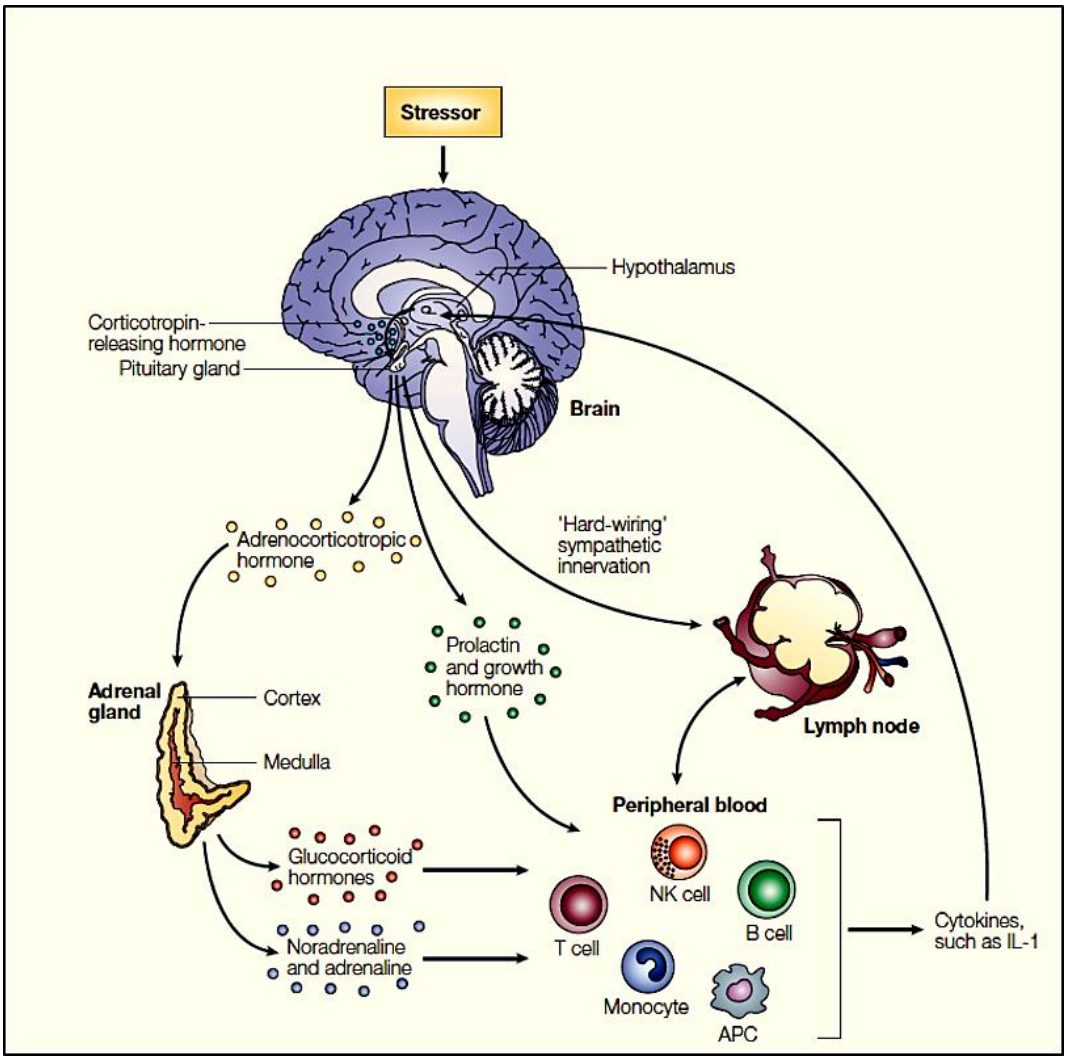

FIGURE 2.3: THE HYPOTHALAMIC PITUITARY ADRENAL AXIS

(From: Glaser & Kiecolt-Glaser, 2005, p.245)

Cortisol has also been implicated in the pathophysiology of depression (Zunszain et al., 2011). HPA axis abnormalities have been observed in patients with major depression, including increased secretion and reactivity of cortisol (Cowen, 2010), elevated CRH (Nemeroff et al., 1984), and increased size and activity of the pituitary and adrenal glands (Nemeroff et al., 1992). Moreover, Steptoe's group recently showed that alterations in the diurnal profile of cortisol were associated with depressed mood in patients with CHD (Bhattacharyya, Molloy, & Steptoe, 2008), and with Type D personality (negative affectivity and social inhibition) in patients following ACS (Molloy, Perkins-Porras, Strike, & Steptoe, 2008b; Whitehead, Perkins-Porras, Strike, Magid, & Steptoe, 2007). HPA axis dysregulation has also been associated with greater cardiac-related mortality in depressed patients (Jokinen &

Nordström, 2009). There are limited studies investigating cortisol in CABG surgery patients, although there is some evidence that there is heightened cortisol output in the post-operative period (Roth-Isigkeit & Schmucker, 1997; Tønnesen, Brinkløv, Christensen, Olesen, & Madsen, 1987) and one study found this pattern to be associated with post-operative complications, in particular delirium (Mu et al., 2010). The relationship between cortisol output, depressed mood and long-term adaptation has not been investigated in CABG patients before.

2.6.4 Inflammatory processes

The immune system is closely linked to the HPA axis via bidirectional feedback (Maier & Watkins, 1998). The signalling molecules of the immune system are called cytokines, of which there are pro- and anti-inflammatory cell types. Systemic infection triggers macrophages to release pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha (TNF-α), which are responsible for coordinating an adaptive whole-body response known as sickness behaviour. Sickness behaviour refers to a cluster of symptoms affecting both behavioural and affective state such as fever, increased sleep, reduced social interaction, malaise, increased negative mood, fatigue and listlessness. Anti-inflammatory cytokines work to moderate the inflammatory response and are responsible for the intensity and duration of sickness behaviour due to their regulatory role in the production and signalling of pro-inflammatory cytokines. Several comprehensive reviews have been published in this area (Dantzer, 2001a, 2001b; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

The inflammatory literature is much more substantial than that of other biological mechanisms, so the main arguments will be described below. Much of the work linking cytokines to depression is reviewed in our paper (Poole, Dickens, et al., 2011).

2.6.4.1 Depression and inflammation

Depression is associated with an innate inflammatory response (Raison, Capuron, & Miller, 2006), and a meta-analysis by Howren and colleagues has shown depressive symptoms to be positively associated with CRP, IL-1 and IL-6 in both clinical and community samples (Howren, Lamkin, & Suls, 2009). A more recent meta-analysis by Dowlati and colleagues (Dowlati et al., 2010) has supported the role of pro-inflammatory markers in depression, in particular IL-6 and TNF-α. Interestingly, depression is associated with both immune up-regulation, characterised by increasing pro-inflammatory cytokines, as well as immune down-regulation such as reduced proliferative responses of immune cells (Blume, Douglas, & Evans, 2011). Epidemiological evidence for the directionality of the depression-inflammation relationship is mixed, with some studies suggesting that depression precedes inflammation (Stewart, Rand, Muldoon, & Kamarck, 2009), while others show that inflammation precedes depression (Gimeno et al.,

2008). The relationship has also been studied experimentally or quasi-experimentally, testing the depressive responses to acute inflammatory stimuli.

Vaccination studies

Inflammatory responses can be stimulated by administration of endotoxin or by inoculation with attenuated vaccines. Reichenberg and colleagues (Reichenberg et al., 2001) used a cross-over design to test the effects of *Salmonella abortus equi* endotoxin or saline on sickness symptoms and mood. Blood was collected at baseline and at hourly intervals for up to 10 hours post-injection. Results showed that healthy participants showed a transient significant increase in their levels of depressive and anxiety symptoms in response to the endotoxin together with increases in IL-6, IL-1 receptor antagonist (IL-1Ra) and TNF-α. No differences in sickness were reported after the endotoxin as compared with placebo. These results were confirmed in a similar study using *S. typhi* vaccine or placebo, reporting negative changes in mood following injection with vaccine that were significantly correlated with increases in IL-6 production (Wright, Strike, Brydon, & Steptoe, 2005). Notably, no significant symptoms of nausea were reported, so it cannot be argued that negative mood arose because the participants were feeling ill. Brain imaging studies indicate that the cytokine-induced mood response to typhoid vaccination is correlated with activity within the subgenual anterior cingulate gyrus (sACC) and with reduced connectivity between the sACC and amygdala, medial prefrontal cortex, nucleus accumbens and superior temporal sulcus (Harrison et al., 2009). Interestingly, the inflammation induced by typhoid vaccination impairs endothelial-dependent vascular dilatation, implicating transient endothelial dysfunction (Hingorani et al., 2000). This may be the mechanism underlying the transient increased risk of ACS in patients following acute infections such as influenza (Smeeth et al., 2004). In summary, vaccination studies have shown that experimentally induced inflammation is capable of triggering negative mood responses.

Immunotherapy-induced depression

A second set of relevant literature concerns clinical studies investigating the effects of treatment with cytokine-based therapy on mood. These studies were stimulated by the observation of depression in some patients with cancer, treated with immunotherapy (Capuron & Miller, 2004). Capuron and colleagues (Capuron et al., 2001) systematically investigated the association between different immunotherapies (IL-2, IL-2 plus interferon (IFN)-α, subcutaneous IFN-α or intravenous IFN-α) and the development of depressive symptoms in 33 patients with cancer. Patients treated with IL-2 or IL-2 plus IFN-α showed concomitant increases in depression symptoms and increased levels of the anti-inflammatory

cytokine IL-10 during treatment. Patients who were susceptible to inflammation-induced depression were more likely to show higher depression symptom scores prior to treatment (Capuron, Ravaud, Miller, & Dantzer, 2004) and a heightened pituitary–adrenal response following the first IFN-α injection (Capuron et al., 2003). Another study showed that around one-third of patients who were free of depression before therapy developed major depression during treatment with IFN-α (Beratis et al., 2005). Interestingly, Musselman and colleagues (Musselman et al., 2001) studied the effects of treatment with an antidepressant on depression induced by IFN-α treatment in a randomised placebo-controlled trial of 40 malignant melanoma patients. The intervention (paroxetine or placebo) began two weeks before initiation of IFN-α therapy and continued for 12 weeks. Results showed that there was a fourfold reduction in risk of developing major depression by pre-treatment with paroxetine (an SSRI). To summarise, cytokine-based immunotherapy induces depressive symptomatology, and these effects can be attenuated by pre-treatment with antidepressant medication.

Animal work

Animal studies have also investigated the mechanisms linking inflammatory responses with depression-like syndromes. A comprehensive review is provided by Dantzer and colleagues (Dantzer et al., 2008), who present two lines of argument in support of the role of inflammation in the development of depression.

First, inflammatory stimuli induce depression-like symptoms. Frenois and colleagues (Frenois et al., 2007) conducted an experiment using two measures considered to be indicative of depressive state in animal models: immobility and decreased preference for sweet solutions. They showed that mice treated with a pro-inflammatory cytokine stimulant (lipopolysaccharide) displayed increased immobility 24 hours after two stress tasks aimed to elicit a depressive response (tail suspension and forced swim), even though motor activity had returned to normal. In addition, preference for sweetened water was also reduced even after food intake and drinking had returned to baseline levels. These effects are more prominent in genetically vulnerable species. For example, fawn-hooded rats, which exhibit many of the symptoms thought to align with depression, are more sensitive to IL-1β-induced immobility in the forced-swim test compared with controls (Simmons & Broderick, 2005).

Second, pharmacological corroboration for the role of inflammation has been provided by studies showing that depression-like symptoms induced by exogenously administered inflammatory stimuli can be attenuated with antidepressant drugs. For example, pre-treatment with the antidepressant drugs imipramine or fluoxetine blocked the reduced intake of sweetened solution and reduced social exploration in rats treated with lipopolysaccharide (Yirmiya, 1996; Yirmiya et al., 2001). In another study, pre-treatment with fluoxetine abolished

the impaired performance of IL-1β-treated rats in a task designed to test reactivity to reward (anhedonia) (Merali, Brennan, Brau, & Anisman, 2003).

These findings indicate that animal models corroborate the human literature with evidence that depression-like symptoms can be experimentally induced by inflammatory stimuli and are likewise responsive to pre-treatment with antidepressant drugs.

2.6.4.2 Depression and low-grade inflammation in CHD patients

Inflammatory processes are involved at several stages of the development of atherosclerosis and CHD, including endothelial dysfunction, smooth muscle cell migration and proliferation, and plaque rupture. Depression has been linked to inflammation in persons with CHD although the literature is somewhat inconsistent. Some evidence shows depressed cardiac patients to have heightened inflammation. For example, Bankier and colleagues (Bankier, Barajas, Martinez-Rumayor, & Januzzi, 2009) studied 72 CHD outpatients of whom 30 were classified as suffering from major depressive disorder. Stepwise multiple regression analyses revealed a significant positive relationship between depression and levels of CRP. Mixed findings were found in a much larger study by Lespérance and colleagues (Lespérance, Frasure-Smith, Théroux, & Irwin, 2004) who assessed 481 outpatients two months after hospitalisation for ACS with diagnostic psychiatric interviews. Depressed participants had higher levels of soluble intracellular adhesion molecule-1, but there was no association with IL-6. Frasure-Smith and colleagues (Frasure-Smith et al., 2007; Frasure-Smith, Lespérance, Irwin, Talajic, & Pollock, 2009) found patients with elevated depression symptoms to have higher levels of CRP, but not IL-6, as compared with non-depressed cardiac patients.

However, other studies have not supported this observation. Schins and colleagues (Schins et al., 2005) conducted a case-controlled study of depressed (n = 57) and non-depressed (n = 46) MI patients, and found no differences between the groups in levels of IL-6, TNF-α or CRP. Frasure-Smith and colleagues (Frasure-Smith et al., 2007) followed up 741 patients for two years after ACS for major adverse cardiac events and showed that elevated CRP and BDI scores two months after the cardiac event were both associated with increased risk to a similar extent. In other studies, Empana and colleagues (Empana et al., 2005) and more recently Davidson and colleagues (Davidson et al., 2009) did not find that inflammation mediated the association between depression and cardiac outcome.

One difficulty in the interpretation of this literature is the impact of medications such as statins. In addition to their effects on cholesterol synthesis, statins have marked immunomodulatory and anti-inflammatory properties, and modulate vascular endothelial function (Greenwood & Mason, 2007). Other cardiovascular medications, such as aspirin, are also anti-inflammatory, and have not been consistently taken into account. There has also

been controversy concerning the relevance of inflammation to prognosis in patients with stable coronary artery disease due to methodological concerns. Contrary to guidelines issued by the American Heart Association (Pearson et al., 2003), some authors (Hemingway et al., 2010; Kushner, Broder, & Karp, 1978) have demonstrated that the literature relating elevated CRP with poor prognosis is seriously flawed, with poor control for confounders, poor methodology and publication bias. The significance of any associations between inflammatory markers and future CHD risk in patients with established disease is therefore uncertain.

2.6.4.3 Inflammation during ACS and depression

The depression-inflammation relationship has also been studied by looking at the inflammatory response during the cardiac event. An ACS is associated with a massive acute inflammatory response (Kushner et al., 1978; Suleiman et al., 2003). The magnitude of the acute inflammatory response during ACS is predictive of poor cardiac outcome. For example, Biasucci and colleagues (Biasucci et al., 1999) showed in unstable angina patients that increases in IL1-Ra and IL-6 measured 48 hours after hospital admission were associated with greater risk of in-hospital cardiac events, while elevated CRP predicted 14 day mortality in unstable angina and non-Q wave MI independently of troponin responses (Morrow et al., 1998). Further studies have confirmed this positive association in non ST-segment elevation ACS patients (Kosuge et al., 2008) and acute MI patients (Berton et al., 2010; Bursi et al., 2007; Kosuge et al., 2008; Suleiman et al., 2003, 2006; Yip et al., 2005). A recent meta-analysis of 20 cohort and randomised controlled trials showed that CRP levels >10 mg/l measured within 72 hours of ACS onset were associated with a relative risk of 2.18 (95% C.I. 1.77 – 2.68) for recurrent cardiovascular events or death compared with values ≤3 mg/l (He, Tang, Ling, Chen, & Chen, 2010). Most of these studies controlled for age, sex, cardiac enzyme levels, ejection fraction, heart failure and other markers of risk, suggesting that the impact of acute inflammation is independent of multiple risk indicators. The association between these large acute inflammatory responses and subsequent depression has not been tested.

CABG surgery is also associated with an acute inflammatory response. The contact with the surfaces of the extracorporeal circuit inherent in cardiopulmonary bypass surgery (on-pump) triggers a systemic inflammatory response which in severe cases can lead to systemic inflammatory response syndrome; this is a serious disorder capable of causing major organ dysfunction and death (Day & Taylor, 2005). Clinical management of the perioperative inflammatory response is therefore critical to patient outcomes. An observational study of 29 cardiopulmonary bypass patients by Holmes and colleagues (Holmes et al., 2002) used a median split to compare outcomes between those patients who showed a heightened inflammatory response at four hours post-CABG, to those who did not. Findings showed that

hyper-responders in IL-8, IL-6 and CR3 (an anaphylatoxin) had greater risk of adverse clinical outcomes. However, the small sample size limits the generalisability of these findings. More recently, pre-operative CRP has been shown to predict adverse outcomes in CABG patients (De Lorenzo, Pittella, & Rocha, 2012). In this study, 76 patients had CRP assessed prior to surgery, with results showing that those with elevated CRP (≥3 mg/l) had significantly greater risk of post-operative mortality; other work has replicated this finding (Perry et al., 2010). Kaireviciute and colleagues (Kaireviciute et al., 2010) have shown that perioperative measures of high sensitivity (hs)-CRP and IL-6 are associated with greater risk of atrial fibrillation post-operatively. Additionally, an acute inflammatory response is not only observed in on-pump but also off-pump surgery (Biglioli et al., 2003). The extent of the inflammatory response is thought largely to reflect the amount of trauma derived from the surgical procedure itself and is associated with a host of clinical outcomes, both cardiac and non-cardiac in scope (Biglioli et al., 2003; Levy & Tanaka, 2003). Only one study to date has assessed the association between depression and inflammation in CABG patients (Yang et al., 2012). These authors studied 232 patients undergoing CABG surgery and found that higher pre-operative hs-CRP was predictive of depression symptoms up to six months following surgery, after controlling for covariates. However, there still remains a lack of studies in which perioperative variables have been adjusted for, limiting the conclusions to be drawn from this literature. In summary, both ACS and CABG surgery are associated with an acute inflammatory response. In ACS patients this inflammation is linked to prognosis. Although the literature points towards this being true in CABG populations as well, more high quality research is needed.

2.6.4.4 A sickness behaviour model of depression

Parallels can be drawn between sickness behaviour and the symptoms of depression, including lassitude, fatigue and dysphoric mood, and this similarity forms the basis for a sickness behaviour model of depression in patients experiencing ACS or CABG (Dantzer et al., 2008; Poole, Dickens, & Steptoe, 2011). Table 2.1 shows the characteristics of sickness behaviour and their parallel symptoms in depression; it is important to note that these two syndromes do not perfectly overlap, with some sickness symptoms not having a parallel in depression while others relate to an opposing symptom. Sickness behaviour is thought to be adaptive in organising bodily responses that fight infection, promoting cellular (T-helper 1) immunity which targets intracellular organisms through activation of macrophages, cytotoxic T lymphocytes and natural killer cells (Dantzer, Castanon, Lestage, Moreau, & Capuron, 2006). This hypothesised model posits that, in the case of ACS and CABG, the extent of tissue trauma invokes a large inflammatory response, capable of triggering a series of sickness behaviours. In these vulnerable individuals, where the immune response is exacerbated in duration and

intensity, decompensation (i.e., functional deterioration) occurs, causing a shift in balance between pro-inflammatory and anti-inflammatory cytokines towards one of inflammation.

TABLE 2.1: CHARACTERISTICS OF SICKNESS BEHAVIOUR AND THEIR PARALLELS IN DEPRESSIVE SYMPTOMATOLOGY

Sickness behaviour	*Depression*
Symptoms with a direct parallel:	
Anhedonia	Dysphoric mood/sadness
Behavioural withdrawal	Inability to work/perform daily tasks
Decreased social interaction	Social withdrawal
Reduced sexual behaviour	Loss of libido
Sleep	Increased sleep/fatigue*
Loss of appetite	Loss of appetite/weight loss*
Increased pain	Increased pain**
Symptoms without a direct parallel:	
Fever	-
Malaise	-
Symptoms with an incongruent parallel:	
Reduced aggression	Increased irritability

*N.B. in some depressed patients sleep is decreased and appetite increased.
**e.g. Bair, Robinson, Katon, & Kroenke (2003)

This sickness behaviour model suggests there may be a direct biological element to the development of depression, although there is still something lacking in this argument—inflammation elicits a behavioural syndrome that resembles depression, yet it is not quite depression. One explanation could be that these sickness behaviours act as an additional burden among people who are already vulnerable. Alternatively, it might be that there are neurocognitive changes associated with inflammation that account for the behaviours and possibly result in mood changes. Underlying this could be the effects of inflammatory mediators on neurotransmitters such as serotonin (Wichers & Maes, 2002) or even minor damage to the central nervous system (Denes, Thornton, Rothwell, & Allan, 2010). More research is needed to delineate these mechanisms in greater detail. In addition, more understanding is needed regarding why some individuals show a hyper-inflammatory response to a cardiac event. One hypothesis that has attracted recent attention is the psychiatric version of the hygiene hypothesis, which states dysregulation of the inflammatory response arises due to decreased exposure to microorganisms (Raison & Miller, in press; Raison, Lowry, & Rook, 2010). These authors suggest that increased sanitation in industrialised societies has led to our immune systems mounting inappropriate inflammatory responses to a wide range of stimulus,

including psychosocial stressors. This hyper-response could partly explain why some individuals who perceive cardiac surgery as particularly threatening or stressful have an increased inflammatory response, which in turn is capable of triggering depression; further work is needed to investigate this theory in CABG patients.

Other pathways and processes are undoubtedly at work alongside the inflammatory pathway. If an inflammatory pathway is relevant, it would have several implications (Poole, Dickens, et al., 2011). Firstly, one would expect the magnitude of the acute inflammatory response to predict the development and duration of depression following acute cardiac events or CABG. Second, the size of acute inflammatory responses might be associated with the other biological mechanisms related to future cardiac morbidity that are associated with depression, including reduced HRV, HPA axis dysregulation and impaired platelet function. Third, the association between depression after ACS or CABG and adverse cardiac outcomes would be expected to be reduced if inflammation was included in the model. Finally, one would expect that interventions that reduce acute inflammation during cardiac events might reduce the magnitude of depressive responses. Current trials are evaluating techniques for limiting acute inflammatory responses, for example, the MRC-ILA-HEART study (Crossman et al., 2008). If these trials are successful, they would provide the opportunity to test links between inflammation and the development of depression in ACS patients.

2.6.4.5 Other plausible biological mechanisms

Other less investigated mechanisms may also play a role in the depression-cardiac prognosis relationship. For example, ventricular electrical instability, which refers to inducible ventricular tachycardia or ventricular fibrillation, is associated with greater risk of mortality following MI (Richards et al., 1983; Richards & Denniss, 2007). In addition, depression has been shown to better predict fatal cardiac arrhythmias and cardiac mortality than it is able to predict non-fatal MI (Carney & Freedland, 2003). It is not clear why depression may increase the risk of lethal arrhythmias, but it is possible that depression increases vulnerability to transient myocardial ischaemia due to its effect on pro-thrombotic factors (discussed in Section 2.6.2). Another possible mechanism that has received interest recently is endothelial dysfunction, which has been observed in depressed populations (Broadley, Korszun, Jones, & Frenneaux, 2002; Rajagopalan et al., 2001) and has been related to elevated depression symptoms (BDI ≥10) in those with established CHD (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005). Anaemia has also recently been posited to be a possible biological mechanism linking ACS with depression, and has been shown to be predictive of recurrent cardiac events up to one year post-MI (Steptoe, Wikman, Molloy, & Kaski, 2012).

The role of polyunsaturated fatty acids, particularly omega-3, has also been investigated since dietary intake of omega-3 is known to be implicated in endothelial function and inflammatory processes (Hjerkinn et al., 2005; Pischon et al., 2003; Ros et al., 2004). Moreover, low levels of omega-3 (including two forms largely found in oily fish, docosahexaenoic acid and eicosapentaenoic acid) have been associated with cardiac mortality and sudden cardiac death (Albert et al., 2002; Kris-Etherton, Harris, & Appel, 2002), as well as major depression and suicidal ideation (Hibbeln, 1998; Tanskanen et al., 2001). Moreover, there is some evidence that depressed post-ACS patients have lower plasma levels of omega-3 than their non-depressed counterparts (Amin, Menon, Reid, Harris, & Spertus, 2008; Frasure-Smith, Lespérance, & Julien, 2004); the effect of this association on long-term cardiac outcomes has yet to be tested.

Another possibility is that of the so-called vascular depression hypothesis (Alexopoulos et al., 1997), which posits that cerebrovascular disease can cause or perpetuate late-onset depression in elderly individuals. Since cerebrovascular disease is commonly observed in older-aged patients with advanced CHD, this would again suggest cardiac prognosis is a function of disease severity, not depression *per se*. However, this hypothesis has received mixed support, with some studies finding structural or functional brain abnormalities in late onset depression (Krishnan, Hays, & Blazer, 1997), while others have not (Greenwald et al., 1996). While there is some evidence in support of this view in ACS patients (Rapp et al., 2010), age is typically adjusted for in analyses, with the effect of depression on cardiac morbidity and mortality being upheld. What is more, recent analyses have not identified greater risk of vascular depression in new onset depression patients with CHD (Habra et al., 2010). Therefore, further work is needed to substantiate this hypothesis in cardiac patients.

2.7 Chapter summary

A summary of the literature described in both Chapter 1 and 2 of this thesis is displayed in Table 2.2. This chapter has discussed the direction of the causal relationship linking depression and CHD, highlighting the evidence in favour of an antecedent, rather than a consequence, model. It also raised the issue of new onset depression after ACS and CABG, which may present an exception to this argument. Depression has also been described as mediator in the relationship between CHD and cardiac prognosis, irrespective of disease severity. Many mechanisms are likely to partly explain the relationship between depression and cardiac outcome, including behavioural and social factors, cognitive factors and biological processes. Key to understanding these causal pathways is to take a holistic, integrative view, looking for the interrelationship between these seemingly separate factors, in order to generate a unified model. Figure 2.4 provides a summary of factors affecting recovery after CABG surgery.

TABLE 2.2: SUMMARY OF LITERATURE REVIEW

Main findings from previous literature	*What my PhD will add*
1. Depression is highly prevalent in ACS populations, but is less well studied in CABG populations.	• My PhD will study depression in a CABG surgery population.
2. The direction of the causal relationship between depression and CHD has been well-studied, but the reverse causality argument cannot be ruled out.	• Depression will be assessed as a risk factor for poor recovery, independent of disease severity; depression-CHD causality will not be directly tested.
3. Depression is thought to be an important prognostic marker in cardiac patients, but a wide range of recovery endpoints have yet to be investigated in CABG patients.	• Multiple recovery endpoints will be studied, including clinical, physical, emotional and quality of life factors.
4. The relevance of changes in depression over time is thought to be important, but is not easily studied in ACS patients due to problems with recall bias.	• Depression will be studied prospectively, both pre- and post-operatively.
5. Different symptom subtypes of depression have been studied in ACS patients and are thought to affect cardiac prognosis, but have not been well-studied in CABG patients.	• Depression symptom subtypes will be explored in relation to recovery, including both somatic/affective and cognitive/affection symptoms.
6. Multiple mechanisms are thought to exist by which depression may affect recovery, but these are yet to be systematically studied.	• Information on multiple possible mechanisms, including behavioural, social, cognitive and biological factors will be collected.

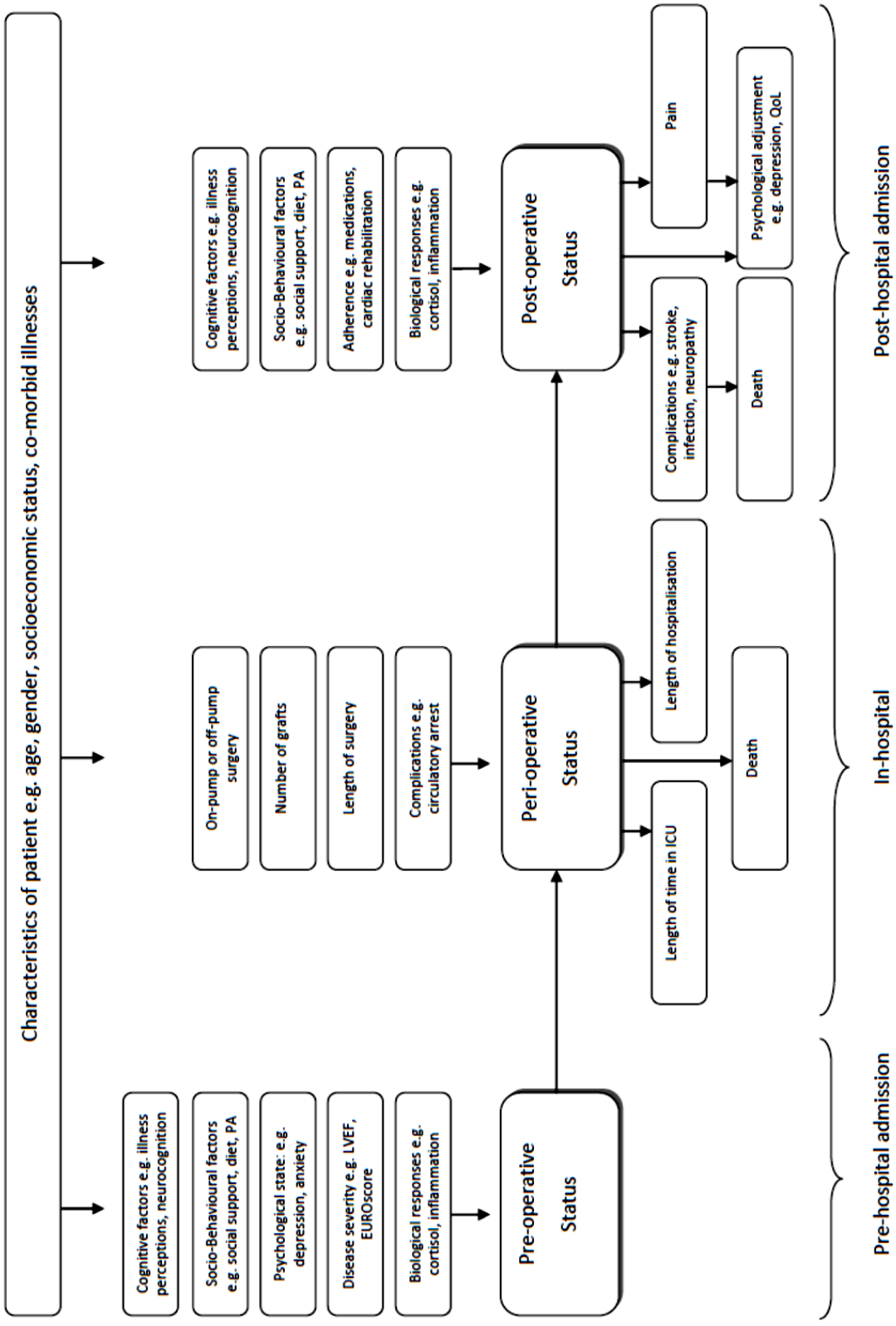

FIGURE 2.4: A MODEL REPRESENTING THE PATHWAYS FROM PRE-SURGERY TO POST-SURGERY PHASES OF RECOVERY IN CABG PATIENTS

LVEF: left ventricular ejection fraction; ICU: intensive care unit; PA: physical activity; QoL: quality of life

Chapter 3. Method: Pilot study

3.1 Introduction and study aims

Emotional adjustment, and in particular depression, has been described in the literature review as a significant risk factor for poor prognosis in CHD, both in ACS and CABG patients. By using CABG patients, as opposed to ACS patients, we can advance our understanding of the causal pathways by which CHD and depression are associated and how they interact to affect recovery. As previously discussed, research is beginning to explore these mechanisms, but a comprehensive study of all the different factors has yet to be undertaken and there is a need for longitudinal, prospective exploration to elucidate the independent contribution and interaction of these competing pathways.

To investigate the causes and consequences of poor emotional adaptation and adjustment in cardiac surgery patients requires the development of such a study. In particular the study must aim to extend the current literature in three ways. Firstly, using a prospective longitudinal design, rather than a cross-sectional study, will enable the temporal sequence of depression and the recovery process to be observed. Next, by using a multidisciplinary approach the study will simultaneously be able to assess behavioural, social, psychological, cognitive and biological factors, all of which are thought to operate along the causal pathway. Lastly, the use of pre-operative and post-operative time points will allow for the collection of baseline mood and disease severity measures, against which to compare follow-up assessments.

The Adjustment and Recovery after Cardiac Surgery (ARCS) study was coined so as to investigate the causes and consequences of poor emotional wellbeing following CABG surgery, and their implications for patient quality of life and physical recovery. To establish the method for this study, a pilot study was first designed to test the feasibility of conducting the ARCS study and to establish the suitability of the measures for the sample. The development of the ARCS study and the undertaking of the pilot study form the first part of this PhD. The aims for the ARCS pilot study (P-ARCS) can be stated as:

1. To design a prospective, longitudinal study for repeated assessment of psychosocial and cognitive factors relevant to recovery and quality of life in cardiac surgery patients.
2. To establish a collaboration with a hospital and clinical team for the purpose of data collection.
3. To conduct preliminary analyses on the collected data to assess the feasibility of the ARCS study and the suitability of questionnaire measures and to ascertain initial associations between variables.

3.2 Recruitment and data collection site

In order to set-up P-ARCS, collaboration with Professor Marjan Jahangiri (MJ) from the cardiothoracic surgery team at St. George's Hospital, University of London[5], was established in order to identify and target the sample population. This hospital was selected for a number of reasons. St. George's has one of the largest cardiology departments in the country and is part of the southwest London cardiac network; it was named, in 2006, as the heart attack centre in southwest London due to its 24-hour angioplasty service. The cardiothoracic surgery team consists of five consulting surgeons who perform CABG surgery, with data from 2008-2009 showing an average survival rate of 98.7% (542 operations) and 6.2% of patients having in-hospital stay of more than 14 days (Care Quality Commission, 2010). In addition, Steptoe's (AS) group has previously worked with St. George's cardiology department researching ACS patients (Steptoe, Molloy, et al., 2011a; Steptoe, Molloy, et al., 2011b; Steptoe, Wikman, Molloy, & Kaski, 2012).

3.3 Participants

We planned consecutive recruitment of up to 100 CABG surgery patients for P-ARCS, with minimal exclusions. We decided upon this sample size in order to give ourselves time to adapt the protocol where necessary, to establish the rate of refusal to participate and withdrawal and to have enough data on which to run preliminary analyses of associations between variables. The inclusion criteria were patients who were undergoing first-time, elective CABG surgery or CABG plus valve replacement, at St George's Hospital, London. We decided to exclude emergency cases for both logistical and methodological reasons. Emergency cases are usually admitted through accident and emergency wards and as such are usually stabilised overnight before surgery the following day. Therefore, there is little time to obtain informed consent of these patients and, for those in agreement, to complete the questionnaires. Moreover, baseline values of emotional distress are likely to differ from elective patients who have been to the pre-assessment clinic; this reasoning also applies for re-do cases, which is why we chose to use first-time CABG patients only. Other inclusion criteria were that patients must have been able to complete the research interviews and questionnaires in English, and have been 18 years or older. Participants with communication or cognitive impairments were excluded since this would have affected their ability to complete the questionnaires; this was assessed on the recommendation of the pre-assessment nursing staff. Participants who were too unwell or clinically unstable were also excluded for ethical reasons.

[5] http://www.stgeorges.nhs.uk/services_cardiology.asp

3.4 Study design and procedure

P-ARCS used a prospective, longitudinal design incorporating three assessments spanning the pre-operative period until two months following cardiac surgery. The time one (T1) assessment was planned to occur approximately one to three weeks prior to surgery when patients attended their pre-assessment clinic appointment in the hospital outpatients department. The time two (T2) assessment took place three to five days after surgery while patients were in hospital on the cardiac care ward. The time three (T3) appointment took place approximately six to eight weeks after surgery via post. These time points were selected to maximise access to patients. By recruiting patients at the pre-assessment clinic ensured patients could be met in person by one of the research team and have the opportunity to ask any questions about the research study. The T2 assessment was chosen in order to assess patients in the acute phase of recovery while still in the hospital. Finally, patients are expected to be able to return to normal functioning within two months of surgery and are usually discharged from their surgeon's care at the six-week post-surgery outpatient appointment; hence T3 was selected to coincide with this point.

As stated in the aims, P-ARCS was designed to assess psychosocial and cognitive factors; biological factors were not included at this stage. The study obtained ethical approval (South West London REC1, 09/H0708/38). The procedure for assessing participants at each of the three time points is described below. Full details of measures included at each time point are provided in Section 3.5.

Time 1 (1-3 weeks before surgery): Prior to being approached in person, a letter introducing the study and a participant information sheet was sent to all patients scheduled for elective CABG surgery. This first point of contact was made by the clinical team to avoid breach of confidentiality. A member of the research team (Dr Tara Kidd (TK) and Ms Lydia Poole (LP)) then approached patients in the waiting area of the pre-assessment surgery clinic and asked if they would be willing to participate in the study. The procedure was explained, before obtaining signed consent. The researcher discreetly conducted a brief interview with the patient in the waiting area to collect demographic information and to assess health literacy. The participant was also issued with a postal questionnaire to self-complete and return in a freepost envelope. The measures assessed included demographic information, emotional distress, health behaviour, health status, social support, marital functioning and illness perceptions.

Time 2 (3-5 days after surgery): Participants were approached in the cardiac care ward during their post-surgery recovery and asked if they would be willing to participate in the second assessment. Having gained verbal consent, the researcher discreetly conducted a brief

structured interview. The interview included questionnaire measures of emotional distress, pain, and physical symptoms.

Time 3 (6-8 weeks after surgery): Participants were telephoned and asked if they would be willing to participate in the final assessment. If in agreement, a postal questionnaire was sent for self-completion. This incorporated measures used at T1 and T2 as well as an additional measure of surgery satisfaction. A freepost envelope was provided for return of the completed questionnaire.

3.5 Measures

3.5.1 Identifying measures

P-ARCS used questionnaire measures for the assessment of psychosocial and cognitive factors. This has particular implications for the measurement of depression, where clinical diagnosis can be given only through administration of a clinical interview. As such, questionnaire measures are said to capture depression symptoms and not depression *per se*. This decision was taken for a number of reasons. Principally, it was a decision of cost and time, with questionnaire measures being cheaper and quicker to administer than clinical interviews. Furthermore, it was also a logistical decision regarding access to patients and ease of follow-up: questionnaires can be self-completed and returned via post. Questionnaire measures of depression symptoms have been widely used in cardiac populations, however there is some discrepancy in their sensitivity (the proportion of depression cases correctly identified as such) and specificity (the proportion of non-depression cases correctly identified as such) (Thombs et al., 2008). As such we were aware of the need for careful choice of cut-offs and planned to use continuous variables where possible.

All questionnaire measures were researched and selected based on several criteria. First, measures that have been used previously in cardiac populations were given preference. Second, those measures that have been shown to be valid over repeated time points and thus suited to the longitudinal study design were deemed most appropriate. Third, validated brief or shortened versions were chosen over and above full versions to reduce the questionnaire burden on participants. Where this was not possible, some subscales were used, rather than the full measure. Although from a methodological perspective this latter approach is not ideal, this decision was taken in order to reduce conceptual overlap across items and also to minimise the questionnaire length. The T2 measures were administered as an interview to aid completion. Table 3.1 presents the questionnaire measures used at each assessment. Full details of individual measures are given below and are included in Appendices 2 and 3.

TABLE 3.1: MEASURES IN THE ARCS PILOT STUDY

BDI: Beck Depression Inventory; BIPQ: Brief Illness Perception Questionnaire; CROQ-CABG: Coronary Revascularisation Outcomes Questionnaire; ESSI: ENRICHD Social Support Instrument; HADS: Hospital Anxiety and Depression Scale; IPAQ: International Physical Activity Questionnaire; MARS: Medication Adherence Report Scale; MPQ-SF: McGill Pain Questionnaire – Short Form; SAQ: Seattle Angina Questionnaire; SF-12: Short Form health survey – 12 item; STOFHLA: Short Test of Functional Health Literacy in Adults; YCBQ: York Cardiac Beliefs Questionnaire.

Mode of assessment	*T1* *Interview/ Postal*	*T2* *Interview*	*T3* *Postal*
Time	*1-3 weeks pre-CABG*	*3-5 days post-CABG*	*6-8 weeks post-CABG*
Measures			
Socio-demographics – general	✓	-	-
Socio-economic status - income	✓	-	-
Cardiac rehabilitation attendance	-	-	-
Clinical information	-	-	✓
Emotional distress			
Depression (BDI)	✓	✓	✓
Anxiety (HADS subscale)	✓	✓	✓
Health status			
Health status (SF-12)	✓	-	✓
Health behaviour			
Adherence (MARS)	✓	-	✓
Physical activity (IPAQ – walking)	✓	-	✓
Diet	✓	-	✓
Sleep (Jenkins Scale)	✓	-	✓
Smoking	✓	-	✓
Alcohol	✓	-	✓
Cognitive function			
Health literacy (STOFHLA – prose subscale)	✓	-	-
Illness beliefs			
Illness perceptions (BIPQ)	✓	-	✓
Cardiac beliefs (YCBQ)	✓	-	✓
Social support			
Social network	✓	-	_
Social support (ESSI)	✓	-	✓
Marital quality	✓	-	✓
Physical symptoms			
Angina (SAQ adapted)	✓	-	✓
Pain (MPQ-SF)	-	✓	✓
Symptoms (CROQ-CABG)	-	✓	✓
Satisfaction			
Satisfaction (CROQ-CABG)	-	-	✓

3.5.2 Demographic information

Personal details were collected from all participants to include age, marital status, ethnicity and religious affiliation. In addition, three markers of socio-economic status were obtained: level of education, household income and occupational status. All educational qualifications were self-reported and categorised as: no educational qualifications, school certificate, GCE O-levels/GCSEs/O-levels/CSEs, GCE A-levels, undergraduate degree, postgraduate degree and other. For statistical purposes, these groupings were categorised as none, secondary education (school certificate/ CSEs/ RSA/ City & Guilds/ GCE O-levels/ GCSEs/ ONC/ OND), higher secondary (GCE A-levels/ HND/ HNC) and degree (undergraduate/ postgraduate). Annual household income was categorised as under £10,000, £10,000 to £20,000, £20,000 to £30,000 and more than £40,000. Occupational status was assessed by asking participants to specify their job title. If retired, participants were asked to record their last major occupation. Occupations were classified according to the UK Office for National Statistics 2010 guidelines (Office for National Statistics, 2010). According to these guidelines, nine occupational classifications were assigned: managers, directors and senior officials, professional occupations, associate professional and technical occupations, administrative and secretarial occupations, skilled trade occupations, caring, leisure and other service occupations, sales and customer service occupations, process, plant and machine operatives, elementary occupations.

3.5.3 Clinical information

Clinical information was gathered from patients' medical notes. Information gathered included, pre-operative details such as medical history and co-morbidities, cardiac history, height, weight, medications, perioperative details including graft sites, cardiopulmonary time, intra-operative blood products, and post-operative details including medications, complications and length of intensive care unit (ICU) stay.

We employed two markers of disease severity: LVEF and the European System for Cardiac Operative Risk Evaluation (euroSCORE). LVEF was measured by echocardiogram and refers to the percentage of blood pumped through the heart's left ventricle with each contraction; it is commonly used as a proxy measure of heart function. We dichotomised LVEF into high (≥ 50%) and low (≤ 49%), with higher scores indicative of normal functioning. The euroSCORE (Roques et al., 1999) is a composite measure of risk based on 17 factors comprising patient-related factors (e.g. age, gender), cardiac-related factors (e.g. unstable angina, recent MI) and surgery-related factors (e.g. surgery on thoracic aorta). Appendix 4 provides a copy of the scoring sheet for the euroSCORE using the additive method; full details are available on the

euroSCORE website[6]. Scores for the 17 factors were summed to produce a total score, ranging from 1 to 39, with higher scores indicating greater risk.

3.5.4 Emotional distress

3.5.4.1 Beck Depression Inventory

The BDI (Beck, Steer, & Carbin, 1988) can be used to determine the intensity of depression in psychiatrically diagnosed populations and also to diagnose depression in healthy, non-psychiatric individuals. Moreover, the National Heart, Lung and Blood Institute Working Group recommend its use in epidemiological studies and to gain a depression severity rating during a trial (Davidson et al., 2006). A systematic review suggested the BDI to be preferable to the HADS for measuring depression symptoms in cardiac patients (Thombs et al., 2006). It is a 21-item questionnaire which provides groups of four statements per question and asks the respondent to choose the one statement which best reflects how they have been feeling over the past two weeks.

The BDI was scored by summing each chosen answer (on a scale of 0 to 3), higher scores indicating greater emotional disturbance, with a range of 0 to 63. A score of 0 to 10 indicates a person is not depressed, 11 to 20 suggests a person is mildly to borderline clinically depressed, 21 to 30 signifies moderate depression and a score of 31 to 63 indicates severe to extreme depression. The BDI is thought to be suitable for use in repeated measure designs, showing high sensitivity to change across time (Richter, Werner, Heerlein, Kraus, & Sauer, 1998).

A systematic review (Thombs et al., 2008) of screening instruments used to detect depression in cardiac patients cites three studies using a BDI cut-off score of ≥10 with a mean sensitivity range between 82% and 88% and a mean specificity score range between 58% and 79% (Frasure-Smith, Lespérance, & Talajic, 1995; Freedland et al., 2003; Strik, Honig, Lousberg, & Denollet, 2001). One study used a BDI cut-off ≥13 finding a mean sensitivity value of 83% and a mean specificity value of 94% (Gutierrez & Davis, 1999). Therefore, where necessary we applied a conservative cut-off of ≥13. The Cronbach's alpha for this questionnaire in P-ARCS was 0.78, 0.78 and 0.75, at T1, T2 and T3 respectively.

3.5.4.2 Hospital Anxiety and Depression Scale

The HADS was designed as a self-report, 14-item measure of anxiety and depression for use in an outpatient clinical setting (Zigmond & Snaith, 1983) and as such does not include any somatic symptom questions. The HADS has been found to be sensitive to change across time in

[6] http://www.euroscore.org/index.htm

medical patients and in response to therapeutic intervention, making it suitable for use in longitudinal studies (Herrmann, 1997). The HADS has been used in cardiac patients, with a systematic review of its use in MI patients finding it to under-report depression prevalence as compared to the BDI and clinical interviews, probably due to its omission of somatic symptoms which may overlap with the physical symptoms of heart disease (Thombs et al., 2006). Therefore, in the ARCS study we used the seven-item anxiety subscale only. This subscale was favoured over other anxiety questionnaires, such as the 21-item Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988), because of its brevity. The validity of the HADS has recently been scrutinised, with concerns regarding its latent structure and its ability to differentiate between cases of depression and anxiety (Cosco, Doyle, Ward, & McGee, 2012; Coyne & van Sonderen, 2012). These latter authors also point out issues surrounding use of colloquialisms in the HADS such as "butterflies in the stomach" and the subtlety of the reverse phrasing of some items such as "I can sit at ease and feel relaxed", which they argue leads to response errors by participants. The limitations of this measure will therefore be borne in mind throughout this thesis.

Questions are answered on a Likert scale ranging from 0 to 3, to indicate the extent to which the symptom has been experienced over the past two weeks. Items were summed to generate an overall score, with reverse coding on item 4 (*I can sit at ease and feel relaxed*) and item 5 (*I get a sort of frightened feeling like 'butterflies' in the stomach*). Scores range from 0 to 21 and the recognised cut-off for moderate anxiety is ≥8, with higher scores indicating greater anxiety. The Cronbach's alpha for this questionnaire in P-ARCS was 0.91, 0.76 and 0.76, at T1, T2 and T3 respectively.

3.5.5 Health status

3.5.5.1 Short form health survey – 12 item

The Short Form health survey–12-item (SF-12) (Ware, Kosinski, & Keller, 1996) has been developed as a brief version of the SF-36 and is a measure of health related quality of life, or 'health status', along two dimensions – mental and physical. Findings suggest that the SF-12 is comparable to the SF-36 in detecting change across time in longitudinal studies, for both the mental and physical component scores (Jenkinson et al., 1997). The SF-36 has been used widely in cardiac patients and has recently been used in CABG patients to evaluate the effects of a telephone-delivered collaborative care programme for the treatment of post-CABG depression (Rollman et al., 2009). The shorter SF-12 was selected over the SF-36 for P-ARCS to reduce the questionnaire burden on participants. Different items on the SF-12 have different response categories, some questions having a binary response (yes/no), while others have a Likert scale (3- or 5-point). Questions were coded, summarised and calibrated into a scale

ranging from 0 (worst possible health) to 100 (best possible health) to give a mental and physical score, both with a normative value of 50. The Cronbach's alpha for this questionnaire in P-ARCS was 0.62 and 0.51 at T1 and T3 respectively for the physical component score and 0.61 and 0.65 at T1 and T3 respectively for the mental component score.

3.5.6 Health behavior

3.5.6.1 Physical activity

Physical activity was assessed using the walking item from the International Physical Activity Questionnaire (IPAQ) (Booth, 2000), which asks the number of days a participant walked for at least 10 minutes at a time in the past week, and the average length of time spent walking on one of those days. This was used to calculate average time spent walking per week, in hours. Given the target population in P-ARCS we chose not to use other items from this measure, which capture moderate and vigorous physical activities, since these are rare in a population of older people with advanced CHD.

3.5.6.2 Diet

Dietary choices were assessed using a two-item fruit and vegetable scale (Cappuccio et al., 2003) which asks the participant to estimate the average number of portions of fruit and vegetables (excluding potatoes) they consume per day and how often they eat less than this per week. Results were used to calculate average daily fruit and vegetable intake (pieces/week). Dietary fat intake was assessed using a nine-item scale relating to the frequency certain fatty foods are consumed, such as butter, cheese and processed meats. Scores range from 0 to 27, with higher scores reflecting a higher fat diet.

3.5.6.3 Smoking

Smoking of tobacco, including cigarettes, cigars and pipes, was assessed using standard survey questions to allow participants to be classified as a current smoker, an ex-smoker, or someone who had never smoked. Smokers were also asked to estimate the number of cigarettes smoked in a day. Current use of nicotine replacement therapy was also measured.

3.5.6.4 Alcohol consumption

Estimated weekly alcohol consumption in units was self-reported (one unit = half a pint of beer, one small glass of wine, or one measure of spirit). These responses were used to produce an estimate of weekly intake of alcohol units.

3.5.6.5 Medication Adherence Report Scale

The Medication Adherence Report Scale (MARS) was developed by Horne and Weinman (Horne & Weinman, 1999) as a brief five-item measure of medication adherent behaviours. The MARS has been used previously in cardiac populations (Molloy et al., 2012; Williams, O'Connor, Grubb, & O'Carroll, 2011) and has been validated against electronic monitoring devices (Cohen et al., 2008). The items of the MARS are: 1) I forget to take my medicines, 2) I alter the dose of my medicines, 3) I stop taking my medicines for a while, 4) I decide to miss out a dose, 5) I take less than instructed. Responses are given on a five-point Likert scale ranging from 0 (*Never*) to 4 (*Always*). Items were summed, with a range of 0 to 20; higher scores indicating greater medication non-adherence. The Cronbach's alpha for this questionnaire in P-ARCS was 0.80 and 0.72, at T1 and T3 respectively.

3.5.6.6 Jenkins Sleep Problems Scale

Sleep problems were assessed using an adapted version of the Jenkins Sleep Problems Scale (Jenkins, Stanton, Niemcryk, & Rose, 1988), a widely used brief self-report instrument which was specifically developed for use in clinical populations. In addition to the original four-item scale, a fifth item was included: "how often in the past month did you have disturbed or restless sleep?" (Kumari et al., 2009). The Jenkins scale has been used to assess sleep problems in cardiac surgery patients in a prospective study which was designed to investigate predictors of cardiac symptoms up to six months following surgery (Jenkins et al., 1996). Participants are asked to respond to the questions by estimating the number of days each sleep complaint was experienced during the previous month. A total score was derived by summing responses from 0 (*Not at all*) to 5 (*21 to 31 days of the month*). Scores could range from 0 to 25, with higher scores indicating greater sleep disturbance. The Cronbach's alpha for this questionnaire in P-ARCS was 0.88 and 0.90, at T1 and T3 respectively.

3.5.7 Physical symptoms

3.5.7.1 Seattle Angina Questionnaire

The Seattle Angina Questionnaire (SAQ) (Spertus et al., 1995) was developed as a disease-specific measure of health-related quality of life. SAQ is a 19-item self-administered questionnaire which measures five dimensions of CHD: physical limitation, angina stability, angina frequency, treatment satisfaction and disease perception. The scale has been found to be a valid and reliable measure of quality of life in cardiac populations and was found to be sensitive to clinical change. It has been previously used in CABG populations as an outcome measure to assess CABG recovery (Folkmann et al., 2010; Huber, Goeber, Berdat, Carrel, &

Eckstein, 2007) and to evaluate the effectiveness of a post-CABG home-based psycho-educational programme (Lie, Arnesen, Sandvik, Hamilton, & Bunch, 2009). In order to avoid overlap with the SF-12, in P-ARCS we employed an adapted six-item version, assessing the dimensions of angina frequency and treatment satisfaction only. Questions require responses using either a five- or six-point Likert scale. Two scores were derived: an angina frequency score ranging from 0 to 15 and a treatment satisfaction score ranging from 0 to 12; higher scores on the former indicate poorer functioning and on the latter indicate greater treatment satisfaction. The Cronbach's alpha for angina frequency in P-ARCS was 0.58 and 0.59, at T1 and T3 respectively, and for treatment satisfaction it was 0.87 and 0.91, at T1 and T3 respectively.

3.5.7.2 McGill Pain Questionnaire – Short Form

The McGill Pain Questionnaire – Short Form (MPQ-SF) (Melzack, 1987) was developed as a brief version of the standard MPQ and is suitable for use in post-surgical patients. The MPQ has been used in CABG surgery patients to assess recovery (Bruce et al., 2003; Eisenberg, Pultorak, Pud, & Bar-El, 2001; Parry et al., 2010). There are three components to the MPQ-SF: the first is a list of 15 affective (e.g. fearful) and sensory (e.g. throbbing) descriptor words for which respondents are asked to rate their current experience of that particular type of pain from 0 (*none*) to 3 (*severe*)*,* the second is a rating scale of total pain and the final component is a present pain intensity scale from 0 (*no pain*) to 5 (*excruciating*). The MPQ-SF has been shown to be sensitive to change according to analgesic use and can be used for repeated measure assessments (Melzack, 1987). After piloting the scale on several participants (n = 4) at T2, we decided to employ an adapted version, changing the rating scale from a visual analogue scale to a numerical rating scale to aid completion for our patient group. We derived four separate scores. The affective pain score is the sum of the intensity values for the affective descriptor words (range: 0 to 12) and, similarly, the sensory pain score is the sum of the intensity values for the sensory descriptor words (range: 0 to 33). The Likert scale response for the numerical rating scale (range: 0 to 10) and the pain intensity scale (range: 0 to 5) comprise the scores for these items. The Cronbach's alpha for the sensory pain subscale in P-ARCS was 0.61 and 0.73, at T2 and T3 respectively, and for the affective pain subscale it was 0.45 and 0.56, at T2 and T3 respectively.

3.5.7.3 Coronary Revascularisation Outcomes Questionnaire

The Coronary Revascularisation Outcomes Questionnaire (CROQ) (Schroter & Lamping, 2004) was designed to assess quality of life and health outcomes following cardiac surgery. The CROQ is comprised of several subscales relevant to the pre-operative period, such as angina symptoms, physical functioning and psychosocial functioning, and the post-operative period

such as physical symptoms for CABG patients and angioplasty patients. The pre-operative scales greatly overlap with the SF-12 and SAQ which are included in P-ARCS. Therefore, this study only used the 11-item post-surgery physical symptom subscale from the version designed for CABG surgery patients. This scale asks patients to rate the extent to which they have experienced certain physical symptoms related to their surgery such as bruising, numbness and tingling and swelling, using a five-point Likert scale ranging from 0 (*Not at all*) to 4 (*A lot*). Responses were summed, ranging from 0 to 44, with higher scores indicating greater negative symptoms. The Cronbach's alpha for this questionnaire in P-ARCS was 0.48 and 0.78, at T2 and T3 respectively.

We also used the CROQ six-item satisfaction scale, which asks patients to rate the extent to which they are satisfied with their care and their recovery. Participants responded to the first three of these items on a four-point Likert scale ranging from 0 (*very dissatisfied*) to 3 (*very satisfied*). The fourth item used a five-point Likert scale ranging from 0 (*much worse*) to 4 (*much better*); the fifth item used a three-point Likert scale ranging from 0 (*slower than expected*) to 2 (*faster than expected*) and the sixth item also used a three-point Likert scale ranging from 0 (*worse than expected*) to 2 (*better than expected*). Responses were summed, ranging from 0 to 17, with higher scores indicating better satisfaction. The Cronbach's alpha for the satisfaction subscale at T3 was 0.73.

3.5.8 Cognitive function

3.5.8.1 The Short Test of Functional Health Literacy in Adults

The Short Test of Functional Health Literacy in Adults (STOFHLA) is a validated abbreviated version of the original 20-item test (Baker, Williams, Parker, Gazmararian, & Nurss, 1999). The STOFHLA consists of four numeracy items and two prose passages and is designed to offer a brief assessment of functional health literacy, which refers to a person's ability to read and understand information in a health care environment. This assessment has been used in cardiac populations, including hypertension (Levinthal, Morrow, Tu, Wu, & Murray, 2008) and heart failure (Morrow et al., 2006) patients. We utilised the 11-item comprehension task (prose passage A) of the STOFHLA, which describes the imaginary medical scenario of undergoing a stomach x-ray. Participants were required to complete the sentences using one of four given words.

The full STOFHLA requires scores to be summed and weighted in order to derive a total score. Since we were utilising just a sub-section of the full measure, we planned to simply sum responses for use as a continuous measure; higher scores would indicate better health literacy. However, after piloting the STOFHLA on several participants (n = 6) it became apparent that for those who had difficulty in completing the measure, the waiting room was an unsuitable

environment for its administration. Due to limited research room availability at the time of the pilot study, we were forced to remove the STOFHLA from P-ARCS.

3.5.9 Social support

3.5.9.1 Social networks

Social networks refer to the size of a person's social support structure. We employed a questionnaire developed by Cohen and colleagues (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997) which asks participants to think back over a typical two-week period and rate the frequency of social interaction with 11 sets of possible contacts, such as children, friends, neighbours and work colleagues. In line with work published previously by Steptoe's group in cardiac patients (Molloy, Perkins-Porras, Strike, et al., 2008), we scored responses according to the number of social contacts a participant spoke with (either in person or by telephone), with each type of relationship being assigned a score of 1. Scores range from 0 to 13, with greater values indicating more diverse social networks.

3.5.9.2 The ENRICHD Social Support Instrument

The ENRCIHD Social Support Instrument (ESSI) is a validated seven-item scale to assess the quality of social support. This measure was developed specifically for use in the ENRCIHD study of cardiac patients (Mitchell et al., 2003). The items relate to structural (i.e. partner) support, instrumental (i.e. tangible) support and emotional (i.e. caring) support. Example items include: "is there someone available to whom you can count on to listen to you when you need to talk?" and "is there someone there to help you with daily chores?" The response categories are on a five-point Likert scale ranging from 1 (*None of the time*) to 5 (*All of the time*). Responses to item 7 ("Are you currently married or living with a partner?") were scored 4 (*Yes*) and 2 (*No*) in accordance with the scoring guidelines from the original scale. Responses were summed to produce a total score, ranging from 8 to 34; higher scores indicate greater social support. The Cronbach's alpha for this questionnaire in P-ARCS was 0.93 at both T1 and T3.

3.5.9.3 Marital quality

The marital quality scale was developed by Troxel and colleagues (Troxel, Matthews, Gallo, & Kuller, 2005) as a brief, seven-item, measure of marital satisfaction in the Pittsburgh Healthy Women Study. This measure asks participants to rate the amount of satisfaction they perceived with their cohabiting partner or spouse, across seven different domains: time spent together, communication, sexual activity, agreement on financial matters, and similarity of interests, lifestyle and temperament. This questionnaire was only completed by participants to whom it was applicable. Possible scores range from 0 to 21, with scores awarded on a four-

point Likert scale from 0 (*Not at all satisfied*) to 3 (*Very satisfied*); greater scores indicating higher marital quality. The Cronbach's alpha for this questionnaire in P-ARCS was 0.85 and 0.82, at T1 and T3 respectively.

3.5.10 Illness beliefs

3.5.10.1 Brief Illness Perceptions Questionnaire

The Brief Illness Perceptions Questionnaire (BIPQ) (Broadbent, Petrie, Main, & Weinman, 2006) was designed as a short nine-item version of the IPQ to provide rapid assessment of emotional and cognitive representations of illness. The IPQ has been used in cardiac surgery populations previously to assess emotional adaptation following surgery (Dunkel, Kendel, Lehmkuhl, Hetzer, & Regitz-Zagrosek, 2011; Juergens et al., 2010). The brief version was utilised in P-ARCS to minimise the questionnaire load. The first eight items ask respondents to rate the extent to which a statement corresponds to their views on a scale from 0 to 10. The last item asks respondents to list the three most important factors that they believe caused their illness. A total score of the first eight items was derived by summing the responses, with items 3, 4 and 7 reverse coded. The range for this questionnaire is 0 to 80. Individual items can also be used to reflect the different illness perception dimensions: consequences, timeline, personal control, treatment control, identity, concern, emotional representation, and illness comprehensibility. The responses to item 9 were scored by grouping the proffered causes into categories such as hereditary, stress, lifestyle etc., and then performing categorical analysis. The Cronbach's alpha for this questionnaire (items 1-8) in P-ARCS was 0.67 and 0.82, at T1 and T3 respectively.

3.5.10.2 The York Cardiac Beliefs Questionnaire

The York Cardiac Beliefs Questionnaire (YCBQ) (Furze et al., 2009) was designed as a measure of common misconceptions that patients often have about living with heart disease, such as "people who have heart disease should never get excited or upset" and "heart problems are a sign that you have a worn out heart". There are three subscales to this questionnaire, one which covers common misconceptions relating to heart disease, one relating to angina and another relating to MI; this study utilised the 12-item heart disease subscale only. There are also two versions, one for use in clinical practice and another for use in research; the latter was used in P-ARCS. Respondents are asked to rate the extent to which they agree or disagree with 12 statements on a scale from 0 (*strongly disagree*) to 4 (*strongly agree*). A total score was derived by summing the responses (scores ranging from 0 to 48), with items 6 and 7 reverse coded. Higher scores reflect more misconceptions. The Cronbach's alpha for this questionnaire in P-ARCS was 0.85 at both T1 and T3.

3.6 Data storage

Data were collated and stored in line with ethical guidelines and University College London (UCL) policy. All data were treated as strictly confidential. The project was registered with the UCL Data Protection Office. Consent forms and patient personal details were stored separately from the questionnaire data; all data were stored in locked filing cabinets, in locked offices at UCL. Anonymised raw data were entered into a computer database for statistical analysis; personal identification information was kept in a separate file to the questionnaire responses. Data were kept on password protected computers, in files accessible only to the study researchers. Data may be kept in this secure manner for up to 20 years prior to being destroyed.

3.7 My involvement and contribution

The research question regarding depression symptoms and cardiac recovery was mutually established between myself and AS. AS has worked extensively in the depression and ACS field and under his tutelage I first authored a review paper of the ACS and depression literature (Poole, Dickens, et al., 2011). In researching the literature for this review paper I became interested in the cardiac surgery population and through discussion with AS, the ARCS study began to take shape. AS established the collaboration with St. George's hospital and introduced me to MJ. Together, AS and I applied for National Health Service (NHS) ethical approval and host site approval. I began to liaise with the nursing team to set-up the study and to establish a protocol for recruitment. TK and I began recruiting for the pilot study in December 2009 and data collection for T2 and T3 assessments continued through to October 2010. Clinical data was collected by a clinical research associate (Dr Kate Evans). I was responsible for creating all the P-ARCS questionnaires and resources. In addition, I was in charge of maintaining participant records and T3 assessments and prompts. Along with help from another PhD student (Ms Elizabeth Leigh [EL]), I completed all the data entry for the pilot study. I conducted all the statistical analyses myself, with guidance from my supervisor, AS.

3.8 Statistical analysis

All statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, Illinois, USA). The significance level was set to $p < 0.05$ for all analyses, with precise p values reported for all test results. Specific details on the analyses conducted are presented in the results section of Chapter 4.

Chapter 4. Results: Pilot study

4.1 Introduction

P-ARCS was carried out between December 2009 and October 2010. To reiterate, the aims of the pilot study were threefold:

1. To design a prospective, longitudinal study for repeated assessment of psychosocial and cognitive factors relevant to recovery and quality of life in cardiac surgery patients.
2. To establish a collaboration with a hospital and clinical team for the purpose of data collection.
3. To conduct preliminary analyses on the collected data to assess the feasibility of the ARCS study and the suitability of questionnaire measures, and to ascertain initial associations between variables.

Having described the first of these two aims in Chapter 3, this chapter will present the results pertaining to the third aim. First the recruitment statistics will be described, followed by descriptive analyses of the questionnaire measures. Lastly, preliminary analyses of associations between data will be presented, specifically the associations between pre-operative illness perceptions and recovery and pre-operative sleep disturbance and recovery.

4.2 Uptake, attrition and missing data

TABLE 4.1: ATTRITION NUMBERS AND REASONS

Reason for non-completion	*Time point missing*	*n*
Clinical events		5
Death	T3	3
Stroke	T3	2
Non-return of questionnaires		25
T1 questionnaires never returned	T1	9
T2 questionnaires – participant refused to complete at this time point	T2	8
T2 questionnaires – patient discharged at weekend	T2	1
T3 questionnaires never returned	T3	7
Clinical data		5
Unable to track medical notes	T3	5

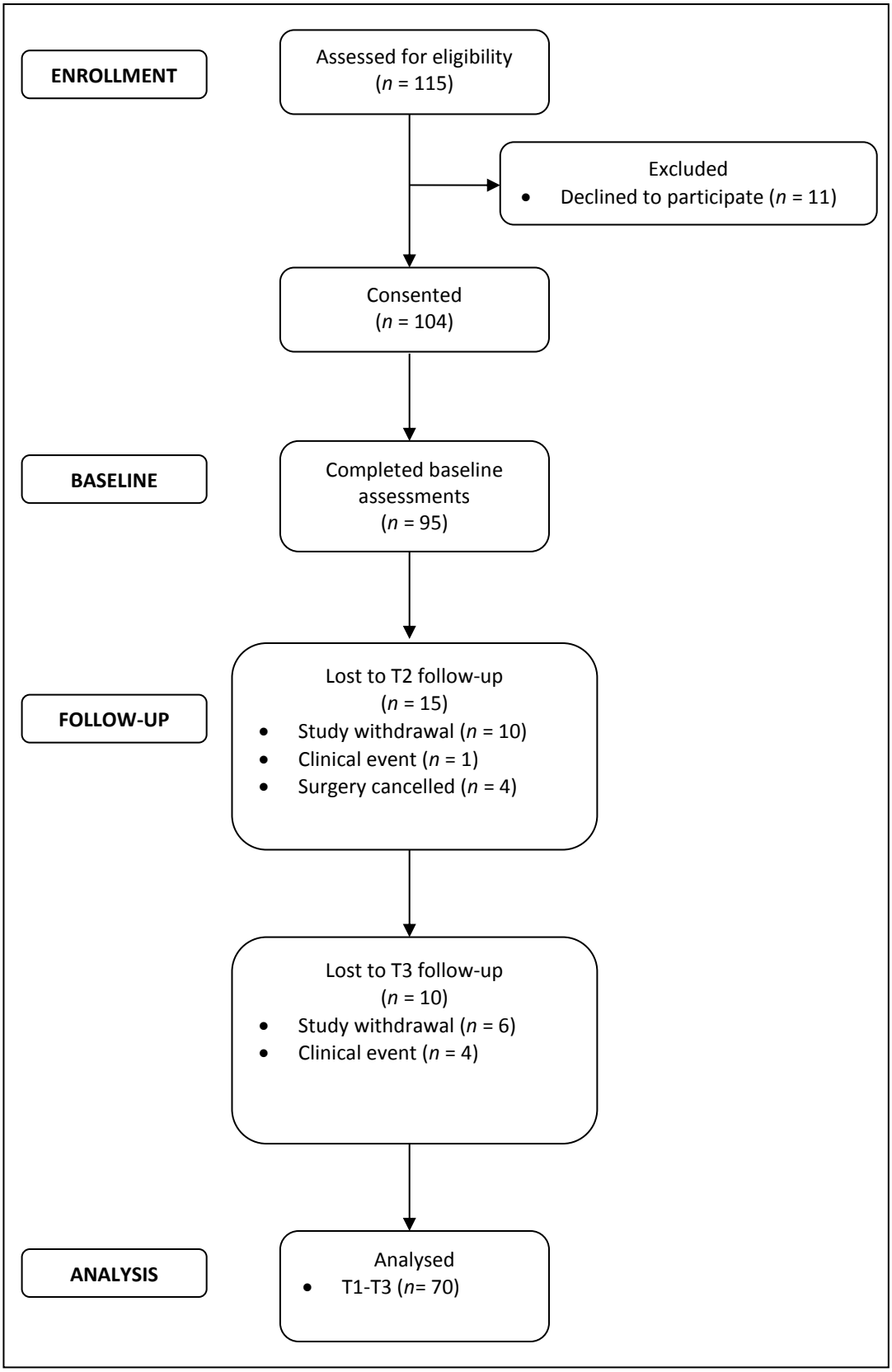

FIGURE 4.1: FLOW DIAGRAM OF PARTICIPANTS' PROGRESSION THROUGH THE PILOT STUDY

TABLE 4.2: TYPES OF MISSING QUESTIONNAIRE DATA IN ANALYTIC SAMPLE (N = 70)

Measures	*T1*	*T2*	*T3*
Socio-demographics			
Education	2	-	-
Income	13	-	-
Cardiac rehabilitation attendance	-	-	5
Emotional distress			
Depression (BDI)	8	4	16
Anxiety (HADS subscale)	2	0	5
Health status			
Health status (SF-12) – Physical	0	-	5
Health status (SF-12) – Mental	0	-	5
Health behaviour			
Adherence (MARS)	0	-	5
Physical activity (IPAQ – walking)	2	-	8
Diet – fruit	1	-	5
Diet – vegetables	1	-	4
Diet – fat intake	1	-	7
Sleep (Jenkins Scale)	4	-	5
Illness beliefs			
Illness perceptions (BIPQ)	12	-	10
Cardiac beliefs (YCBQ)	5	-	8
Social support			
Social network	18	-	-
Social support (ESSI)	12	-	13
Marital quality	34	-	27
Physical symptoms			
Angina symptoms (SAQ)	9	-	10
Angina treatment satisfaction (SAQ)	11	-	9
Pain (MPQ-SF) - Sensory	-	5	10
Pain (MPQ-SF) - Affective	-	3	6
Symptoms (CROQ-CABG)	-	11	7
Satisfaction			
Satisfaction (CROQ-CABG)	-	-	9

One hundred and four participants were recruited to take part in the pilot study, of whom four participants did not eventually undergo CABG and so were withdrawn from the study. Nine participants consented to participate but did not return the T1 questionnaire, leaving a total sample of 91. A flow diagram of uptake and attrition is presented in Figure 4.1. Five participants suffered from clinical events following surgery and 16 participants failed to

complete T2 and T3 questionnaires. Further details of missing data are provided in Table 4.1, showing loss of participants across time points was roughly equal. Due to attrition, the final total of participants who completed the questionnaires at all three time points was 70.

Reasons for missing data are not entirely clear, though are likely to involve both accidental and deliberate non-completion of items. For example, the high rates of missing data on the SAQ can be attributed to some participants stating they do not suffer from angina; therefore these questions were not applicable. Similarly, those participants who were not married or cohabiting (n = 22) were not required to complete the marital functioning questionnaire. Some participants had difficulty completing the BIPQ which is presented as a numerical rating scale; specific examples will be added to the main ARCS study to aid completion. Questions that were sensitive in nature, such as household income and libido on the BDI, may partly account for high levels of missing data on these scales. Missing data regarding clinical information is documented in Section 4.3 (Table 4.5).

4.3 Sample characteristics

Table 4.3 and Table 4.4 describe the characteristics of the entire sample and analytic sample, respectively, at baseline. Clinical data of the analytic sample is displayed in Table 4.5. The analytic sample had an age range between 22 to 83 years, was predominantly male (75.7%) and overweight (BMI >25 = 63.6%). The majority of participants were retired (76.5%), one participant was registered disabled and four participants were unemployed, one of which was a university student. The majority of the analytic sample had either no or only secondary educational qualifications (67.6%). Fifty-six per cent of participants had a family history of CHD. Co-morbidities were prevalent in the analytic sample. The majority of participants had on-pump (cardiopulmonary bypass) surgery (71.7%) in isolation. Post-operative complications occurred in 29 participants, some of whom had more than one. Serious complications occurred particularly in one patient who suffered from atrial fibrillation, cardiac arrest, MI and renal impairment.

Cross-tabulations were performed on age, total yearly household income, education and sex, to compare the characteristics of those who completed all three time points (n = 70) to those who did not (n = 21). Age was converted to a categorical variable for chi-squared analysis (<50 years, 50-60 years, 60-70 years, 70-80 years, >80 years). There was no statistical difference between groups in terms of age groups (χ^2 = 2.646, df = 4, N = 91, p = 0.619). The mean age, in years, was slightly lower in the non-completers (Mean: 66.90 ± SD: 11.02) compared with the completers (Mean: 68.01 ± SD: 9.53), but this did not reach statistical significance (t = -0.451, p = 0.653). Nor was there a significant difference between completers and non-completers in terms of income group (χ^2 = 2.866, df = 4, N = 76, p = 0.580), education

group (χ^2 = 1.773, df = 3, *N* = 89, *p* = 0.621), and sex (χ^2 = 0.157, df = 1, *N* = 91, *p* = 0.692). Markers of disease severity did also not significantly differ between completers and non-completers in terms of both euroSCORE (χ^2 = 13.165, df = 11, *N* = 88, *p* = 0.283) and LVEF (χ^2 = 1.129, df = 1, *N* = 89, *p* = 0.288) groups.

Kolmogorov-Smirnov tests were performed revealing scores on all continuous measures apart from the SF-12 physical score, the BIPQ and the YCBQ to be non-normally distributed (*p* > 0.05). Both non-parametric and parametric tests were performed on the data, but since results were similar, the parametric results are presented here.

TABLE 4.3: CHARACTERISTICS OF THE ENTIRE SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	91	67.76±9.84
Female	91	23 (25.3)
BMI (kg/m^2)	63	27.52±4.67
Married/cohabiting	91	62 (68.1)
Ethnicity – White British/other White	91	84 (92.3)
Currently employed	91	16 (17.6)
Employment grade of current/last major occupation		
Unemployed		8 (9.2)
Managers, directors and senior officials		6 (6.9)
Professional		26 (29.9)
Associate professional and technical		9 (10.3)
Administrative and secretarial	87	8 (9.2)
Skilled trades		16 (18.4)
Caring, leisure and other service		5 (5.7)
Sales and customer service		2 (2.3)
Process, plant and machine operatives		3 (3.4)
Elementary		4 (4.6)
Yearly household income		
≤ 10,000 GBP		21 (27.6)
10,000 – 20,000 GBP	76	22 (28.9)
20,000 – 30,000 GBP		12 (15.8)
30,000 – 40,000 GBP		16 (21.1)
≥40,000		5 (6.6)
Education		
None		37 (41.6)
Secondary	89	22 (24.7)
Higher secondary		13 (14.6)
Degree		17 (19.1)

TABLE 4.4: CHARACTERISTICS OF THE ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	70	68.01±9.53
Female	70	17 (24.3)
BMI (kg/m^2)	55	27.18±4.54
Married/cohabiting	70	48 (68.6)
Ethnicity – White British/other White	70	67 (95.7)
Currently employed	70	11 (15.7)
Employment grade of current/last major occupation		
Unemployed	68	4 (5.9)
Managers, directors and senior officials		6 (8.8)
Professional		20 (29.4)
Associate professional and technical		7 (10.3)
Administrative and secretarial		8 (11.8)
Skilled trades		15 (22.1)
Caring, leisure and other service		3 (4.4)
Sales and customer service		1 (1.5)
Process, plant and machine operatives		2 (2.9)
Elementary		2 (2.9)
Yearly household income		
≤ 10,000 GBP	57	13 (22.8)
10,000 – 20,000 GBP		18 (31.6)
20,000 – 30,000 GBP		9 (15.8)
30,000 – 40,000 GBP		13 (22.8)
≥40,000		4 (7.0)
Education		
None	68	27 (39.7)
Secondary		19 (27.9)
Higher secondary		10 (14.7)
Degree		12 (17.6)

TABLE 4.5: CLINICAL CHARACTERISTICS OF THE ANALYTIC SAMPLE AT BASELINE

Characteristic	*Missing*	*N*	*n (%)*
*Co-morbidities**			
Diabetes	9	61	13 (21.3)
Renal failure (requiring dialysis)	10	60	1 (1.7)
Chronic respiratory disease	9	61	10 (16.4)
Hypothyroidism	9	61	3 (4.9)
Other chronic illness			39 (63.9)
Rheumatoid arthritis	9	61	1 (1.6)
Arthritis			17 (27.9)
Disease severity			
Ejection fraction < 50	1	69	16 (23.2)
euroSCORE			
0			5 (7.2)
1-4	1	69	37 (53.6)
5-7			24 (34.8)
8-10			3 (4.3)
Surgical details			
Off-pump	10	60	17 (28.3)
CABG in isolation	10	60	43 (71.7)
Graft sites			
1			5 (8.5)
2	11	59	13 (22.0)
3			27 (45.8)
4			12 (20.3)
5			2 (3.4)
Post-operative recovery			
Intensive care stay > 2 days	12	58	3 (5.2)
Post-operative infection	10	60	15 (25.0)
Reoperation necessary	10	60	4 (6.7)
At least 1 complication			29 (47.5)
Atrial fibrillation/arrhythmia/tachycardia			17 (27.9)*
Ventricular fibrillation			1 (1.6)*
Atrial flutter	9	61	2 (3.3)*
Pleural effusion/heart failure			3 (4.9)*
Pneumothorax			2 (3.3)*
Cardiac arrest			1 (1.6)*
Myocardial Infarction			1 (1.6)*
Cardiac rehabilitation attendance	5	65	31(47.7)

*Absolute number of cases in sample.

4.4 Descriptive analyses of predictor and outcome measures

In order to evaluate the pilot study it was important to establish whether the questionnaire measures utilised were sensitive, that is that they were able to produce a range of scores in

the population targeted in this sample. As such, frequency analyses were performed to identify potential ceiling effects.

4.4.1 Emotional distress

4.4.1.1 Depression symptoms

The timeframe for answering questions on the BDI at T1 and T3 was the previous two weeks, while at T2 it was the past few days since the surgery. Figure 4.2 represents the frequency of scores on the BDI across all three time points, showing scores to be clustered towards the lower end and middle of the scale, but with a wide range (0-46). The widest distribution of scores occurred at T1. To analyse the distribution further, scores were grouped into categories in accordance with the BDI handbook cut-offs. Results from the frequency analysis of these categories are displayed in Table 4.6 showing that the majority of participants had normal levels of depression symptoms at each time point (T1 >10 = 24.2%; T2 >10 = 39.4%; T3 >10 = 20.4%). These data also show a higher proportion of participants with mild depression at T2 than at other assessments. Individual items on the BDI were examined using paired samples *t*-tests to compare scores at T1 and T2 (Table 4.7). These analyses show that before surgery, participants were more likely to report significantly higher symptoms of irritability and lack of interest in others (social withdrawal), than after surgery at T2. However, following surgery at T2, participants were more likely to report significantly higher symptoms of difficulty in working, sleep problems, fatigue and loss of appetite than at T1. Therefore, the higher proportion of participants with mild depression at T2 is likely due to the higher reporting of somatic symptoms and symptoms associated with the in-hospital environment. Similar numbers of participants had moderate-severe-extreme scores (≥21) at each time point (Table 4.6).

Paired samples *t*-tests were performed on the BDI mean scores showing BDI scores were lower before surgery (Mean: 8.40, SD: 7.94) compared with the days following surgery (Mean: 9.95, SD: 6.83), but this was not significant ($t(57) = -1.629$, $p = 0.109$). However, from T2 (Mean: 10.02, SD: 6.86) to T3 (Mean: 7.08 ± SD: 4.86) there was a significant decrease in depression symptom scores, with levels falling to just below baseline scores ($t(49) = 2.970$, $p = 0.005$). There was no significant difference between scores at T1 (Mean: 8.45 ± SD: 8.12) compared with T3 (Mean: 7.27 ± SD: 4.68) ($t(48) = 1.255$, $p = 0.216$).

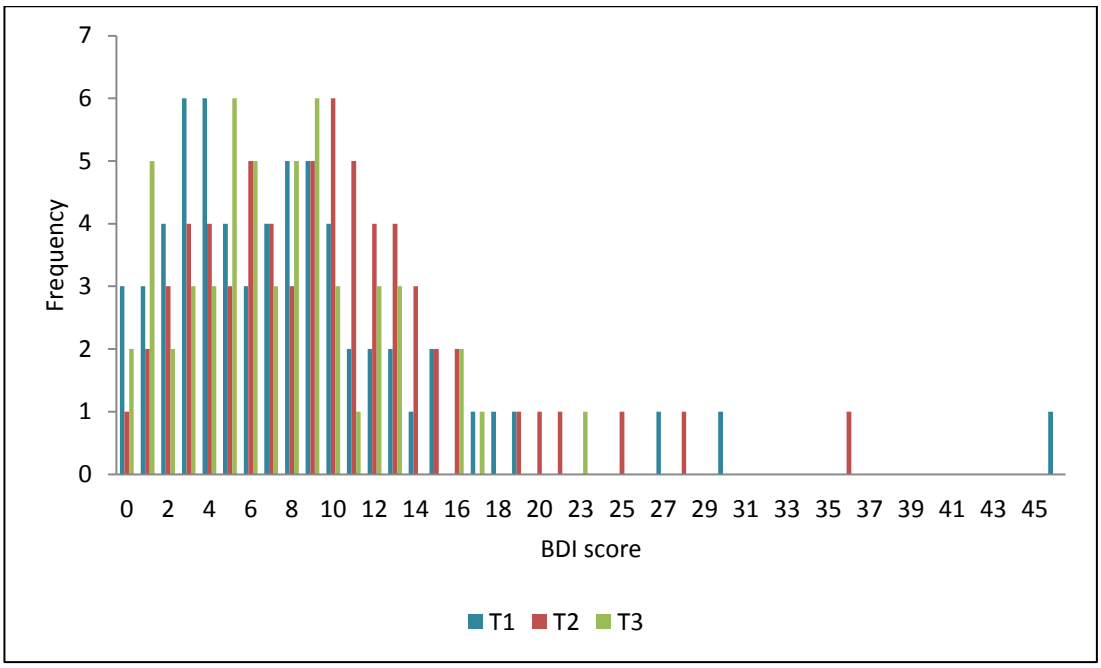

FIGURE 4.2: FREQUENCY OF SCORES ON THE BDI ACROSS TIME

TABLE 4.6: FREQUENCY OF SCORES ACCRODING TO BDI SUBGROUP

BDI score	*BDI Classification*	*n (%)*		
		T1 (N=62)	*T2 (N=66)*	*T3 (N=54)*
0-10	Normal	47 (75.8)	40 (60.6)	43 (79.6)
11-16	Mild	9 (14.5)	20 (30.3)	9 (16.7)
17-20	Borderline clinical	3 (4.8)	2 (3.0)	1 (1.9)
21-30	Moderate	2 (3.2)	3 (4.5)	1 (1.9)
31-40	Severe	-	1 (1.5)	-
41-63	Extreme	1 (1.6)	-	-

To examine caseness on the BDI, a binary cut-off was implemented in accordance with previous literature at a conservative ≥13 (Gutierrez & Davis, 1999). According to this cut-off, 21.4% of participants were depressed at baseline, 26.1% were depressed at T2 and 9.2% were depressed at T3. Eight groups were created in order to examine the pattern of depression symptoms across time. Results from these analyses are shown in Table 4.8 revealing that six participants can be classified as having persistent depression after surgery and one participant can be classified as developing post-CABG onset depression. A further 14 participants had depression that had resolved by T3.

TABLE 4.7: PAIRED SAMPLES T-TESTS OF BDI ITEMS AT T1 AND T2

Symptom	*N*	*Mean ± SD*	*t*	*p*
1. Sadness				
T1	69	0.36± 0.57	2.190	0.032
T2		0.22± 0.45		
2. Pessimism				
T1	69	0.29± 0.60	1.839	0.070
T2		0.13± 0.45		
3. Sense of failure				
T1	69	0.22± 0.64	0.962	0.340
T2		0.14± 0.58		
4. Dissatisfaction				
T1	68	0.47± 0.63	0.727	0.470
T2		0.40± 0.65		
5. Guilt				
T1	68	0.07± 0.32	0.000	1.000
T2		0.07± 0.26		
6. Punishment				
T1	69	0.12± 0.44	0.469	0.641
T2		0.09± 0.41		
7. Self-dislike				
T1	69	0.25± 0.53	0.575	0.567
T2		0.20± 0.44		
8. Self-accusations				
T1	69	0.25± 0.53	1.472	0.146
T2		0.14± 0.52		
9. Suicidal ideas				
T1	69	0.07± 0.31	1.000	0.321
T2		0.04± 0.21		
10. Crying				
T1	69	0.26± 0.63	1.927	0.058
T2		0.12± 0.37		
11. Irritability				
T1	68	0.59± 0.74	2.921	0.005
T2		0.31± 0.53		
12. Social withdrawal				
T1	69	0.22± 0.51	2.802	0.007
T2		0.07± 0.40		
13. Indecisiveness				
T1	69	0.33± 0.61	1.636	0.106
T2		0.20± 0.63		

14. Body image change				
T1	69	0.20± 0.56	-0.207	0.837
T2		0.22± 0.48		
15. Work difficulty				
T1	69	0.91± 0.78	-2.082	0.007
T2		1.35± 1.10		
16. Insomnia				
T1	68	0.93± 0.97	-2.995	0.004
T2		1.43± 1.24		
17. Fatigue				
T1	68	1.00± 0.57	-4.042	<0.001
T2		1.59± 1.01		
18. Loss of appetite				
T1	69	0.35± 0.61	-6.981	<0.001
T2		1.41± 1.06		
19. Weight loss				
T1	68	0.35± 0.77	0.287	0.775
T2		0.32± 0.58		
20. Somatic preoccupation				
T1	68	0.68± 0.80	1.539	0.128
T2		0.50± 0.66		
21. Loss of libido				
T1	64	0.91± 1.15	0.424	0.673
T2		0.83± 1.16		

TABLE 4.8: DEPRESSION CASENESS ACCORDING TO TIME POINT

Depression type	*BDI ≥ 13*			*n (%)*
	T1	*T2*	*T3*	
Persistent	✓	✓	✓	1 (2.2)
Post-CABG onset	x	x	✓	1 (2.2)
Transient	x	✓	x	10 (22.2)
Delayed onset	x	✓	✓	-
Never depressed	x	x	x	26 (57.8)
Resolved	✓	✓	x	2 (4.4)
Persistent	✓	x	✓	3 (6.7)
Resolved	✓	x	x	2 (4.4)

4.4.1.2 Anxiety

Figure 4.3 represents the frequency of scores on the HADS anxiety subscale across all three time points, showing scores to be clustered towards the lower end of the scale, but with a wide range (0-21). The widest distribution of scores occurred at T1. To analyse the distribution further, scores were grouped into categories in accordance with the HADS severity cut-offs. Results from the frequency analysis of these categories are displayed in Table 4.9 showing a higher proportion of participants with borderline and case anxiety at T1 than at other assessments. Paired samples *t*-tests were performed on the HADS anxiety mean scores showing there to be a significant decrease from before surgery (Mean: 6.04 ± SD: 4.50) to the days following surgery (Mean: 3.84 ± SD: 3.56) ($t(67) = 4.048$, $p < 0.001$) and from before surgery (Mean: 5.62 ± SD: 4.07) to T3 (Mean: 3.48 ± SD: 2.82) ($t(62) = 5.295$, $p < 0.001$). From T2 (Mean: 3.65 ± SD: 3.52) to T3 (Mean: 3.60 ± SD: 2.86) there was no significant change in anxiety scores ($t(64) = 0.104$, $p = 0.917$).

To examine participants with borderline to case anxiety on the HADS, a binary cut-off was implemented in accordance with previous literature at ≥8. Eight groups were created in order to examine the pattern of anxiety across time. Results from these analyses are shown in Table 4.10 revealing that three participants can be classified as having persistent anxiety after surgery. A further 12 participants had anxiety that had resolved by T3. Overall, there were very few cases of anxiety.

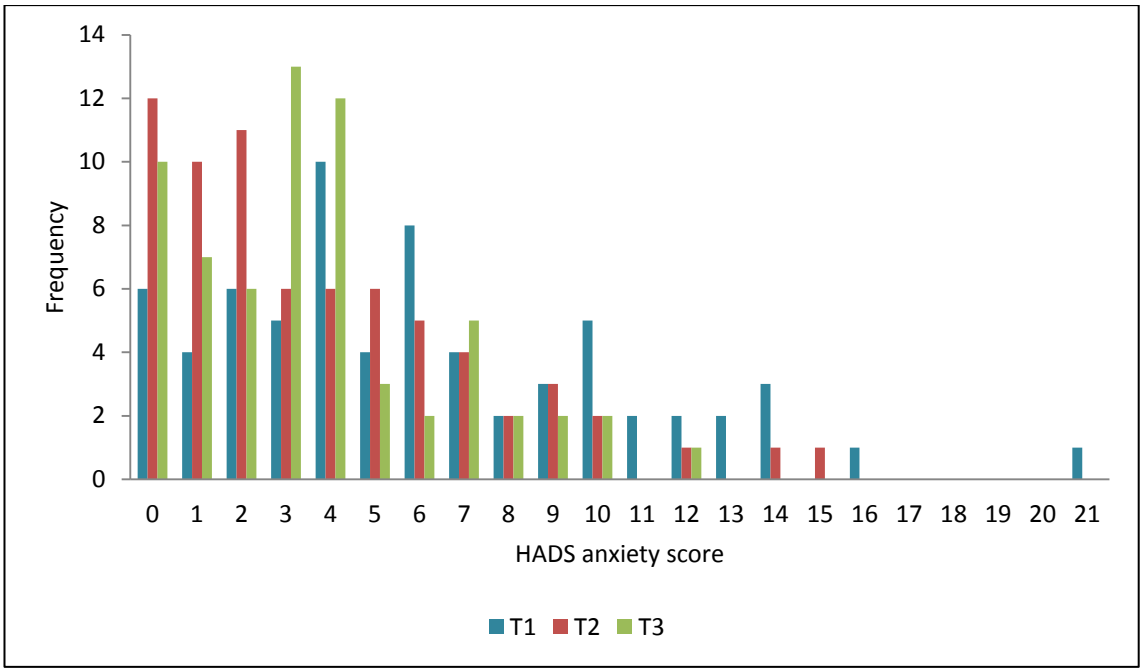

FIGURE 4.3: FREQUENCY OF SCORES ON THE HADS ACROSS TIME

TABLE 4.9: FREQUENCY OF HADS ANXIETY SCORES

HADS anxiety score	*HADS classification*	*n (%)*		
		T1 (N=68)	*T2 (N=70)*	*T3 (N=65)*
≤7	Normal	47 (69.1)	60 (85.7)	58 (89.2)
8-10	Borderline	10 (14.7)	7 (10.0)	6 (9.2)
≥11	Caseness	11 (16.2)	3 (4.3)	1 (1.5)

TABLE 4.10: ANXIETY TYPE ACCORDING TO TIME POINT

Anxiety type	*HADS ≥ 8*			*n (%)*
	T1	*T2*	*T3*	
Persistent	✓	✓	✓	3 (4.8)
Post-CABG onset	x	x	✓	1 (1.6)
Transient	x	✓	x	3 (4.8)
Delayed onset	x	✓	✓	-
Never anxious	x	x	x	42 (66.7)
Resolved	✓	✓	x	2 (3.2)
Persistent	✓	x	✓	2 (3.2)
Resolved	✓	x	x	10 (15.9)

4.4.2 Health status

4.4.2.1 Physical and mental health status

Figure 4.4 and Figure 4.5 show the distribution of scores on the SF-12 for the mental and physical components, respectively. Scores show a wide range across both time points indicating no ceiling effects. The scores on the mental component were clustered around the normative value of 50, in line with findings from the BDI. In comparison, the physical component had a much higher percentage of scores below 50, with the majority of participants reporting reduced physical health status at T1 (85.7%) and T3 (95.4%) (see Table 4.11). Paired samples *t*-tests showed no change in mental health status from T1 (Mean: 56.12 ± SD: 6.27) to the T3 post-operative assessment (Mean: 56.79 ± SD: 6.92) ($t(64) = -0.816$, $p = 0.417$). However, paired samples *t*-tests showed there was a significant decrease in physical health status from T1 (Mean: 39.22 ± SD: 10.12) to T3 (Mean: 35.09 ± SD: 8.28) ($t(64) = 2.813$, $p = 0.007$).

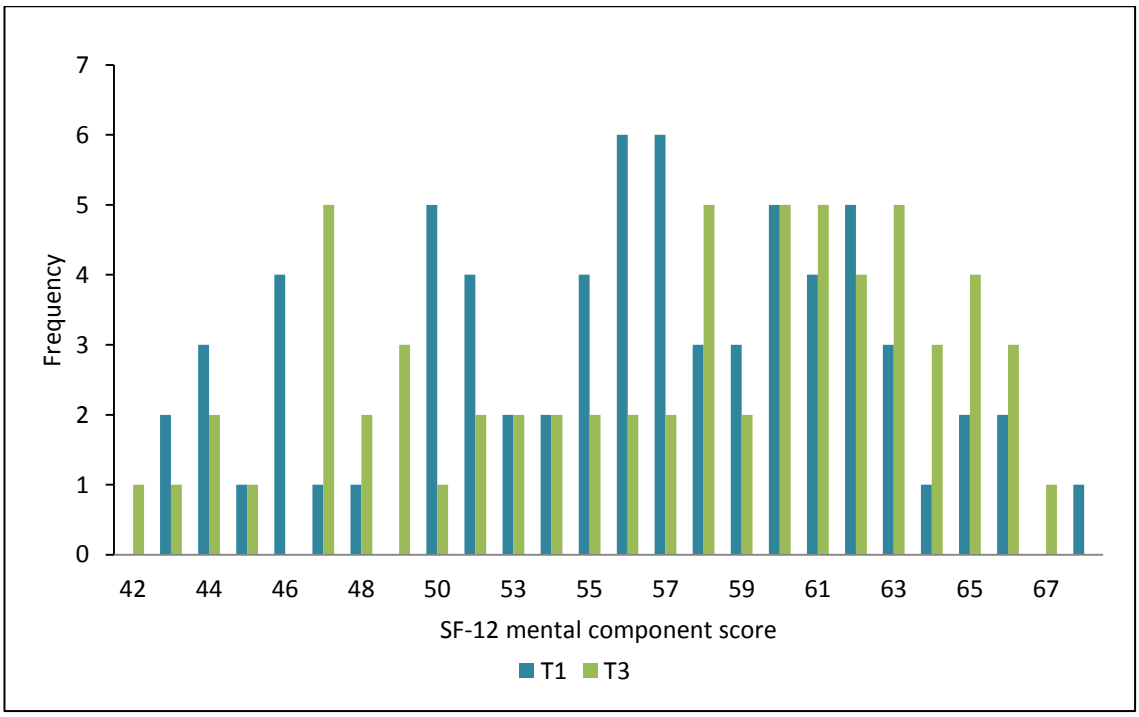

FIGURE 4.4: FREQUENCY OF SF-12 MENTAL COMPONENT SCORE AT T1 AND T3

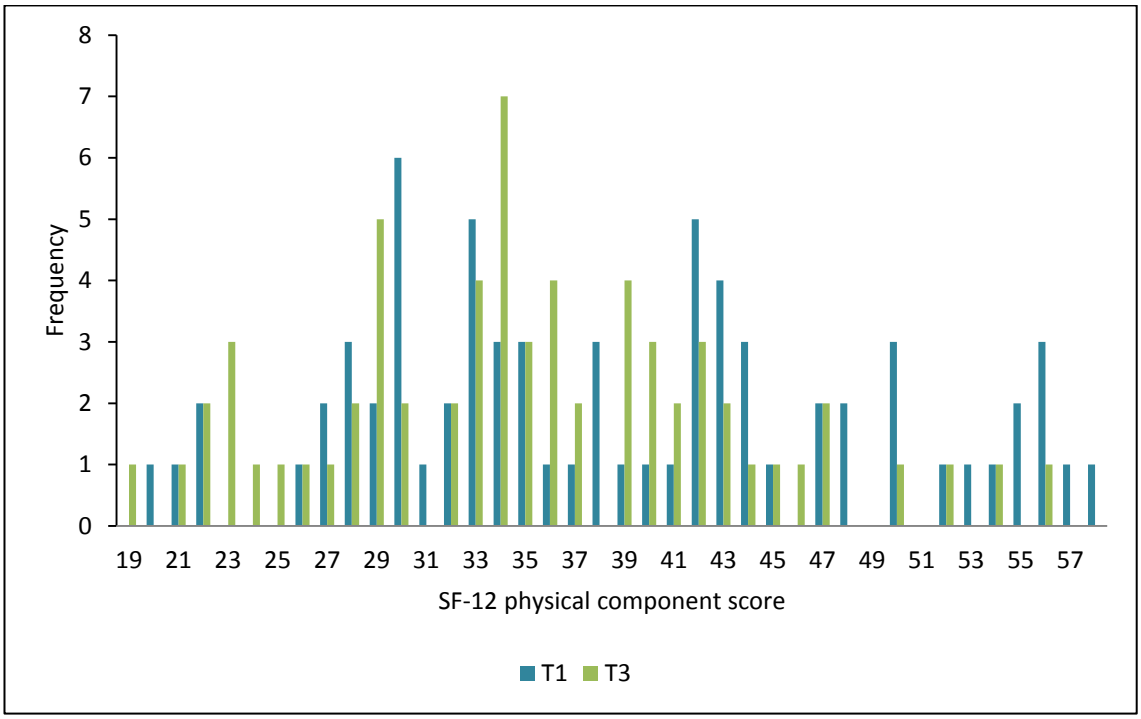

FIGURE 4.5: FREQUENCY OF SF-12 PHYSICAL COMPONENT SCORE AT T1 AND T3

TABLE 4.11: FREQUENCY OF SCORES ON SF-12

SF-12 Score Range	*SF-12 Mental n (%)*		*SF-12 Physical n (%)*	
	T1 (N = 70)	*T3 (N = 65)*	*T1 (N = 70)*	*T3 (N = 65)*
10-20	-	-	1 (1.4)	1 (1.5)
21-30	-	-	17 (24.3)	19 (29.2)
31-40	-	-	21 (30.0)	29 (44.6)
41-50	17 (24.3)	16 (24.6)	21 (30.0)	13 (20.0)
51-60	35 (50.0)	24 (36.9)	10 (14.3)	3 (4.6)
61-70	18 (25.7)	25 (38.5)	-	-

4.4.3 Health behaviour

4.4.3.1 Adherence

Figure 4.6 shows the distribution of scores on the MARS at T1 and T3. Scores were skewed, with most participants reporting no to minimal non-adherence at both time points (T1 mean: 1.17 ± SD: 1.77; T3 mean: 0.83 ± SD: 1.50). Paired samples *t*-tests showed no significant change in non-adherence levels from pre- to post-operative assessments ($t(64) = 1.925$, $p = 0.059$). Since scores were skewed, categorical analyses was also performed, computing binary scores for adherence at both T1 and T3. Adherers were classed as all those people who had a total score of 0, and non-adherers were those who scored ≥1. Cross-tabulation results are displayed in Table 4.12, showing that only 44.6% of the sample was medication adherent and 36.9% of the sample was non-adherent at both T1 and T3. Few people changed from being adherent at T1 to non-adherent at T3 (6.5%), though 29.4% of non-adherers at T1 went on to become adherent following surgery. A Chi-square analysis was performed showing there was a significant difference between adherent and non-adherent groups over time ($\chi^2 = 27.793$, df = 1, $N = 65$, $p < 0.001$).

TABLE 4.12: CROSS-TABULATION OF ADHERERS AND NON-ADHERERS AT T1 AND T3

			T3		*Total*
			Adherer	*Non-adherer*	
T1	*Adherer*	*n*	29	2	31
		% within T1	93.5	6.5	100.0
	Non-adherer	*n*	10	24	34
		% within T1	29.4	70.6	100.0
Total			39	26	65
			60.0	40.0	100.0

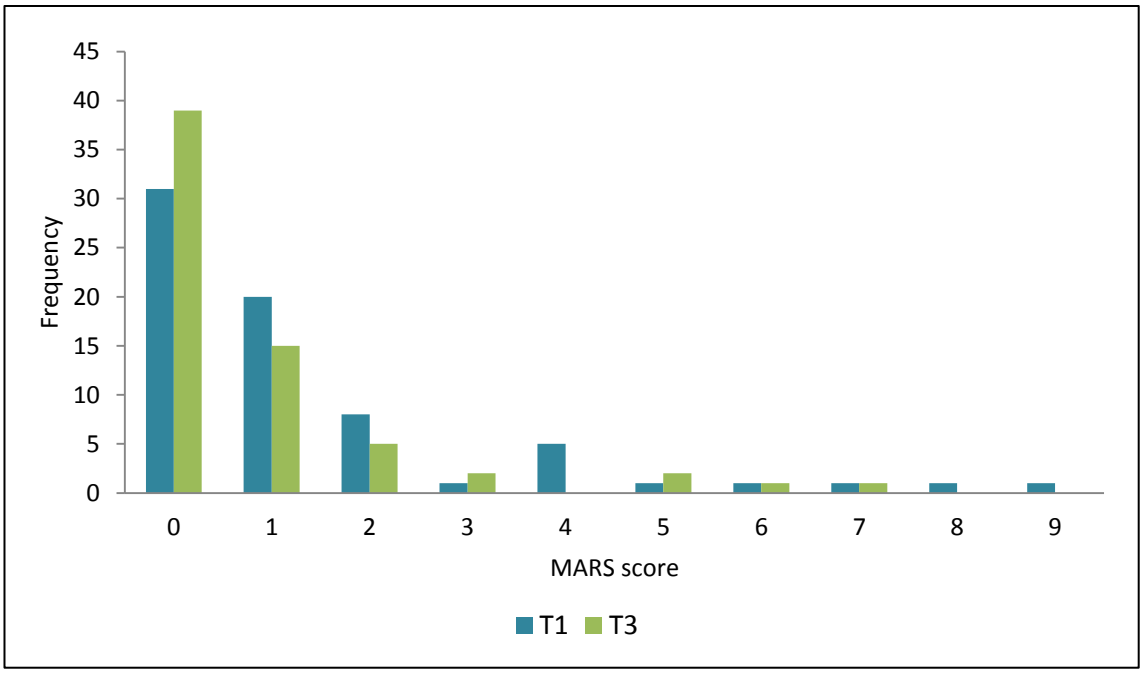

FIGURE 4.6: FREQUENCY OF MARS SCORES AT T1 AND T3

4.4.3.2 Physical activity

Average weekly walking time in hours varied considerably across the sample, ranging from 0-35 hours per week at T1 (Mean: 5.19 ± SD: 7.39) to 0-10.5 hours per week at T3 (Mean: 2.88 ± SD: 1.89). Moreover, a paired samples *t*-test showed a significant decrease in physical activity levels from pre- to post-operative assessments ($t(59) = 2.368$, $p = 0.021$).

4.4.3.3 Diet

TABLE 4.13: PAIRED SAMPLES T-TESTS OF DIET AT T1 AND T3

Measure	*N*	*Mean ± SD*	*t*	*p*
Fat				
T1	62	15.76±3.10	3.580	0.001
T3		14.68±2.69		
Fruit (pieces/week)				
T1	64	14.22±11.10	-1.332	0.188
T3		15.94±8.74		
Vegetables (pieces/week)				
T1	65	15.92±8.60	-0.549	0.585
T3		16.62±10.30		

Paired samples *t*-tests results (Table 4.13) showed participants tended to make dietary improvements after surgery, compared to their baseline values. Fat intake significantly decreased after surgery; fruit and vegetable intake slightly increased following CABG but these changes were not significant.

4.4.3.4 Sleep

Figure 4.7 shows the distribution of scores on the Jenkins sleep problems questionnaire at T1 and T3. The amount of self-reported sleep problems varied considerably across the sample, ranging from 0-25 at both time points, with a wide spread of scores. A paired samples *t*-test showed a significant increase in self-reported sleep problems from T1 (Mean: 9.60 ± SD: 7.13) to T3 (Mean: 11.98 ± SD: 7.56) (t(61) =-2.970, $p = 0.004$).

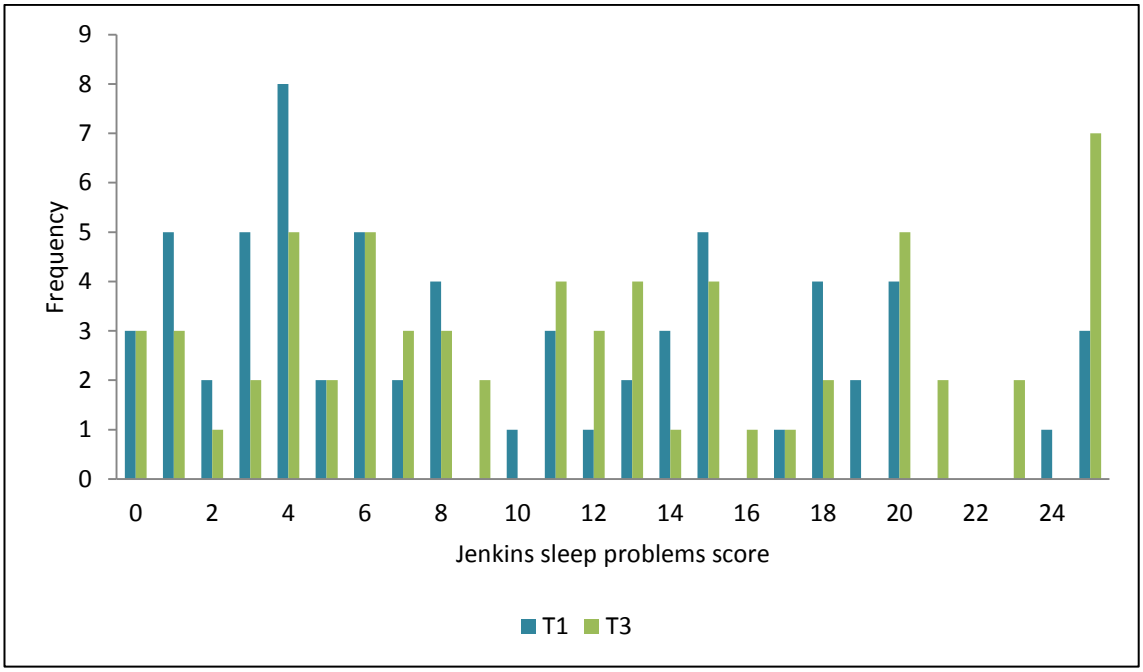

FIGURE 4.7: FREQUENCY OF JENKINS TOTAL SCORE AT T1 AND T3

Analyses were also performed on the individual items of the Jenkins questionnaire to look at the particular characteristics of sleep that changed across time. Table 4.14 displays the paired samples *t*-test results comparing each item at T1 and T3. Results show that problems falling asleep significantly increased in frequency following surgery, as did symptoms of waking during the night and troubles staying asleep.

TABLE 4.14: PAIRED SAMPLES T-TESTS OF JENKINS ITEMS AT T1 AND T3

Sleep problem	*N*	*Mean ± SD*	*t*	*p*
1. Trouble falling asleep				
T1	65	1.02±1.47	-3.713	<0.001
T3		1.75±1.78		
2. Waking during night				
T1	64	2.53±1.80	-2.124	0.038
T3		2.94±1.76		
3. Trouble staying asleep				
T1	64	2.30±1.80	-2.588	0.012
T3		2.83±1.76		
4. Waking feeling tired/ worn out				
T1	63	1.57±1.79	-1.382	0.172
T3		1.86±1.86		
5. Disturbed/restless sleep				
T1	63	2.11±1.91	-1.683	0.097
T3		2.51±1.98		

4.4.3.5 Smoking

TABLE 4.15: CURRENT AND PAST SMOKING HISTORY

	n (%)	
	T1 (N = 70)	*T3 (N = 66)*
Current smoker	5 (7.1)	2 (3.0)
Type		
Cigarettes	4 (5.7)	-
Self-rolled cigarettes	1 (1.4)	-
Frequency (cigarettes/day)		
≤ 5	1 (1.4)	-
6-15	2 (2.9)	2 (3.0)
>15	2 (2.9)	-
Duration (years)		
30-40	3 (4.3)	-
>40	2 (2.9)	-
Past smoker *	41 (64.1)	-
Time since quitting (months)		
<6	6 (9.4)	-
6–12	1 (1.6)	-
>12	34 (53.1)	-
Currently using nicotine replacement	3 (4.7)	2 (3.0)

*$N = 64$

Smokers were classified as current and past, with frequency rates displayed in Table 4.15. Only a small minority of participants were current smokers at T1, but many had smoked in the past (64.1%). At T3, only two participants continued to smoke and two of the non-smokers were using nicotine replacement therapy.

4.4.3.6 Alcohol

Forty-nine participants were alcohol drinkers at baseline, with 21 abstainers. At T3 the number of drinkers had reduced to 31, with 35 abstainers. Table 4.16 shows participants' average alcohol unit consumption per week, before and after surgery. A paired samples *t*-test showed there was a significant decrease in mean alcohol consumption from T1 (Mean: 9.63 ± SD: 11.75) to T3 (Mean: 6.46 ± SD: 10.37) (t(62) = 3.421, $p = 0.001$) assessments.

TABLE 4.16: CURRENT WEEKLY ALCOHOL CONSUMPTION

	n (%)	
Alcohol consumption (units/week)	*T1 (N = 68)*	*T3 (N = 65)*
<1	30 (46.9)	36 (55.4)
1-10	13 (19.1)	16 (24.6)
11-20	10 (14.7)	6 (9.2)
21-30	10 (14.7)	4 (6.2)
31-40	5 (7.4)	3 (4.6)
>40	-	1 (1.5)

4.4.4 Illness beliefs

4.4.4.1 Illness perceptions

Figure 4.8 shows the distribution of scores on the BIPQ at T1 and T3. Scores were evenly distributed across the scale, with a greater spread of scores at T3 (range: 0-61) compared to T1 (range: 14-62). Mean illness perception scores were lower at follow-up compared to pre-surgery scores, with a paired samples *t*-test confirming a significant decrease from T1 (Mean: 35.92 ± SD: 11.26) to T3 (Mean: 28.26 ± SD: 14.40) ($t(53) = 4.538$, $p = 0.001$). These findings indicate participants viewed their illness as less threatening after surgery than before.

The causal beliefs data were grouped into nine categories, with absolute frequencies for each causal belief cited displayed in Table 4.17. Multiple citations of the same category by a participant were not included. Participants were able to cite up to three causal beliefs at each time point; *N* represents the number of participants who cited at least one. Lifestyle was the most commonly cited reason participants gave for the cause of their heart disease, at both time points.

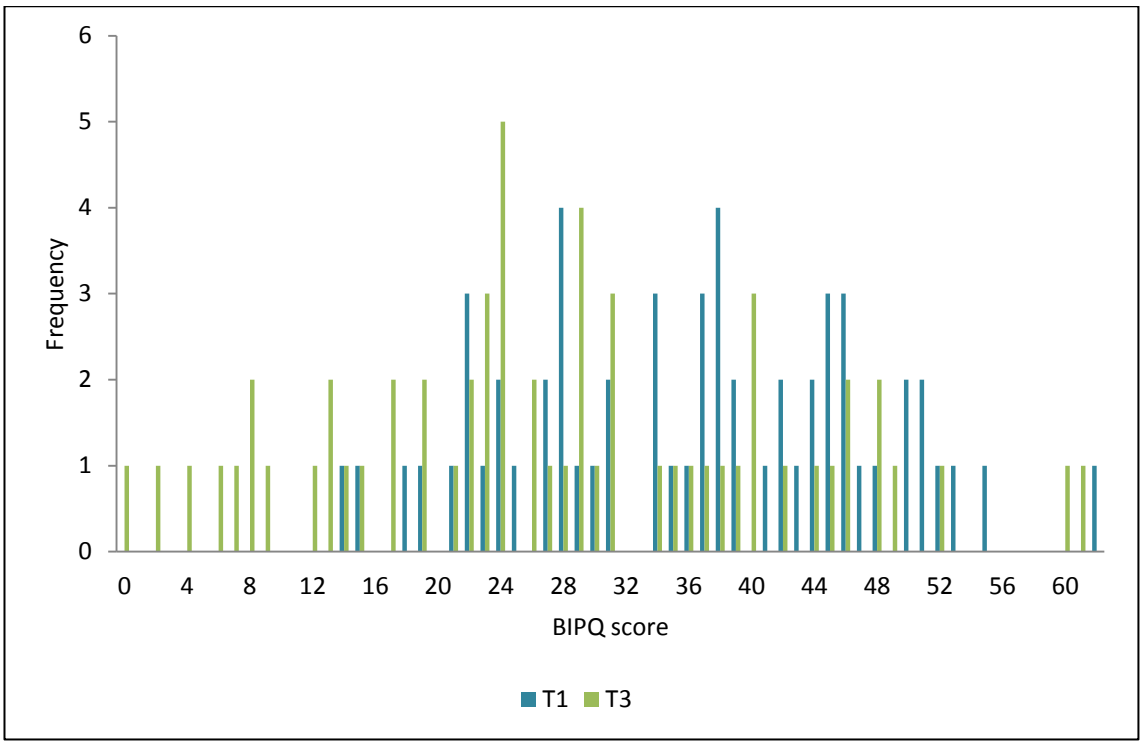

FIGURE 4.8: FREQUENCY OF ILLNESS PERCEPTION SCORES AT T1 AND T3

TABLE 4.17: ABSOLUTE FREQUENCIES OF CAUSAL BELIEFS AT T1 AND T3

Causal belief	*Example/explanation*	*n(%)*	
		T1 (N=60)	*T3 (N=62)*
Lifestyle	Diet, exercise, smoking, work	45 (75.0)	47 (75.8)
Stress	Stress, worries, other emotions	13 (21.7)	21 (33.9)
Genetics	Family history, genetics, inherited	19 (31.7)	19 (30.6)
Biology	Faulty valve, blood pressure, diabetes	16 (26.7)	18 (29.0)
Congenital	From birth	2 (3.3)	1 (1.6)
Age	Old age	8 (13.3)	6 (9.7)
Medical care	Poor medical care, GP delay	1 (1.7)	-
Fate	Fate, bad luck	1 (1.7)	2 (3.2)
Social support	Lack of social support	-	2 (3.2)

4.4.4.2 Cardiac beliefs

Figure 4.9 shows the distribution of scores on the YCBQ at T1 and T3. Scores were evenly distributed across the scale at both time points. Mean cardiac misconception scores were relatively stable across time, with a paired samples *t*-test confirming there was no significant change from T1 (Mean: 21.41 ± SD: 7.04) to T3 (Mean: 20.62 ± SD: 7.42) ($t(57) = 1.261$, $p = 0.212$). This lack of observed change is interesting given 47.7% of the sample attended cardiac rehabilitation classes (Table 4.5).

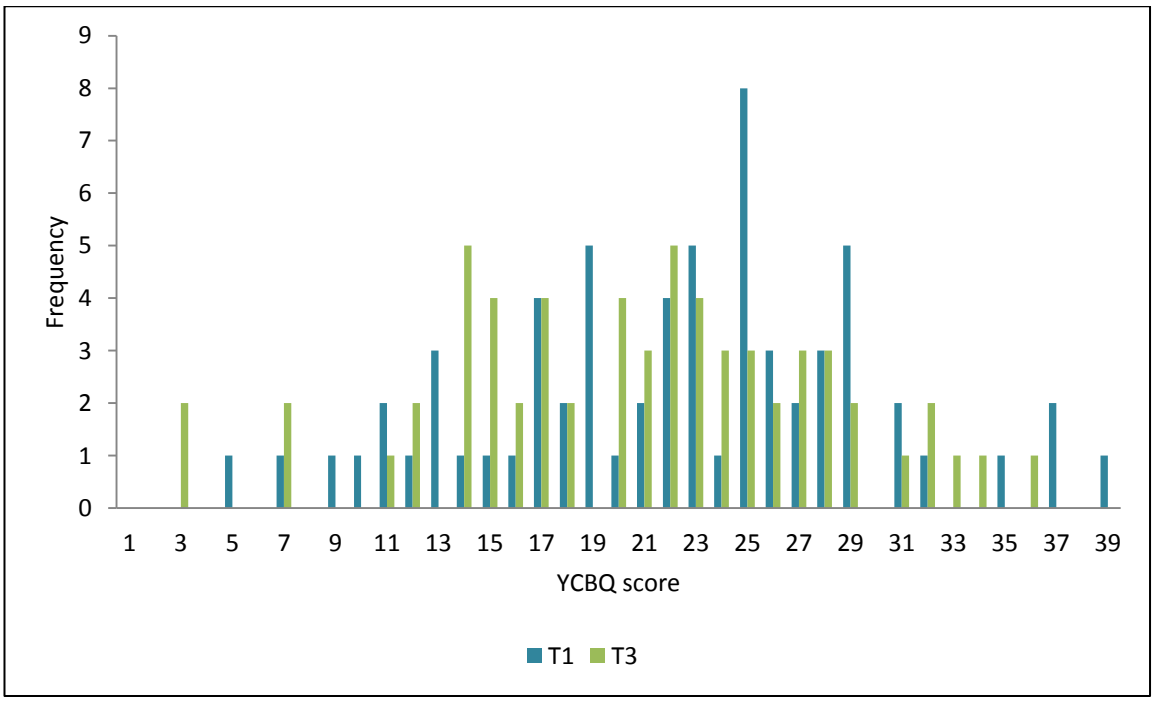

FIGURE 4.9: FREQUENCY OF CARDIAC MISCONCEPTIONS SCORE AT T1 AND T3

4.4.5 Social support

4.4.5.1 Social networks

Social networks showed a normal distribution, with a range of 1-9 social contacts (see Figure 4.10). The mean network size in the sample was 4.67 (SD: 1.84) contacts.

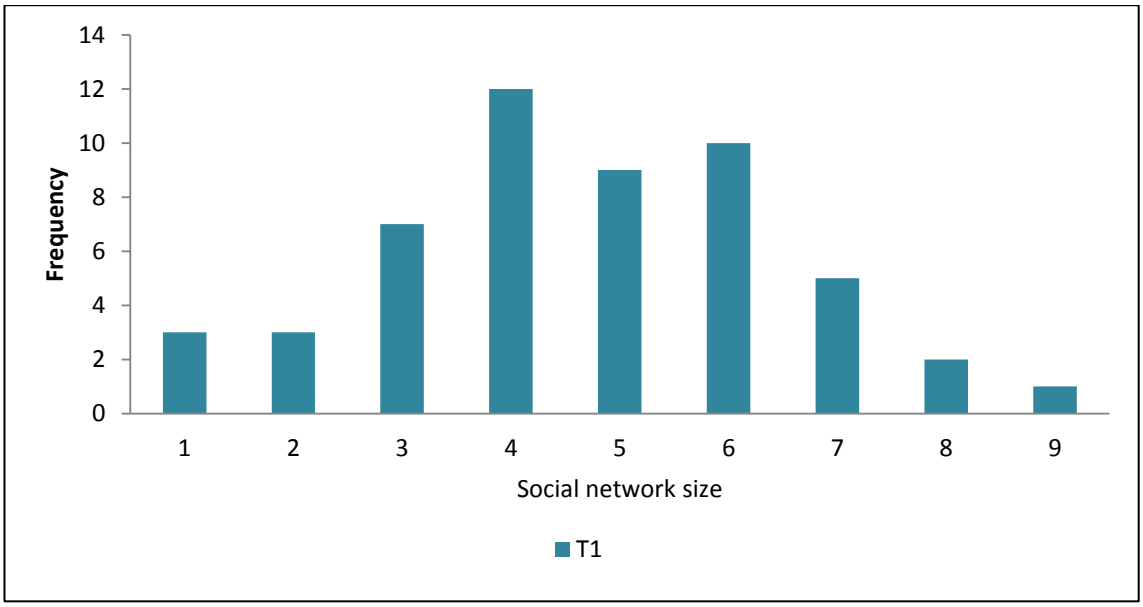

FIGURE 4.10: FREQUENCY OF SOCIAL NETWORK SIZE AT T1

4.4.5.2 Social support

Figure 4.11 shows the distribution of scores on the ESSI questionnaire at T1 and T3. Scores were skewed towards the higher end of the scale and had an identical range (T1: 10-34, T3: 10-34) at both time points. The maximum score on this questionnaire is 34, therefore ceiling effects have been observed. Paired samples *t*-tests showed no significant change in self-reported social support from T1 (Mean: 29.62 ± SD: 6.11) to T3 (Mean: 29.63 ± SD: 6.18) ($t(64) = -0.044$, $p = 0.965$).

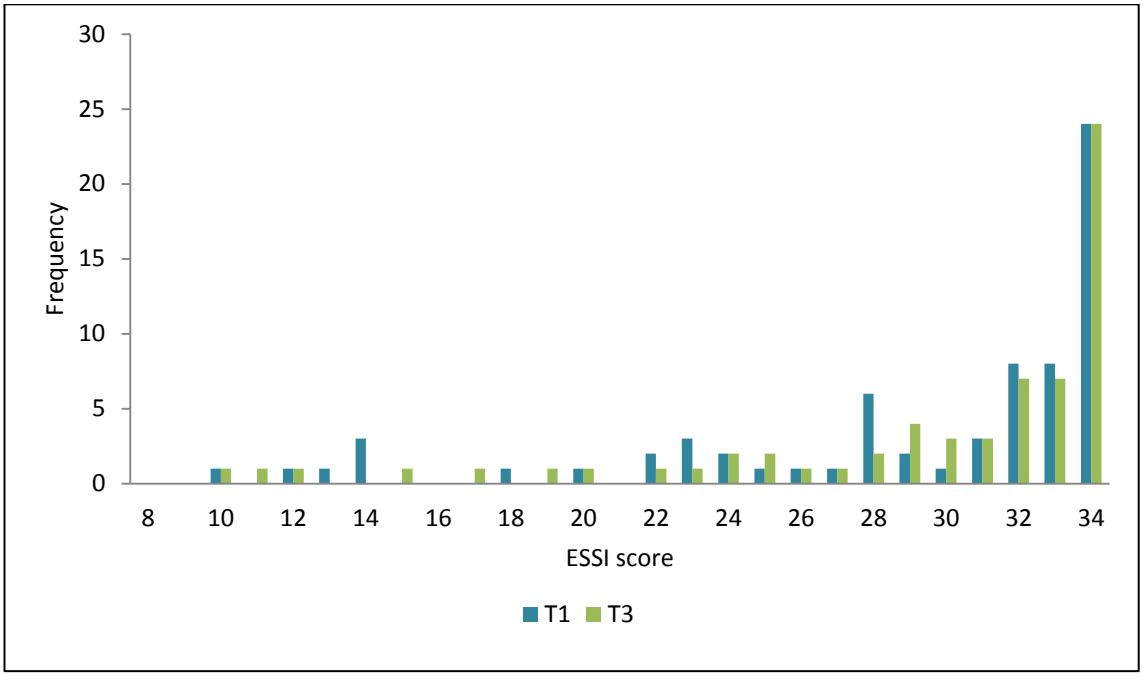

FIGURE 4.11: FREQUENCY OF ESSI SOCIAL SUPPORT SCORE AT T1 AND T3

4.4.5.3 Marital quality

Figure 4.12 shows the distribution of scores on the marital quality questionnaire at T1 and T3. Scores were skewed towards higher scores and had an identical range (7-21) at both time points. These results suggest a ceiling effect as the maximum score on this questionnaire was 21. Paired samples *t*-tests showed no significant change in self-reported marital quality from T1 (Mean: 18.00 ± SD: 3.25) to T3 (Mean: 17.74 ± SD: 3.32) ($t(33) = 0.902$, $p = 0.374$).

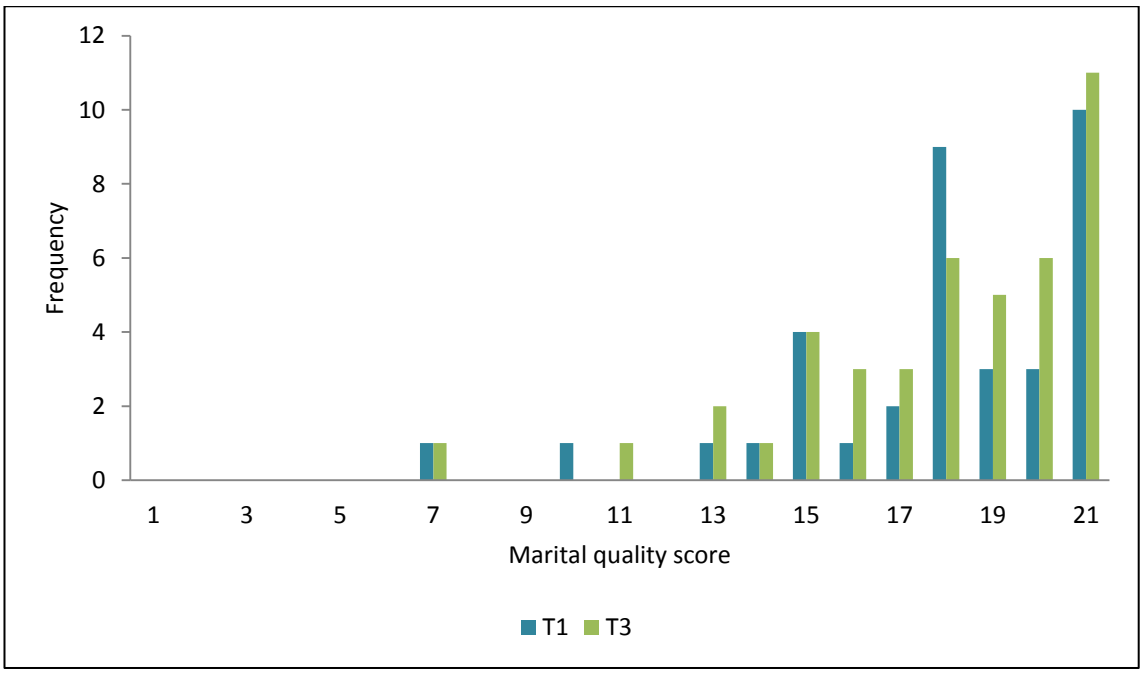

FIGURE 4.12: FREQUENCY OF MARITAL QUALITY SCORE AT T1 AND T3

4.4.6 Physical symptoms

4.4.6.1 Angina

Figure 4.13 and Figure 4.14 show the distribution of scores on the SAQ subscales, angina symptoms and treatment satisfaction, at T1 and T3. Angina symptoms were evenly distributed across the scale, whereas treatment satisfaction scores clustered towards the higher end of the scale. Mean angina symptom scores were lower at follow-up compared to pre-surgery scores, with a paired samples *t*-test confirming a significant decrease from T1 (Mean: 4.04 ± SD: 2.82) to T3 (Mean: 2.56 ± SD: 2.63) ($t(53) = 2.915$, $p = 0.005$). There was no significant change in treatment satisfaction across time from T1 (Mean: 10.35 ± SD: 2.22) to T3 (Mean: 9.57 ± SD: 3.27) ($t(53) = 1.750$, $p = 0.086$).

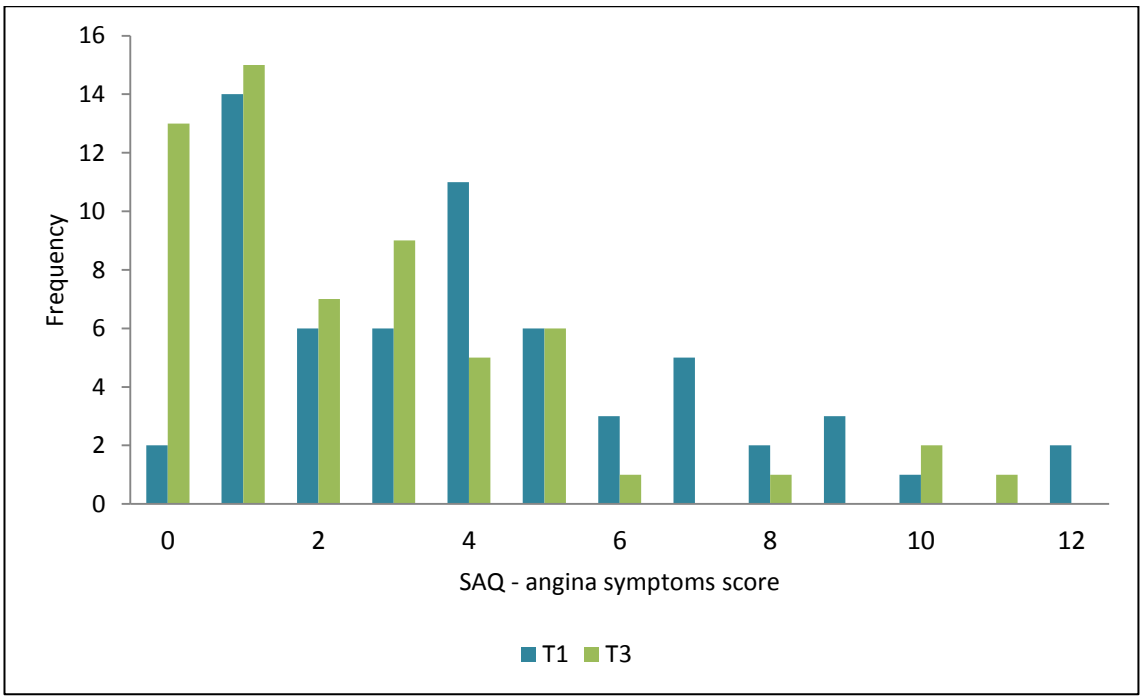

FIGURE 4.13: FREQUENCY OF ANGINA SYMPTOMS AT T1 AND T3

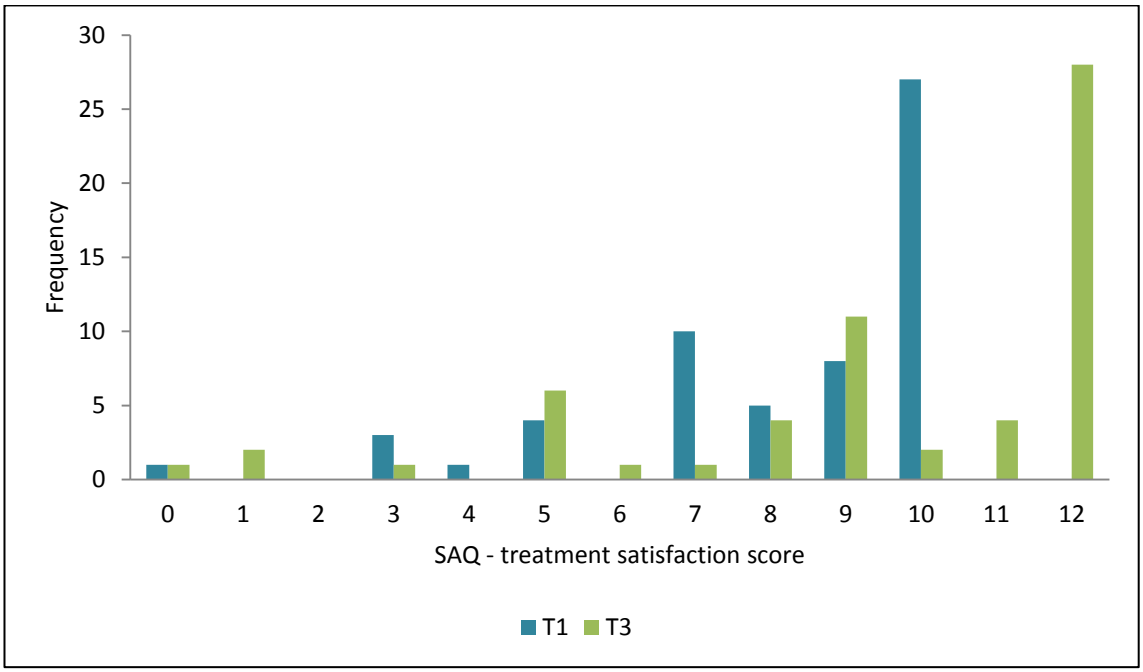

FIGURE 4.14: FREQUENCY OF TREATMENT SATISFACTION SCORES AT T1 AND T3

4.4.6.2 Pain

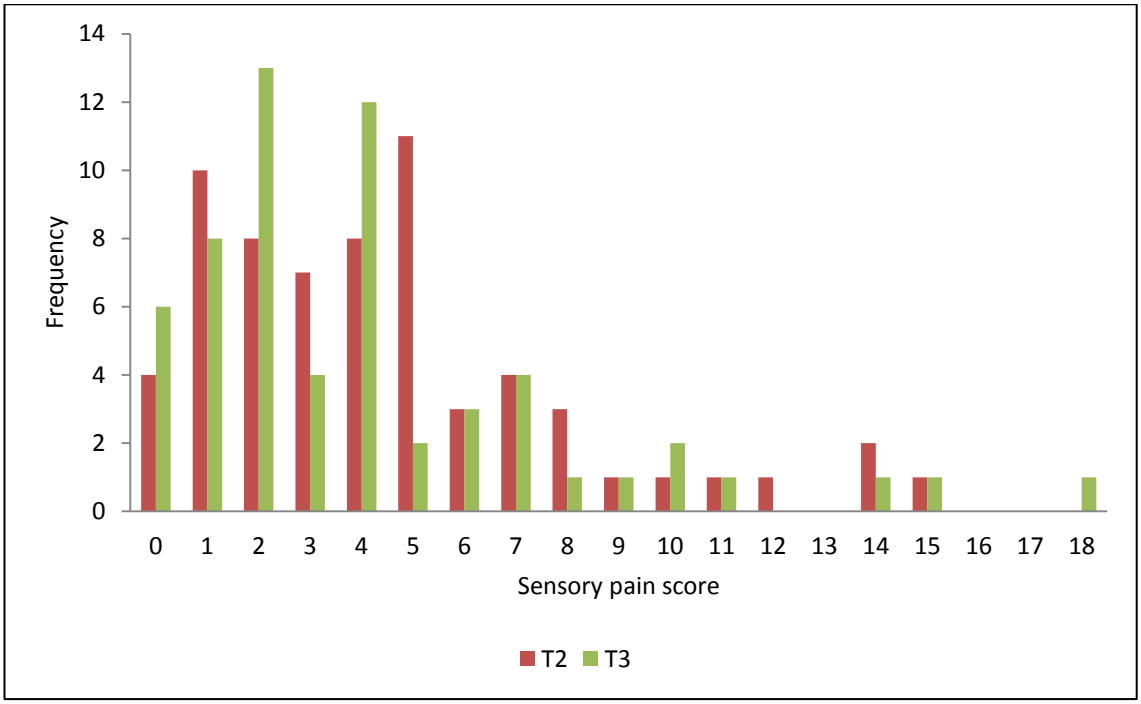

FIGURE 4.15: FREQUENCY OF SENSORY PAIN SCORES AT T2 AND T3

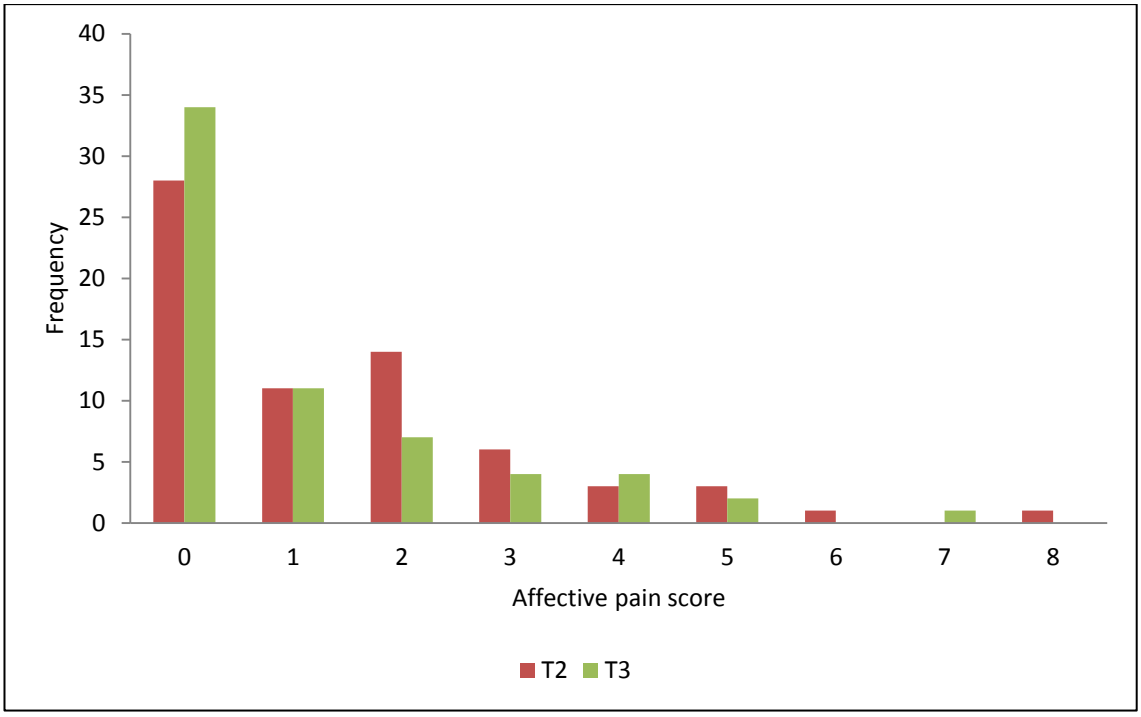

FIGURE 4.16: FREQUENCY OF AFFECTIVE PAIN SCORES AT T2 AND T3

Figure 4.15 and Figure 4.16 show the distribution of scores on the MPQ-SF for the affective and sensory pain scores, respectively. A wider range of scores were reported for sensory pain at T3 (0-18) than at T2 (0-15); affective pain scores showed a similar range at T2 (0-8) and T3 (0-7). Paired samples *t*-test results (Table 4.18) showed pain decreased significantly following surgery from T2 to T3, as measured using the numerical rating scale and the current pain descriptor. Sensory and affective pain scores did not significantly differ over time, indicating that the cognitive and emotional experience of pain did not resolve by T3.

TABLE 4.18: PAIRED SAMPLES T-TEST RESULTS OF PAIN AT T1 AND T3

Pain measure	*N*	*Mean ± SD*	*t*	*p*
Sensory pain				
T2	56	4.11±3.27	-0.039	0.969
T3		4.13±3.88		
Affective pain				
T2	61	1.39±1.72	1.618	0.111
T3		1.05±1.54		
Numerical rating scale				
T2	63	3.87±2.16	3.449	0.001
T3		2.87±2.43		
Current pain descriptor				
T2	66	1.56±1.08	2.889	0.005
T3		1.17±0.87		

4.4.6.3 Symptoms

Higher scores on the CROQ indicate greater negative symptoms. The distribution of negative symptom scores on the CROQ is represented in Figure 4.17 showing participants reported fewer negative symptoms at T2 (Mean: 10.94 ± SD: 4.60) than at T3 (Mean: 15.17 ± SD: 7.75); this was confirmed to be significant using a paired samples *t*-test ($t(55) = -3.870$, $p < 0.001$). This could be due to symptoms such as numbness and tingling not being fully apparent to the participant while in hospital, perhaps being masked by the use of medications. Other problems such as wound infections are likely to only develop after discharge, since all patients are routinely prescribed prophylactic antibiotics in the hospital. A wider range of scores were observed at T3. Ceiling effects were not apparent at either assessment. The frequencies of the different types of symptoms reported are displayed in Table 4.19. Pain, tenderness, bruising and swelling of the feet and ankles were all commonly reported at both time points after surgery, this suggests that negative symptoms continue up to two months after CABG.

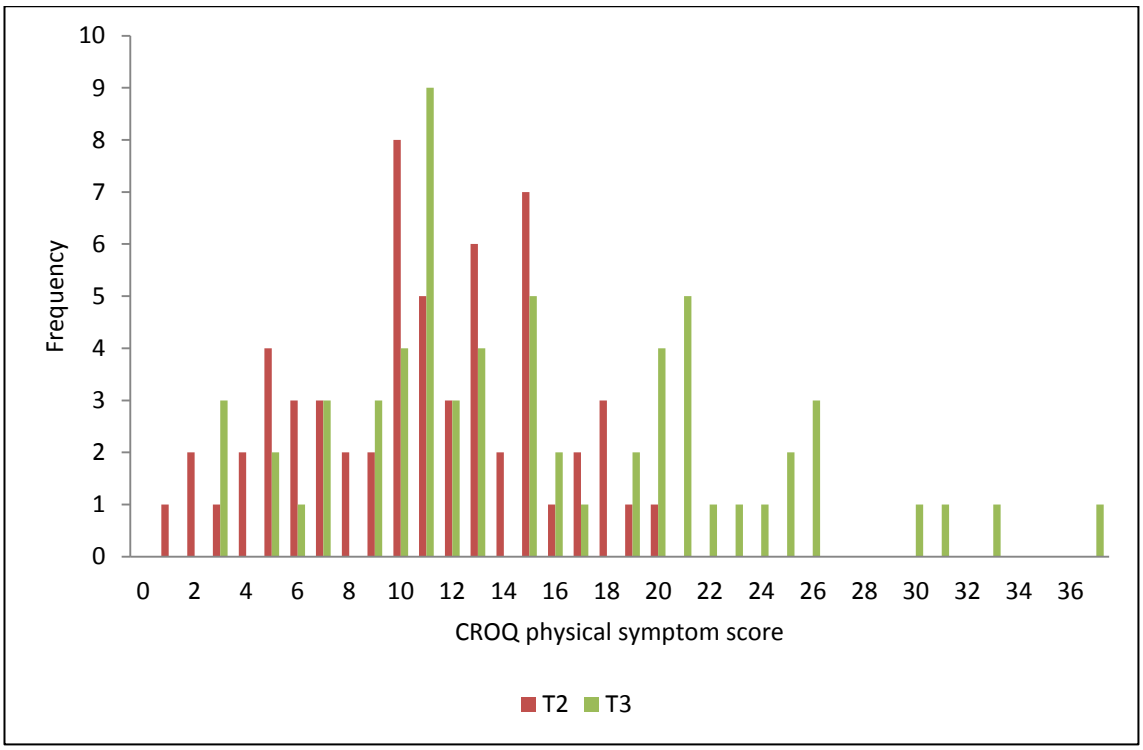

FIGURE 4.17: FREQUENCY OF PHYSICAL SYMPTOM SCORES AT T2 AND T3

TABLE 4.19: TYPE OF PHYSICAL SYMPTOM SCORES REPORTED AT T2 AND T3

Symptom severity (Moderate to A lot)	*T2*		*T3*	
	N	*n (%)*	*N*	*n (%)*
Pain in chest wound	70	51 (72.9)	66	29 (43.9)
Infection in chest wound	68	1 (1.5)	66	5 (7.6)
Tenderness around chest wound	70	41 (58.6)	66	37 (56.1)
Numbness/tingling around chest wound	70	5 (7.1)	66	25 (37.9)
Bruising around chest wound	64	6 (9.4)	66	16 (24.2)
Pain in arm/leg wound	70	28 (40.0)	63	34 (54.0)
Other pain in arm/leg due to operation	70	7 (10.0)	63	23 (36.5)
Infection in arm/leg wound	69	-	63	18 (28.6)
Numbness/tingling in arm/leg due to operation	70	16 (22.9)	63	31 (49.2)
Bruising arm/leg where vein was removed	65	26 (40.0)	63	30 (47.6)
Swollen feet/ankles	69	36 (52.2)	63	39 (61.9)

4.4.7 Satisfaction

Satisfaction with the results of surgery scores were skewed towards the higher end of the scale (see Figure 4.18), with a mean score of 12.98 (SD: 3.17). This indicates the majority of participants were satisfied with their CABG surgery.

FIGURE 4.18: FREQUENCY OF SURGERY SATISFACTION SCORES AT T3

4.5 Inferential statistical analyses

4.5.1 T1 depression symptoms and impaired adaptation following CABG

The association between depression symptoms and poor recovery was examined using Pearson's correlations to analyse the prospective relationship between baseline depression symptoms and post-operative pain, physical symptoms and health status. Specifically, it was hypothesised that greater depression symptoms before and after surgery would be associated with greater reports of pain and physical symptoms and poorer physical and mental health status following surgery. To clarify, lower scores on the SF-12 indicate poorer health status. To deal with missing data, on questionnaires where respondents had provided valid responses on at least half the questionnaire items, responses were scaled up. For example, if an individual who completed 16 items on the 21-item BDI had a total score of 6, this would be scaled to the full scale by computing (6/16)*21 = 7.9. This procedure maintained the full range of possible scores while maximising the number of participants for analysis.

Correlation results shown in Table 4.20 revealed that baseline depression symptoms were correlated with pain in the days shortly following surgery. In addition, T1 BDI scores were significantly negatively associated with T3 SF-12 mental component scores. Scores on the BDI were not associated with T3 scores of affective and sensory pain and physical health status, or with physical symptom scores on the CROQ at T2 or T3.

TABLE 4.20: PEARSON'S CORRELATIONS OF T1 TOTAL BDI SCORE AND T3 RECOVERY

Measure	*N*	*T1 BDI total score*
T2 Recovery		
T2 Sensory pain		
r	63	0.346
p		0.005
T2 Affective pain		
r	60	0.365
p		0.002
T2 Physical symptoms		
r	59	0.088
p		0.507
T3 Recovery		
T3 Sensory pain		
r	60	0.240
p		0.065
T3 Affective pain		
r	64	0.193
p		0.126
T3 Physical symptoms		
r	63	0.127
p		0.320
T3 Mental health status		
r	65	-0.358
p		0.003
T3 Physical health status		
r	65	-0.049
p		0.699

Cross-sectional analyses were also performed to study the associations between T3 depression symptoms and indices of T3 recovery. Pearson's correlations showed T3 BDI scores to be significantly associated with T3 sensory (r = 0.419, p = 0.003) and affective (r = 0.464, p <0.001) pain, as well as T3 mental (r = -0.382, p = 0.004) and physical (r = -0.321, p = 0.018) health status.

Clinical indices of disease severity and recovery, including LVEF, euroSCORE, reoperation, length of intensive care stay, post-operative infection and other complications were not significantly associated with baseline or T3 depression symptoms; this suggests depression symptoms occurred independently of clinical risk factors. However, due to the small sample size this needs to be corroborated in the main ACS study.

4.5.2 T1 illness perceptions and recovery

In order to assess the prospective relationship between illness perceptions and emotional adaptation following surgery, regression analyses were performed using pre-surgical data to predict post-surgical recovery endpoints. Specifically, it was hypothesised that patients who reported a more negative view of their illness before surgery would be more likely to have greater physical symptoms, poorer mental and physical health status and poorer emotional adaptation in the days and months after surgery, and that the associations would be independent of baseline mood, demographic and disease severity factors.

Multiple regression analyses were used to examine the relationship between pre-operative illness perceptions (total BIPQ score) and post-operative physical and emotional recovery, adjusting for age, sex, and disease severity (LVEF and euroSCORE). To control for the possible confounding effects of emotional distress, baseline scores of anxiety (HADS) and depression symptoms (BDI) were also added to the models as covariates. Models predicting T3 health status also adjusted for baseline scores on the SF-12.

4.5.2.1 T1 illness perceptions and post-operative physical recovery

Regression analyses were carried out to assess whether baseline illness perceptions predicted physical symptom reporting at T2 and T3. The T2 results displayed in Table 4.21 show baseline illness perception score (t = 2.213, p = 0.031) was a significant predictor in the model after controlling for covariates. The complete model accounted for 17.9% of the variance. The T3 results displayed in Table 4.22 show baseline illness perception score (t = 2.081, p = 0.042) was a significant predictor in the model after controlling for covariates. The complete model accounted for 24.2% of the variance.

TABLE 4.21: MULTIPLE REGRESSION ON PHYSICAL SYMPTOMS AT T2

Model	*B*	*SE*	*ß*	*p*
Age	-0.165	0.096	-0.316	0.090
Sex	-0.507	1.564	-0.041	0.747
euroSCORE	0.201	0.398	0.097	0.615
LVEF	-0.356	1.816	-0.029	0.845
T1 Anxiety	-0.407	0.195	-0.368	0.041
T1 BDI total score	0.024	0.109	0.038	0.825
T1 Illness perceptions	0.172	0.078	0.397	0.031

Note R^2 = 0.179.

TABLE 4.22: MULTIPLE REGRESSION ON PHYSICAL SYMPTOMS AT T3

Model	*B*	*SE*	*ß*	*p*
Age	0.259	0.149	0.324	0.088
Sex	5.962	2.422	0.317	0.017
euroSCORE	-0.357	0.640	-0.107	0.579
LVEF	-0.326	2.848	-0.017	0.909
T1 Anxiety	-0.430	0.307	-0.249	0.167
T1 BDI total score	0.034	0.164	0.035	0.835
T1 Illness perceptions	0.248	0.119	0.370	0.042

Note $R^2 = 0.242$.

TABLE 4.23: MULTIPLE REGRESSION ON PHYSICAL HEALTH STATUS AT T3

Model	*B*	*SE*	*ß*	*p*
Age	0.052	0.166	0.063	0.756
Sex	-2.001	2.697	-0.103	0.461
euroSCORE	0.324	0.713	0.094	0.651
LVEF	1.021	3.171	0.052	0.749
T1 Anxiety	0.597	0.342	0.334	0.087
T1 BDI total score	-0.013	0.182	-0.013	0.942
T1 Illness perceptions	-0.280	0.133	-0.403	0.040

Note $R^2 = 0.122$.

Regression analyses were next carried out to assess whether baseline illness perceptions predicted physical health status (SF-12) at T3. The results displayed in Table 4.23 show baseline illness perception score (t = -2.106, p = 0.040) was a significant predictor in the model after controlling for covariates. This was a negative association such that higher pre-operative illness perceptions scores, indicative of a more negative view of one's illness, were associated with lower T3 SF-12 scores, which reflect poorer health status. The complete model accounted for 12.2% of the variance.

4.5.2.2 T1 illness perceptions and post-operative emotional recovery

Table 4.24 displays the regression coefficients for the model using baseline illness perceptions to predict T3 BDI depression symptoms scores. Baseline illness perceptions were a significant predictor of greater depression symptoms following surgery (t = 2.140, p = 0.037), independently of covariates. The complete model accounted for 37.5% of the variance. These findings suggest that more negative illness perceptions before surgery were associated with greater depression symptoms up to two months following surgery. However, baseline illness

perceptions were not a significant predictor of T3 mental health status (t = -0.830, p = 0.410); in fact there were no significant predictors in this model.

TABLE 4.24: MULTIPLE REGRESSION ON DEPRESSION SYMPTOMS AT T3

Model	*B*	*SE*	*ß*	*p*
Age	-0.008	0.112	-0.012	0.944
Sex	3.030	1.831	0.197	0.104
euroSCORE	-0.365	0.478	-0.134	0.449
LVEF	-0.911	2.127	-0.059	0.670
T1 Anxiety	-0.411	0.249	-0.264	0.105
T1 BDI total score	0.353	0.122	0.431	0.006
T1 Illness perceptions	0.191	0.089	0.339	0.037

Note R^2 = 0.375.

4.5.3 T1 sleep and recovery

The aim of the subsequent analyses was to examine the relationship between pre-operative sleep disturbance and post-operative physical and emotional recovery, both in the days and months following CABG surgery. Specifically, it was hypothesised that patients who reported poorer sleep before surgery would be more likely to have worse physical recovery and emotional adaptation in the days and months after surgery, including greater self-reported physical symptoms, greater depression symptoms and impaired physical and mental health status, and that the associations would be independent of baseline mood, demographic and disease severity factors. In addition, it was hypothesised that the specific sleep symptoms would be differentially predictive of recovery outcomes.

Multiple regression analyses were used to examine the relationship between pre-operative sleep (total Jenkins sleep score) and post-operative recovery, adjusting for age, sex, and disease severity (LVEF and euroSCORE). To control for the possible confounding effects of anxiety, baseline scores on the anxiety subscale of the HADS were also added to the models as a covariate. Models predicting T3 health status also adjusted for baseline scores on the SF-12. Regression models with the same covariates, but with the individual items of the Jenkins sleep scale entered as predictor variables of recovery, were also used. Please note all analyses were run with item 16 of the BDI (sleep problems) removed.

4.5.3.1 T1 sleep and post-operative physical recovery

Table 4.25 displays the regression coefficients for the model using baseline sleep to predict T2 CROQ physical symptoms scores. Baseline sleep disturbance was a significant predictor of

greater T2 physical symptoms (t = 2.015, p = 0.048) independently of covariates. The complete model accounted for 16.5% of the variance. However, at T3, baseline sleep disturbance no longer predicted CROQ physical symptoms (t = 1.344, p = 0.184). Models using individual Jenkins items as the predictor variable found only item 5 (disturbed or restless sleep) (t = 2.090, p = 0.041) to be significant predictor of T2 CROQ physical symptoms; other items were not significant predictors in the models.

TABLE 4.25: MULTIPLE REGRESSION ON PHYSICAL SYMPTOMS AT T2

Model	*B*	*SE*	*ß*	*p*
Age	-0.217	0.097	-0.413	0.028
Sex	-1.561	1.533	-0.134	0.313
euroSCORE	0.483	0.412	0.234	0.246
LVEF	-0.749	1.820	-0.064	0.682
T1 Anxiety	-0.243	0.184	-0.218	0.194
T1 BDI total score*	0.037	0.117	0.054	0.755
T1 Sleep	0.190	0.094	0.283	0.048

Note R^2 = 0.165. *Item 16 removed.

TABLE 4.26: MULTIPLE REGRESSION ON PHYSICAL HEALTH STATUS AT T3

Model	*B*	*SE*	*ß*	*p*
Age	0.153	0.164	0.179	0.355
Sex	-0.273	2.662	-0.014	0.919
euroSCORE	-0.057	0.713	-0.016	0.936
LVEF	2.446	3.122	0.128	0.437
T1 Anxiety	0.118	0.110	0.147	0.285
T1 BDI total score*	0.192	0.322	0.104	0.554
T1 SF-12 physical	0.156	0.203	0.141	0.446
T1 Sleep	-0.394	0.162	-0.361	0.018

Note R^2 = 0.174. *Item 16 removed.

Regression analyses were next carried out to assess whether baseline sleep predicted physical health status (SF-12) at T3. The results displayed in Table 4.26 show baseline sleep was a significant predictor in the model (t = -2.434, p = 0.018) after controlling for covariates. This is a negative association such that higher pre-operative sleep scores, indicative of poor sleep, were associated with lower T3 SF-12 scores, which reflect poorer health status. The complete model accounted for 17.4% of the variance in SF-12 scores at T3. Models using individual Jenkins items as the predictor variable found item 2 (wake up several times per night) (t = -2.514, p = 0.015), item 3 (trouble staying asleep, including waking far too early) (t =

-2.543, p = 0.014) and item 4 (wake up after usual amount of sleep feeling tired and worn out) (t = -2.246, p = 0.029) to all significantly predict SF-12 physical health at T3. Item 5 (disturbed or restless sleep) (t = -2.003, p = 0.050) was of borderline significance.

4.5.3.2 T1 sleep and post-operative emotional recovery

Table 4.27 summarises the regression model on T3 BDI scores. Baseline sleep was a significant predictor of greater post-operative depression symptoms (t = 2.787, p = 0.007), independently of covariates. The complete model accounted for 35.6% of the variance in T3 depression symptoms. Models using individual Jenkins items as the predictor variable found item 4 (wake up after usual amount of sleep feeling tired and worn out) (t = 2.390, p = 0.020) and item 5 (disturbed or restless sleep) (t = 2.813, p = 0.007) significantly predicted T3 BDI scores.

TABLE 4.27: MULTIPLE REGRESSION ON DEPRESSION SYMPTOMS AT T3

Model	*B*	*SE*	*ß*	*p*
Age	-0.068	0.079	-0.141	0.398
Sex	-0.162	1.332	-0.015	0.904
euroSCORE	0.202	0.349	0.103	0.564
LVEF	-0.571	1.494	-0.054	0.704
T1 Anxiety	0.082	0.166	0.072	0.625
T1 BDI total score*	0.175	0.096	0.277	0.073
T1 Sleep	0.223	0.080	0.345	0.007

Note R^2 = 0.356. *Item 16 removed.

Baseline sleep was not a significant predictor of T3 mental health status (t = -1.165, p = 0.249; the only significant predictor in this model was baseline SF-12 mental health status (t = 3.248, p = 0.002).

4.6 Discussion

4.6.1 Descriptive analyses

In this chapter, data from P-ARCS was explored and described in order to inform the development of the main ARCS study. Descriptive analyses were performed on the data in order to assess the feasibility of the study and to check the suitability of the chosen measures.

4.6.1.1 Feasibility

Descriptive statistics from P-ARCS data were presented to ascertain the feasibility of the ARCS study. Feasibility was defined as the willingness of participants to take part in the study and the completeness of data. Results suggest that uptake to the study was good, with only 17.9%

of participants refusing to take part or failing to complete the first questionnaire. Overall attrition was quite high, with approximately one-third of participants withdrawing by the T3 follow-up. Importantly, cross-tabulations showed there to be no statistical significance between participants who withdrew and remained in the study on demographic and disease severity indices. Therefore, it is unclear why some participants withdrew from the study while others were happy to continue. However, it is possible that a sampling bias has occurred and those who failed to emotionally adjust, or who had a poor physical recovery, were at greatest risk of withdrawal following surgery. If this is the case, it is important to take attrition into account when calculating the sample size for the main ARCS study as a greater number of participants will be needed to demonstrate an effect. It also means there is a risk the study may underestimate the negative emotional outcomes of participants. Attrition will be particularly important in the main ARCS study which will include an additional time point at 12 months after surgery. Telephone calls will be introduced to prompt the return of questionnaires in addition to the reminder letters used during P-ARCS.

Missing data is also an issue to be addressed in the main ARCS study. Reasons for missing data are not entirely clear, though as discussed earlier, for some questionnaires we can attempt to ascertain a cause. For example, the high rates of missing data on the SAQ can be attributed to some participants stating they do not suffer from angina, therefore these questions were not applicable. Similarly, those participants who were not married or cohabiting (n = 22) were not required to complete the marital functioning questionnaire. These non-responses due to questions not being applicable are in large part unavoidable. However, results from P-ARCS suggest that missing data also occurs frequently for the socioeconomic status question, asking participants about yearly household income, and for the BDI. Such questions are sensitive in nature and, therefore, may lead to deliberate non-response on these items. Other questionnaires involved a numerical rating scale which is likely to be an unfamiliar response format for some participants, which may explain missing data on these measures. Specific examples will be added to the main ARCS questionnaire packs to aid completion on measures with numerical rating scales. Additional explanations of why participants are asked to provide details of income and why questions are repeated at each of the time points will also be added to the main ARCS study questionnaire packs. In addition, the need to answer all questions will be discussed with participants during recruitment.

4.6.1.2 Suitability of measures

Descriptive analyses were performed to assess whether the questionnaires used were sensitive, that is that they were able to produce a range of scores in the population targeted in this sample. Ceiling effects were only observed for ESSI and the marital quality questionnaire.

An alternative questionnaire, the Close Person Questionnaire (CPQ) (Stansfeld & Marmot, 1992) has been identified for inclusion in the main ARCS study to replace the marital functioning questionnaire. This replacement was not only made due to the ceiling effect, but also to capture a wider array of marital functioning issues. The CPQ is a short, 15-item questionnaire which assesses the amount to which the participant's partner/spouse has provided practical and emotional support over the past 12-months. The CPQ has been shown to be a valid and reliable measure over repeated assessments. The ESSI questionnaire was retained in the main ARCS study, but the issue of potential ceiling effects will be borne in mind since this will limit the ability to differentiate between people reporting high levels of social support.

Notably, the only measure removed from the questionnaire pack as a result of P-ARCS was the BDI from T2. It was concluded that the length of the BDI and the nature of the questions, which often overlap with the physical symptoms experienced as a result of the surgery and the hospital environment, made it an inappropriate choice. Instead the positive emotional style and negative emotional style scale (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Cohen, Doyle, Turner, Alper, & Skoner, 2003) has been included in the main study as a brief measure of both positive and negative mood. This measure has been previously used in Steptoe's group (Poole, Steptoe, et al., 2011).

4.6.2 Inferential statistical analyses

Preliminary analyses were performed on the P-ARCS data to ascertain initial associations between variables. Due the small sample size in P-ARCS further work is needed to corroborate these findings in the main ARCS study.

4.6.2.1 Depression symptoms and impaired adaptation

Correlation analyses confirmed that baseline depression symptoms were associated with increased pain and poorer mental health status following surgery, but not physical health status nor any of the clinical indices of recovery. These null findings are possibly due to the small sample size reducing the power to detect an effect. Other authors have found depression to be predictive of poorer quality of life and worse health outcomes in CABG patients (Doering et al., 2008, 2005; Kendel et al., 2010). The findings from P-ARCS are largely in line with a study by Burg and colleagues (Burg, Benedetto, Rosenberg, & Soufer, 2003) who found that patients who were depressed prior to CABG surgery were more likely to report poor quality of life and worse recovery following their operation. Moreover, another study found depressed CABG patients to report greater pain symptoms up to 12-months following

surgery (Morone et al., 2010), suggesting these patients are in greatest need for targeted interventions.

Analysis plans for the full dataset from the main ARCS study include examining the types of symptoms patients report on the BDI, such as cognitive/affective or somatic/affective, and assessing how they differentially predict recovery outcomes both in the early- and short-term. In addition, if cases allow, participants will be grouped according to the timing and recurrence of a depressive episode to allow comparisons to be made regarding differences in recovery according to depression onset.

4.6.2.2 Illness perceptions and recovery

Regression analyses were performed to assess the association between negative illness perceptions prior to surgery and poorer recovery in the days and months following surgery. The main findings of these analyses were that a more negative perception of one's illness at baseline was predictive of poorer physical and emotional recovery, independently of baseline mood, disease severity and demographic factors. Specifically, baseline illness perceptions were able to predict increased physical symptoms and poorer physical health status and increased depression symptoms and poorer mental health status following surgery. Moreover, these results were consistent across time points, both in the days and months following CABG.

Previous research has also shown that negative illness perceptions are related to greater depression symptoms in cardiac surgery patients. For example, cross-sectional associations between negative illness perceptions and greater psychological distress have been reported in patients before CABG (Hermele et al., 2007). Moreover, the prospective association, which is in line with my findings, has been reported by Juergens and colleagues (Juergens et al., 2010) who showed pre-surgical negative illness perceptions predicted depression, disability and quality of life three months after surgery. Another study has shown that more negative illness perceptions in the days following hospital admission for MI, were associated with the development of new onset depression in particular (Dickens et al., 2008b). This hypothesis was unable to be tested using the P-ARCS data due to the small sample size; as such future work is needed to test this association in CABG patients.

Work using ACS patients has also shown negative illness perceptions mediate the relationship between depression and health-related quality of life in stable CHD outpatients (Dickens, Cherrington, & McGowan, 2011). However, the results shown here using CABG patients were unable to corroborate this finding, since no association was found between baseline depression and physical SF-12 scores at T3. Instead pre-surgical illness perceptions were shown to independently predict physical health status following surgery. Further work on a larger sample is needed to explore these mediation hypotheses in greater detail.

Confounders of the relationship between illness perceptions and later recovery were considered in the analyses. For example, baseline anxiety was included in models as a covariate and subsequently this is not likely to account for the relationship observed between illness perceptions and recovery. Nor did the analyses find a relationship between illness perceptions and co-morbid conditions which could otherwise have accounted for the relationship. However, other potential covariates such as socio-economic position were not considered. All these factors will be explored in greater detail using data from the main ARCS study. In particular, the mediatory role of illness perceptions to the depression symptoms-recovery relationship will be tested.

4.6.2.3 Sleep and recovery

In the sleep and recovery analyses the associations between self-rated sleep prior to CABG surgery and physical and emotional recovery in the days and months following surgery were examined. The main findings of these analyses were that sleep disturbance before surgery was associated with greater physical symptoms, poorer physical health status and greater depressive symptoms after CABG surgery, independent of baseline mood, disease severity and demographic factors. Time since surgery was an important factor, with baseline sleep a significant predictor of CROQ physical symptoms in the immediate post-operative period but not at T3; the reason for this is not clear. As hypothesised, different characteristics of sleep problems were associated with different recovery outcomes, independent of covariates. For example, disturbed and restless sleep was a predictor of CROQ physical symptoms and the BDI, and was of borderline statistical significance in predicting SF-12 physical health status. Overall, it appeared that the symptoms of sleep that were most predictive of poor recovery were problems maintaining sleep throughout the night as opposed to trouble initiating sleep. Baseline sleep was not associated with emotional health status following surgery after controlling for covariates.

It is important to note that all analyses were run with item 16 of the BDI (sleep problems) removed, with significant findings still being demonstrated. Therefore, the association between poor baseline sleep and recovery outcomes cannot be attributed to poor sleep also being assessed in the BDI. However, it is difficult to unpick the association between poor sleep and greater depression symptoms entirely, since sleep problems are in themselves a symptom of depression. Further work is needed in order to assess the contribution of sleep to depression, however there is some evidence to suggest poor sleep does contribute to depression onset (Baglioni et al., 2011; Cho et al., 2008; Ford & Kamerow, 1989; Roberts et al., 2000).

The findings are in line with the results from Hunt and colleagues (Hunt et al., 2000) and Redeker and colleagues (Redeker et al., 2004) who reported cross-sectional associations between poor sleep and worsened quality of life after CABG. In addition, the results from P-ARCS have demonstrated a prospective relationship, such that poor sleep prior to surgery was associated with poorer recovery following surgery. Edéll-Gustafsson and Hetta (1999) found that those patients reporting greater anxiety were more prone to sleep disturbance. Since baseline anxiety was controlled for in the analyses used in this PhD, this is not likely to account for the relationship observed between sleep and recovery. Nor did the analyses find a relationship between sleep and co-morbid conditions which could otherwise have accounted for the relationship. Other biological pathways may be relevant, but were not tested in these analyses. In their review, Meerlo, Sgoifo and Sucheecki (2008) suggest that changes to autonomic function and neuroendocrine systems may be important in linking poor sleep to health outcomes. For example, sleep deprivation or disruption may act as a stressor, leading to increased sympathetic nervous system activation. If sleep recovery is insufficient these effects continue, with studies showing persistent elevated heart rate and blood pressure (Lusardi et al., 1996; Tochikubo et al., 1996). Changes to the neuroendocrine system have also been observed after sleep loss, although the findings are somewhat inconsistent with some studies reporting a slight elevation in cortisol in response to sleep deprivation (Chapotot et al., 2001; Spiegel, Leproult, & Van Cauter, 1999), while others have reported no changes or even small decrements in cortisol levels (Akerstedt et al., 1980; Follenius et al., 1992). Modulation of cortisol responses may have particular importance as greater cortisol output has been associated with slower wound healing (Ebrecht et al., 2004; Vedhara et al., 2010) and depression in coronary artery disease patients (Bhattacharyya et al., 2008). These biological pathways warrant future investigation in CABG patients.

The findings reported here suggest that the type of sleep complaint is likely to be important in predicting recovery after surgery. For example, the characteristic of disturbed and restless sleep was shown to be significant. Data from large epidemiological studies have also demonstrated that disturbed and restless sleep carries greater cardiac risk (Chandola, Ferrie, Perski, Akbaraly, & Marmot, 2010), but this has been little investigated in studies using CABG surgery patients. The distinction between sleep symptoms is an important line of enquiry for establishing targeted interventions.

The timing of assessment is likely to affect how well the results can predict long-term prognosis. For example, Hedner and colleagues (2002) assessed sleep in just over 1200 individuals prior to CABG surgery and one year following surgery and reported that baseline sleep disturbance was not generally associated with survival at five-year follow-up. The analyses in this PhD have shown baseline sleep to be associated with short-term differences in

recovery; however, it is not clear to what extent these effects would be maintained in the longer term or the impact of sleep disturbance on mortality risk. Future work is needed to address these issues.

Sleep measurement is also likely to be important in studies of this type. Marked discrepancies have been observed between subjective and objective measures of sleep (Fernandez-Mendoza et al., 2011; Lauderdale et al., 2008; Silva et al., 2007; Van Den Berg et al., 2008), with self-rated sleep being modulated by psychosocial characteristics and affect (Jackowska et al., 2011). There is a lack of sleep studies in cardiac patients using objective measures. One exception is a study using polysomnographic recordings to map the pattern of sleep activity before and after CABG surgery; these authors found changes in sleep architecture and decreased night-time sleep and increased daytime sleep after surgery (Edéll-Gustafsson & Hetta, 1999). Another study used objective (actigraphy) and subjective sleep measures in cardiac patients to track improvements in sleep after surgery (Yilmaz & Iskesen, 2007). Only one study to date has combined data from self-report and objective methods in association with post-CABG outcomes. Redeker and colleagues (2004) showed that objective and self-reported measures of sleep quality were related to health status at four and eight weeks following surgery. More studies are needed to investigate the different measurement methods in greater detail.

4.6.2.4 Limitations of P-ARCS

These analyses have a number of strengths and limitations. One of the main strengths of P-ARCS is the longitudinal design. However, the direction of the relationship between illness perceptions/poor sleep and recovery is uncertain: whether illness perceptions/poor sleep causes worse recovery or vice versa, or whether both are related to an unmeasured third factor, such as lifestyle (e.g. alcohol consumption, physical activity, smoking). The sample was restricted to elective surgery participants and, therefore, does not capture the full range of disease severity and co-morbidities that may be apparent in patients undergoing cardiac surgery.

In addition, P-ARCS used self-report measures of sleep and illness perceptions and it is possible these responses may be influenced by negative affectivity (Jackowska et al., 2011). These analyses tried to address this issue by controlling for anxiety and depressive symptoms in the regression models, and indeed the associations remained significant even after these adjustments. Additionally, in the sleep and recovery analyses, sleep medication and history of sleep disorders was not taken into account; although very few patients reported use of sleep medications, records were incomplete so could not be included in the statistical models.

Finally, the small sample size in P-ARCS means further work is needed to corroborate these findings.

4.7 Chapter summary

Descriptive results will be used to inform the development of the main ARCS study, including strategies to decrease attrition and missing data and the choice of questionnaires to be used. Results from the inferential statistical analyses must be interpreted carefully due to the small sample size, but are a useful guide to inform future analyses on the main ARCS dataset. The correlation analyses performed suggest that depression symptoms were associated with poor mental health status and pain, two months after surgery. Moreover, illness perceptions and sleep prior to surgery were related to emotional and physical recovery after surgery. These latter results suggest that both a cognitive and behavioural model may be useful to our understanding of the depression symptoms-impaired adaptation relationship. Future analyses on the main ARCS study will explore these issues in greater detail and will make use of biological data to assess the role of inflammatory and neuroendocrine factors in the depression-recovery relationship.

Chapter 5. Method: The ARCS study

5.1 Introduction

Following completion of the pilot study, the modifications and adjustments were made to the protocol in order to establish the main ARCS study. As in P-ARCS, the ARCS study was developed and designed to investigate the causes and consequences of poor emotional wellbeing following CABG surgery, and their implications for patient quality of life and physical recovery. The ARCS study was developed in order to address the limitations and problems observed in the pilot, and to extend the scope in order to address the biological mechanisms, discussed in Chapter 2 of the literature review, relating depression to poor outcomes following CABG surgery. As such, ARCS builds on the pilot study by focussing on five sets of factors that are potentially relevant to mood and quality of life following CABG: (1) clinical factors, (2) cognitive factors, (3) social factors, (4) psychological factors, (5) biological factors. The biological measures included are saliva samples for the measurement of the neuroendocrine hormone cortisol and blood samples for the measurement of inflammatory markers.

Other distinctions can be made between P-ARCS and the main ARCS study. First, P-ARCS used a maximum follow-up of two months following surgery. Participants were found to still be experiencing negative physical symptoms of surgery at T3, greater than those in the acute period (T2). Therefore, a 12-month assessment was included at time four (T4) as a long-term follow-up of participants following surgery, to enable us to better understand the recovery process. Second, the P-ARCS study was limited in the conclusions which could be drawn relating to patient quality of life due to the inclusion of only a small number of measures. In ARCS we extended the psychosocial measures to include more diverse, global, measures of quality of life, not just those measures specific to health problems. Third, we needed to address the problems of missing data in clinical information experienced in P-ARCS. Therefore we included questions of self-reported physical and mental health questions in ARCS. Lastly, the partners of CABG patients are also at risk of adverse psychological outcomes, and the burden of caregiving has been found to have a negative impact on partners' physical health (Randall, Molloy, & Steptoe, 2009). The ARCS study therefore assesses changes to partners' psychological and physical health following patients' surgery.

The ARCS study aims to address several research questions. What are the causes and consequences of poor emotional adjustment in patients undergoing CABG surgery, and what are their implications for quality of life and patient wellbeing? What is the impact of CABG surgery on the psychological and physical health of partners, and what role does the partner play in the recovery and adaptation of the patient? By successfully answering these questions,

the ARCS study has the potential to guide risk stratification and to help develop targeted and effective interventions to improve patient prognosis following CABG surgery.

5.2 Differentiating my PhD from the ARCS study

The development and completion of P-ARCS formed the first part of this PhD. However, the main ARCS study is a multidisciplinary study involving several researchers and accordingly, other issues will be investigated that are outside the scope of my PhD. For example, the ARCS study will assess changes to partners' psychological and physical health following the patients' surgery; these data will not be included in my PhD. In addition, T4 data collection is on-going, and is due to be completed in the summer of 2013; therefore, these data are not available for use in this thesis. In the following sections I will describe both the methods for the ARCS study as a whole, but will also differentiate those which are applicable to my PhD. The measures included in the partner study and at T4 are outlined in Table 5.1; however, the methods relating to the partner study and 12-month follow-up are not relevant to this thesis and, therefore, are not described.

5.3 PhD aims and hypotheses

Having developed the ARCS study, this PhD aims to characterise the progression of patients from the pre-operative to post-operative phases of recovery following cardiac surgery, and in particular to study the impact of experiences in the weeks prior to surgery on early- and short-term physical and mental adaptation. This PhD will focus on the relationship between depression symptoms and recovery over time and the underlying mechanistic pathways. Three main mechanisms will be explored in detail: social-behavioural, cognitive and biological. To address these aims, this PhD will make use of data from the ARCS study.

It is important to note that, as in the literature review, throughout the subsequent chapters, the terms *adaptation* and *recovery* will be used interchangeably to describe the post-surgery outcomes of the ARCS participants. Adaptation and recovery both imply a return to normal functioning, but obviously this is difficult to characterise in CABG patients with advanced disease, since pre-operative levels of functioning may already be lower than population norms. Indeed, one may expect an improvement in functioning after surgery compared to before, in line with a reduction in the cardiac symptoms which the surgery aims to alleviate. Therefore, recovery and adaptation will be operationalised in this PhD as the endpoints after surgery which capture functional status and suffering. Such factors include measures of clinical recovery such as length of post-operative hospital stay, physical recovery such as pain and surgical healing, emotional recovery such as anxiety and mental and physical quality of life. Some authors would argue that these endpoints actually describe prognosis

(Hemingway, Riley, & Altman, 2009), however for the purpose of this PhD adaptation and recovery will be conceptualised as distinct from prognosis. Instead, prognosis will be used to refer to cardiac endpoints such as recurrent events and mortality.

The hypotheses of this PhD can be stated as:

(1) Depression symptoms are associated with impaired adaptation following CABG surgery

i. Somatic/affective depression symptoms will carry greater risk than no depression symptoms and cognitive/affective depression symptoms for poor adaptation in the days following surgery and up to two months following surgery, including:
   a) Early- and short-term emotional recovery such as anxiety,
   b) Early- and short-term surgical recovery such as length of hospital stay, pain, physical symptom reporting,
   c) Short-term physical and mental adaptation,

   and these associations will be independent of demographic and clinical factors.

ii. Persistent depression and post-CABG onset depression will carry greater risk than no depression and resolved depression for poor adaptation up to two months following surgery, including:
   a) Short-term emotional recovery such as anxiety,
   b) Short-term surgical recovery such as pain and physical symptom reporting,
   c) Short-term physical and mental adaptation,

   and these associations will be independent of demographic and clinical factors.

(2) Social-behavioural factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more negative health behaviours before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show lower social support before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(3) Cognitive factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more neurocognitive impairment before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show more negative illness perceptions before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and these will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(4) Biological factors affect the depression symptoms-poor adaptation relationship

i. Patients who show a flatter diurnal cortisol profile before surgery will be more likely to show poorer emotional and physical recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show greater inflammatory responses in the days after surgery will be more likely to show poorer emotional and physical recovery up to two months following surgery, including:
   a) Early- and short-term emotional recovery,
   b) Early- and short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and these factors will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

iii. Patients who show greater inflammatory responses in the days after surgery will be more likely to display greater depression symptoms up to two months following surgery.

5.4 Sample size

A power calculation was performed using nQuery Advisor version 4.0 (Statistical Solutions, Cork, Ireland) to determine a sample size for the ARCS study. Power was determined using results from a recently published paper by Beresnevaitė et al. (2010), which investigated the effect of pre-operative depression on post-operative complications in CABG patients. This paper was identified as appropriate because the research question clearly defined a CABG population, used a longitudinal cohort design, and employed a measure of recovery (length of hospital stay) as the dependent variable. These authors found, in their regression model to predict length of hospital stay, that covariates accounted for 0.195 of variance. The addition of depression to the model increased the variance explained by 0.105. Using a significance criterion of $\alpha = 0.01$, power at a level of 0.90, for a multiple regression model using up to eight covariate variables and one predictor variable, 103 participants are required to detect an effect. We inflated this to 200 participants in order to allow for missing data, variability in biological data and the testing of various sub-hypotheses within the dataset.

5.5 Participants

We planned consecutive recruitment of up to 300 CABG surgery patients to allow for attrition. As in P-ARCS, the inclusion criteria for ARCS were patients who were undergoing first-time, elective CABG surgery or CABG plus valve replacement, at St George's Hospital, London. Patients must have been able to complete the research interviews and questionnaires in English, and have been 18 years or older. Participants with communication or cognitive impairments were excluded since this would have affected their ability to complete the questionnaires; this was assessed on the recommendation of the pre-assessment nursing staff. Participants who were too unwell or clinically unstable were also excluded. Recruitment began in February 2011 and completed in August 2012.

The sample for this PhD is restricted to those participants who had completed T1 through to T2 for the early-term outcomes and T1 through to T3 for the short-term outcomes, at the time of analysing the results (June 2012). This provides a sample of 216 and 154 participants respectively. Data collection will continue for the remaining participants in this study beyond the timeframe of this PhD.

5.6 Design and procedure

The ARCS study used a prospective longitudinal design incorporating four assessments spanning the pre-operative period for up to 12 months following CABG surgery. However, only the first three assessments are available for this PhD; these time points were the same as in P-ARCS. The T1 assessment occurred approximately one to three weeks before surgery when

patients come to the hospital for their pre-assessment clinic appointment. The T2 assessment took place approximately three to five days after surgery while patients were still in hospital on the cardiac care ward. The T3 follow-up took place six to eight weeks after surgery via post. The study was submitted as a substantial amendment to the original P-ARCS protocol (AM1 25/11/2010) and obtained ethical approval (South West London REC1, 09/H0708/38). Details of the procedures used at each of these time points are described below.

Time 1 (1-3 weeks before surgery): Prior to being approached in person, a letter introducing the study and a participant information sheet was sent to all patients scheduled for elective CABG surgery (see Appendix 5). This first point of contact was made by the clinical team to avoid breach of confidentiality. A member of the research team (TK, LP or EL) then approached patients in the waiting area of the pre-assessment surgery clinic and asked if they would be willing to participate in the study. The procedure was explained, before obtaining signed consent (see Appendix 6). The researcher discreetly conducted a brief interview with the patient in the waiting area to collect demographic information. After attending the clinic appointment with the pre-assessment nurse, participants were taken to a private research office for administration of a health literacy and cognitive assessment. At this time the sampling procedure for the saliva samples was explained and saliva collection tubes were given to participants for the measurement of cortisol over the course of one day; participants were also given a sampling diary to record their samples (see Appendix 7). The participant was also issued with a postal questionnaire to self-complete and return in a freepost envelope. Participants were taken back to the outpatient clinic for blood collection by one of the pre-assessment nurses. Participants were instructed to complete the saliva samples, saliva diary and questionnaire booklet at home at their earliest convenience before surgery.

Time 2 (3-5 days after surgery): Participants were approached in the cardiac care ward during their post-surgery recovery and asked if they would be willing to participate in the second assessment. Having gained verbal consent, the researcher discreetly conducted a brief structured interview. Blood request forms were issued to coincide with patients' post-surgery day 1 and day 4; some variation in these timings were made to avoid bloods being requested on weekend days when the phlebotomy rounds were often operated by bank staff.

Time 3 (6-8 weeks after surgery): Participants were telephoned and asked if they would be willing to participate in the next assessment. If in agreement, a postal questionnaire was sent for self-completion. They were also posted saliva collection tubes to measure cortisol over the course of one day. A freepost envelope was provided for the return of the completed questionnaire and samples.

5.7 Psychosocial measures

Many psychosocial measures were included as part of the ARCS study, these are displayed in Table 5.1. However, only a selection of these measures has been used for the purpose of this thesis, and these are displayed in Table 5.2. Many of the measures have previously been described in Chapter 3 and can be found in Appendices 2 and 3; details of the Appendix cross-reference for these measures are provided in Table 5.2. Only the measures directly applicable to this PhD, and which have not been previously described, will be discussed in detail here. The Cronbach's alphas for questionnaires used in this thesis are presented in Chapters 6 and 7, since different sample sizes were used in the early- and short-term analyses.

5.7.1 Clinical information

The clinical information data collection remained the same as in P-ARCS, with the addition of some self-report items of health and medication use. Specifically, participants were asked to document the number of visits they had made to their GP and the number of emergency and routine hospital visits they had made relating to their heart disease or other conditions. In addition, they were asked to report any co-morbidity and list their use of prescribed and non-prescribed medications. T1 questions were worded to reflect the past 12 months and T3 questions were worded to reflect the period since the patient's surgery. Cardiac-related prescription medicines were classified according to drug type, for example statin and beta-blocker, whereas non-cardiac and non-prescription medications were classified according to their usage, for example analgesic, asthma, and nutritional supplement. In addition, participants were also asked to answer six questions relating to their pre-surgery psychiatric status, including details of any current or past psychiatric diagnosis and any treatment they were receiving in the four weeks prior to their surgery. Treatment categories included antidepressant or anxiolytic medication, counselling or psychotherapy, or other.

P-ARCS implemented the additive method for scoring of the euroSCORE, however in the main ARCS study the logistic scoring method (Roques, Michel, Goldstone, & Nashef, 2003) was implemented. This method uses the same 17 risk factors as in the additive calculation, but enters them into a logistic regression equation to predict mortality. This approach is better able to estimate risk for patients at the higher end of the scale who are at greatest risk from surgery. Details of this calculation can be found in Appendix 8. Scores are presented as a percentage.

TABLE 5.1: MEASURES IN THE ARCS STUDY FOR USE AT PATIENT (T1, T2, T3 & T4) AND PARTNER (P1, P2 & P3) ASSESSMENTS.

AAS-R: Adult Attachment Scale – Revised; BDI: Beck Depression Inventory; BFQ: Benefit Finding Questionnaire; BIPQ: Brief Illness Perception Questionnaire; CASP-19: Control, Autonomy, Self-realisation and Pleasure questionnaire – 19 item; CPQ: Close Persons Questionnaire; CROQ-CABG: Coronary Revascularisation Outcomes Questionnaire; ECQ: Efficacy/Confidence Questionnaire; ESSI: ENRICHD Social Support Instrument; HADS: Hospital Anxiety and Depression Scale; IPAQ: International Physical Activity Questionnaire; LOT: Life Orientation Test; MARS: Medication Adherence Rating Scale; MoCA: Montreal Cognitive Assessment; MPQ-SF: McGill Pain Questionnaire – Short Form; OCBS: Oberst Caregiving Burden Scale; PES/NES: Positive Emotional Style/Negative Emotional Style; SAQ: Seattle Angina Questionnaire; SF-12: Short Form health survey – 12 item; YCBQ: York Cardiac Beliefs Questionnaire.

Mode of assessment	*T1 Interview / Post*	*P1 Post*	*T2 Interview*	*T3 Post*	*P2 Post*	*T4 Post*	*P3 Post*
Time	*2-3 weeks pre-CABG*		*3-5 days post-CABG*	*6-8 weeks post-CABG*		*12 months post-CABG*	
Measures							
Socio-demographics – general	✓	✓	-	-	-	-	-
Socio-economic status - income	✓	-	-	-	-	-	-
Clinical information & euroSCORE	-	-	-	✓	-	-	-
Rehabilitation attendance	-	-	-	✓	-	✓	-
Self-report health status	✓	✓	-	✓	-	✓	✓
Self-report psychiatric history	-	-	-	✓	-	-	-
Emotional distress							
Anxiety (HADS subscale)	✓	✓	✓	✓	✓	✓	✓
Depression (BDI)	✓	✓	-	✓	✓	✓	✓
Positive/Negative affect (PES/NES)[7]	✓	✓	✓	✓	✓	✓	✓
Optimism (LOT[8])	✓	✓	-	-	-	-	-
Chronic stress (from MESA)[9]	✓	✓	-	-	-	✓	✓
Health behaviour							
Adherence (MARS)	✓	-	-	✓	-	✓	-
Physical activity (IPAQ – walking)	✓	✓	-	✓	-	✓	✓
Diet	✓	✓	-	✓	-	✓	✓
Sleep (Jenkins Scale)	✓	✓	-	✓	✓	✓	✓
Smoking	✓	✓	-	✓	-	✓	✓
Alcohol	✓	✓	-	✓	-	✓	✓
Quality of life							
Health status (SF-12)	✓	✓	-	✓	✓	✓	✓

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Quality of life (CASP-19)[10]	✓	✓	-	✓	✓	✓	✓
Benefit finding (BFQ[11])	-	-	-	✓	✓	✓	✓
Efficacy/Confidence (ECQ[12])	-	-	-	✓	-	✓	-
Illness beliefs							
Illness perceptions (BIPQ)	✓	✓	-	✓	-	✓	✓
Cardiac beliefs (YCBQ)	✓	✓	-	✓	-	✓	✓
Partner illness perceptions[13]	-	✓	-	-	-	-	✓
Social support							
Social network	✓	✓	-	-	✓	-	✓
Social support (ESSI)	✓	✓	-	✓	✓	✓	✓
Hospital partner support	-	-	✓	-	-	-	-
Attachment (AAS-R[14])	✓	✓	-	-	-	-	-
Attachment[15]	-	-	-	-	-	✓	-
Marital functioning (CPQ[16])	✓	✓	-	✓	✓	✓	✓
Loneliness (UCLA Scale[17])	✓	✓	-	✓	✓	✓	✓
Physical symptoms							
Angina (SAQ, adapted)	✓	-	-	✓	-	✓	-
Symptoms (CROQ-CABG)	-	-	✓	✓	-	✓	-
Pain (MPQ-SF)	-	-	✓	✓	-	✓	-
Satisfaction							
Satisfaction (CROQ-CABG scale)	-	-	-	✓	-	✓	-
Cognitive function							
Health literacy[18]	✓	-	-	-	-	-	-
Cognitive screen (MoCA)	✓	-	-	-	-	-	-
Caregiver burden							
Caregiving duties (Heart Scan[19])	✓	✓	-	-	✓	✓	✓
Caregiving burden (OCBS[20])	-	✓	-	-	✓	-	✓

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TABLE 5.2: MEASURES APPLICABLE TO MY PHD

BDI: Beck Depression Inventory; BIPQ: Brief Illness Perception Questionnaire; CROQ-CABG: Coronary Revascularisation Outcomes Questionnaire; ESSI: ENRICHD Social Support Instrument; HADS: Hospital Anxiety and Depression Scale; IPAQ: International Physical Activity Questionnaire; MoCA: Montreal Cognitive Assessment; MPQ-SF: McGill Pain Questionnaire – Short Form; SF-12: Short Form health survey – 12 item.

Mode of assessment	*T1* *Interview/ Postal*	*T2* *Hospital Ward*	*T3* *Postal*	*Appendix Reference*
Time	*1-3 week pre-CABG*	*3-5 days post-CABG*	*6-8 weeks post-CABG*	
Measures				
Socio-demographics – general	✓	_	_	2.A
Socio-economic status - income	✓	_	_	2.L
Clinical information	_	_	✓	-
Rehabilitation attendance	_	_	✓	3.C
Self-report health status	✓	_	✓	2.J
Self-report psychiatric history	_	_	✓	3.D
Emotional distress				
Anxiety (HADS subscale)	✓	✓	✓	2.F
Depression (BDI)	✓	_	✓	2.G
Health behaviour				
Physical activity (IPAQ – walking)	✓	_	✓	2.C
Sleep (Jenkins Scale)	✓	_	✓	2.I
Smoking	✓	_	✓	2.B
Alcohol	✓	_	✓	2.D
Health status				
Health status (SF-12)	✓	_	✓	2.E
Illness beliefs				
Illness perceptions (BIPQ)	✓	_	✓	2.K
Social support				
Social support (ESSI)	✓	_	✓	2.H
Physical symptoms				
Symptoms (CROQ-CABG)	_	✓	✓	3.A
Pain (MPQ-SF)	_	✓	✓	3.B
Cognitive function				
Cognitive screen (MoCA)	✓	_	_	9

5.7.2 Health behaviour: Alcohol

We introduced a different series of questions in ARCS compared to those used in P-ARCS to aid participant completion. Participants were asked to think back over the previous week and

record on how many days they drank an alcoholic drink. They were then asked to specify the type of alcohol and to approximate the number of measures consumed in this period. Each glass of wine and pint of beer consumed was estimated to be equivalent to two units of alcohol, while a single measure of a spirit was estimated to be equivalent to one unit of alcohol. These responses were used to produce an estimate of weekly intake of alcohol units.

5.7.3 Emotional distress

5.7.3.1 Beck Depression Inventory

TABLE 5.3: ITEMS CORRESPONDING TO BDI SYMPTOM SUBYTPES

BDI Item	*Somatic/affective score*	*Cognitive/affective score*
1. Sadness	✓	✓
2. Pessimism	✓	✓
3. Sense of failure	-	✓
4. Dissatisfaction	✓	✓
5. Guilt	-	✓
6. Punishment	-	✓
7. Self-dislike	-	✓
8. Self-accusations	-	✓
9. Suicidal ideas	-	✓
10. Crying	✓	-
11. Irritability	✓	-
12. Social withdrawal	✓	✓
13. Indecisiveness	✓	✓
14. Body image change	-	✓
15. Work difficulty	✓	-
16. Insomnia	✓	-
17. Fatigue	✓	-
18. Appetite	✓	-
19. Weight loss	-	-
20. Somatic preoccupation	✓	-
21. Loss of libido	✓	-

As in P-ARCS, the ARCS study scored the BDI by summing each chosen answer (on a scale of 0 to 3), with higher scores indicating greater emotional disturbance. A score of 0 to 10 indicates a person is not depressed, 11 to 20 suggests a person is mildly to borderline clinically depressed, 21 to 30 signifies moderate depression and a score of 31 to 63 indicates severe to extreme depression. In addition to this total score, a cognitive/affective and a

somatic/affective score were calculated in accordance with de Jonge's work in this field (De Jonge, Ormel, et al., 2006). Although various different combinations of items have been proposed using the BDI (Beck & Steer, 1987; Morley, Williams, & Black, 2002), the item loading devised by de Jonge and colleagues (De Jonge, Ormel, et al., 2006) was deemed appropriate due to the use of a cardiac population and since this has been used by Steptoe's group in the past (Steptoe et al., 2012).

The items which comprise these subscales are displayed in Table 5.3. As displayed in this table, these subtypes cannot be deemed mutually exclusive, with some of the affective symptoms being included in both the somatic and cognitive scores. One of the main limitations of this particular scoring method is that this conceptual overlap raises issues of multicollinearity (r = 0.801, p <0.001) and therefore it will not be possible to examine the independent effect of one subtype over and above the effect of the other subtype. Instead, separate models will need to be used to examine each subtype separately. The range of possible scores for the cognitive/affective dimension was 0 to 36 and for the somatic/affective dimension was 0 to 39, with higher scores indicating greater symptoms.

5.7.4 Cognitive function

5.7.4.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)[21] was developed as a brief measure of mild cognitive impairment covering eight cognitive domains (see Appendix 9). Visuospatial awareness is assessed using a clock drawing task and a cube copy task. Several aspects of executive functioning are assessed including an alternation task adapted from the Trail Making B, a phonemic fluency task (using the letter 'F') and a two-item verbal abstraction task. A test of short-term memory recall involves two learning trials in which participants are asked to remember five nouns, with a delayed recall after approximately five minutes. Attention, concentration and working memory are assessed through administration of a serial subtraction task, a sustained attention ask (target detection using tapping), and digits forward and backwards. Several tests of language also take place, including a three-item confrontation naming task with low-familiar animals, repetition of two syntactically complex sentences, and the abovementioned fluency task. Lastly, participants' orientation to time and place is appraised with six questions relating to the date and place of assessment. A maximum of 30 points was awarded, with a cut-off of <26. An extra point is awarded to participants with ≤12 years of education. More recent work suggests using a more conservative cut-off of ≤20 for older adult populations (Waldron-Perrine & Axelrod, 2012) and <24 for cardiovascular samples

[21] www.mocatest.org

(McLennan, Mathias, Brennan, & Stewart, 2011). To side-step this issue, we used results on a continuous scale, rather than splitting participants into groups of impaired or not impaired.

5.8 Biological measures

5.8.1.1 Cortisol sampling

Cortisol can be assessed in saliva and salivary cortisol has been shown to accurately reflect plasma cortisol. Moreover, saliva sampling has the advantage of being a non-invasive and convenient method of assessing diurnal variation of cortisol in a naturalistic setting (Kirschbaum & Hellhammer, 1989, 1994). Saliva sampling relies on participants taking the samples themselves and accurately reporting the time of assessment. This reflects a trade-off, since the control over the measurement is surrendered in order to gain ecological validity.

The saliva samples were collected using Salivettes (Sarstedt, Leicester, UK). Cortisol sampling was described and the salivette method explained at T1. Participants were instructed to choose one day prior to surgery on which to give seven samples at set time points: on awakening, 30 minutes after awakening, 10am, midday, 4pm, 8pm and bedtime. Participants were told not to eat, drink caffeinated beverages, smoke cigarettes, take any medications, or brush their teeth, for the 30-minutes prior to giving the sample. Participants were also required to complete a diary as a record of their sampling schedule (Appendix 7). Each sample had a corresponding set of questions, including time of collection and a brief record of pre-sampling activities and emotions. Saliva samples were obtained at T1 and T3; they were returned using a freepost envelope and stored at -20 degrees Celsius for analysis at a later date. Cortisol levels were assessed using a time resolved immunoassay with fluorescence detection, at the University of Dresden. The intra- and inter-assay coefficients of variation were less than 4%.

Cortisol data were analysed by computing four different measures. The cortisol awakening response (CAR) represents the difference between the sample taken on awakening and 30 minutes later. To generate a valid CAR relies on the waking sample being obtained without a delay, since otherwise the magnitude of the response will be masked (Chida & Steptoe, 2009b). In line with other work in Steptoe's group, participants who reported giving their first sample more than 15 minutes after awakening were excluded from analyses (Dockray, Bhattacharyya, Molloy, & Steptoe, 2008). The estimated area under the curve (AUC) with respect to ground was generated as an approximation of total cortisol output over the day (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The slope of cortisol decline over the day was calculated as the reduction in cortisol per hour, using regression methods. Importantly, the slope excluded the 30-minute post-awakening sample, as is usual with this

data (Messerli-Bürgy et al., 2012). Finally, the difference between waking and bedtime values was calculated, which is closely related to the slope.

5.8.1.2 Immunoassays

To assess inflammatory activity, a 20ml blood sample was drawn into plain serum tubes by venepuncture from the forearm at T1. At T2, two blood samples were drawn on approximately day 1 and day 4 after surgery. For those patients still in ICU this was usually taken from a cannula in the external jugular vein in the neck, otherwise for patients on the ward this was by venepuncture from the forearm. Blood was allowed to clot and centrifuged for 10 minutes at 3000 rpm. The resulting serum was frozen at -80°C until batch analysis at a later date. Assays were performed by Dr David Gaze at St George's Healthcare NHS Trust, using commercial automated immunoassay on the Immulite 1 (Siemens Healthcare Diagnostics, Frimley, Surrey) for IL-6, hs-CRP and TNF-α. Quality control statistics are reported in Table 5.4.

TABLE 5.4: QUALITY CONTROL STATISTICS FOR IMMUNOASSAYS

Assay	*Inter-assay CV (%)*	*Intra-assay CV (%)*	*Total-assay CV (%)*	*Minimal detectable dose*	*Upper limit of the calibration range*
IL-6	-	3.5-6.2	5.1-7.5	2.0 pg/mL	1000 pg/mL
TNF-α	4.0-6.5	2.6-3.6	-	1.7 pg/mL	1000 pg/mL
hs-CRP	-	4.2-6.4	4.8-10.0	0.01 mg/dL	15mg/dL

5.9 Data storage

As in P-ARCS, all ARCS data were collated and stored in line with ethical guidelines and UCL policy. All data were treated as strictly confidential. The project was registered with the UCL Data Protection Office. Consent forms and patient personal details were stored separately from the questionnaire data; all data were stored in locked filing cabinets, in locked offices at UCL. Anonymised raw data were entered into a computer database for statistical analysis; personal identification information was kept in separate files to the questionnaire responses. Data were kept on password protected computers, in files accessible only to the study researchers. Data may be kept in this secure manner for up to 20 years prior to being destroyed.

5.10 My involvement and contribution

Along with the other researchers involved in ARCS (TK and EL), I was directly involved in the development of the main ARCS study, under guidance from AS. I helped compile and select the

questionnaires for inclusion in the study and drafted the substantial amendment submitted to gain ethical approval. I was responsible for creating all the patient ARCS questionnaires and resources. Along with EL, I was in charge of the preparation of all T1 to T4 resources and databases. I was actively involved in participant recruitment and follow-up assessments from February 2011 until April 2012. I was also partly responsible, along with EL, for the day to day management of a research assistant who worked on the administrative aspects of the project from November 2011 to March 2012. I undertook a large proportion of the patient data entry. I conducted all the statistical analyses myself, with guidance from my supervisor, AS.

5.11 Statistical analysis

All statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, Illinois, USA). The significance level was set to $p < 0.05$ for all analyses, with precise p values reported for all test results. In regression analyses, R^2 is presented as an indicator of variance explained by the models relevant to the current sample; adjusted R^2 values which take into account variation across the whole population are not reported here though were generally smaller. It is important to note that these analyses were exploratory in nature, hence multiple hypotheses were tested. The issue of multiple testing remains an important issue, rendering the results subject to careful interpretation. Given the fact all analyses were based on *a priori* hypotheses, no formal statistical adjustments were made. Specific details on the analyses conducted are presented in the results sections of Chapter 6 and 7.

Chapter 6. Results: Early-term outcomes

6.1 Introduction

The ARCS study began in February 2011 and data collection is on-going. The data presented in the succeeding results chapters, Chapter 6 and Chapter 7, comprise all participants who partook up to June 2012. To reiterate, the aim of the ARCS study was to characterise the progression of patients from the pre-operative to post-operative phases of recovery following cardiac surgery, and in particular to study the impact of experiences in the weeks prior to surgery on longer-term adaptation. Using data from the main ARCS study, this PhD focuses on the relationship between depression symptoms and impaired adaptation over time, and the underlying mechanistic pathways. Two main pathways are explored here in detail: psychosocial and biological. This chapter presents results pertaining to early-term outcomes, as measured at baseline and T2. Chapter 7 focuses on recovery outcomes at T3. In this chapter, the recruitment statistics are described, followed by descriptive statistics of predictor and outcome variables, covariates, and candidate mechanisms. Lastly, mediation analyses of associations between depression symptoms and recovery are presented. In particular, this chapter assesses the role of three possible mechanistic pathways: social-behavioural factors, cognitive factors, and biology.

The specific hypotheses to be tested in this chapter are:

(1) Depression symptoms are associated with impaired adaptation following CABG surgery

i. Pre-operative somatic/affective depression symptoms will carry greater risk than no depression symptoms or cognitive/affective depression symptoms for poor adaptation during the in-hospital recovery period, including:
   a) Early-term emotional recovery such as anxiety,
   b) Early-term surgical recovery such as pain and physical symptom reporting,
   c) Early-term clinical recovery such as post-operative complications, length of ICU stay, length of post-operative hospital stay,

   and these associations will be independent of demographic and clinical factors.

(2) Social-behavioural factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more negative health behaviours before surgery will be more likely to have poorer emotional adaptation and recovery during the in-hospital recovery period, including:
   a) Early-term emotional recovery,
   b) Early-term surgical recovery,
   c) Early-term clinical recovery,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show lower social support before surgery will be more likely to have poorer emotional adaptation and recovery during the in-hospital recovery period, including:

a) Early-term emotional recovery,

b) Early-term surgical recovery,

c) Early-term clinical recovery,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(3) Cognitive factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more neurocognitive impairment before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:

a) Early-term emotional recovery,

b) Early-term surgical recovery,

c) Early-term clinical recovery,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show more negative illness perceptions before surgery will be more likely to have poorer emotional adaptation and recovery during the in-hospital recovery period, including:

a) Early-term emotional recovery,

b) Early-term surgical recovery,

c) Early-term clinical recovery,

and these factors will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(4) Biological factors affect the depression symptoms-poor adaptation relationship

i. Patients who show a flatter diurnal cortisol profile before surgery will be more likely to show poorer emotional and physical recovery during the in-hospital period, including:

a) Early-term emotional recovery,

b) Early-term surgical recovery,

c) Early-term clinical recovery,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show greater inflammatory responses in the days after surgery will be more likely to show poorer emotional and physical recovery during the in-hospital period, including:

   a) Early-term emotional recovery,

   b) Early-term surgical recovery,

   c) Early-term clinical recovery,

   and these factors will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

6.2 Uptake, attrition and missing data

At time of analysis, 406 participants had been invited to participate in the ARCS study. Of these, 104 declined to participate; the reasons for decline are displayed in Table 6.1. A flow diagram of uptake and attrition is presented in Figure 6.1**.** In total, 302 participants were recruited to take part in the ARCS study, of whom 13 participants were withdrawn from the study since they did not undergo CABG surgery. A further 46 participants consented to participate but did not return the T1 questionnaire, leaving a total sample of 216 participants. Two participants died prior to surgery, one withdrew and 24 participants failed to complete T2 questionnaires. Of the 24 participants who failed to complete T2, 14 of these participants had not had surgery at time of analysis and ten participants were discharged over the weekend and so it was not possible to conduct their interview. At T3, 62 participants failed to complete their follow-up, 10 of whom had withdrawn from the study and 27 of whom had not reached two months post-surgery. Of the 25 who had not withdrawn but failed to complete T3, seven participants stated they were too unwell, three participants' questionnaires were lost in the post and one patient had a post-operative stroke; a reason was not attained for all other participants.

Due to attrition, the final total of participants who completed the questionnaires at all three time points was 154. This chapter presents data on T1 and T2, therefore describes the 216 participants that completed both these time points. On average participants completed their T1 questionnaire 29.12 days (SD = 30.41) prior to surgery and had their T2 assessment 4.61 days (SD = 4.81) after surgery. The time delay variables were associated with neither depression symptoms nor recovery outcomes in regression analyses.

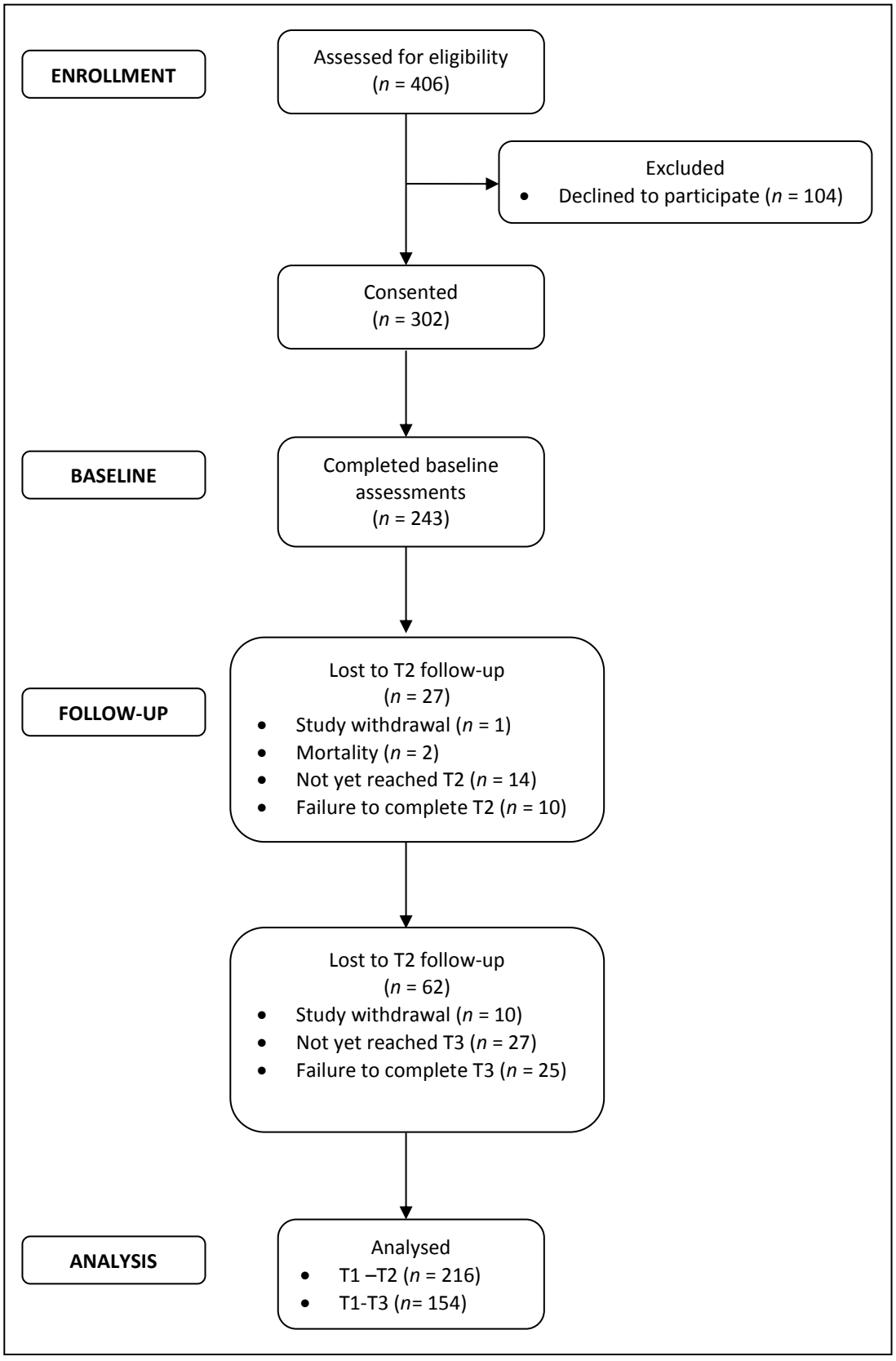

FIGURE 6.1: FLOW DIAGRAM OF PARTICIPANTS' PROGRESSION THROUGH THE ARCS STUDY

TABLE 6.1: REASONS FOR REFUSAL TO PARTICPATE

Reason for non-participation	*n*
Cognitive decline	4
English not adequate	22
Hearing impaired	1
Learning disability	2
Non-UK resident	1
Not enough time prior to surgery	6
Not interested	59
Prisoner	1
Too anxious/stressed	6
Too unwell	1
Visually impaired	1

Missing data on questionnaires meant analyses were performed on a reduced number of participants for some measures. Details of the types of missing questionnaire data are provided in Table 6.2. This table (Table 6.2) also displays the Cronbach's alphas for each questionnaire measure, as applicable. Different methods to deal with missing data exist, with one of the newest approaches being multiple imputations. While this method is a statistically robust procedure, since there was only minimal missing data in ARCS, a simpler 'scaling-up' approach was taken. On questionnaires where respondents had provided valid responses on at least half the questionnaire items, data were scaled up (see Table 6.2). For example, if an individual who completed 16 items on the 21-item BDI had a total score of 6, this would be scaled to the full scale by computing (6/16)*21 = 7.9. This procedure maintained the full range of possible scores while maximising the number of participants for analysis. As such, all analyses in this chapter were performed using the scaled-up data, to increase power. Reasons for missing data are not entirely clear; though it is likely some responses were intentionally not completed, while others were accidentally missed. Questions that were sensitive in nature, such as household income and libido on the BDI, may partly account for high levels of missing data on these scales. In addition, the MoCA was not always administered due to participants' refusal to complete them, or being unable to complete it due to a lack of reading glasses.

TABLE 6.2: TYPES OF MISSING QUESTIONNAIRE DATA IN T1-T2 ANALYTIC SAMPLE

Measure	*T1*			*T2*		
	n	*α*	*Scaled-up*	*n*	*α*	*Scaled-up*
Socio-demographics						
Education	11	-	-	-	-	-
Income	12	-	-	-	-	-
Emotional distress						
Depression symptoms (BDI)	20	0.85	3	-	-	-
Anxiety (HADS subscale)	9	0.87	3	1	0.78	0
Quality of life						
Health status (SF-12) – Physical	0	0.66	-	-	-	-
Health status (SF-12) – Mental	1	0.59	1	-	-	-
Health behaviour						
Physical activity (IPAQ – walking)	15	-	-	-	-	-
Sleep (Jenkins Scale)	2	0.83	2	-	-	-
Cognitive factors				-	-	-
Illness perceptions (BIPQ)	11	0.63	1	-	-	-
Cognitive screen (MoCA)	16	0.53	15	-	-	-
Social support						
Social support (ESSI)	5	0.89	3	-	-	-
Physical symptoms						
Pain (MPQ-SF) - Sensory	-	-	-	7	0.76	1
Pain (MPQ-SF) - Affective	-	-	-	2	0.57	1
Symptoms (CROQ-CABG)	-	-	-	11	0.67	0

6.3 Sample characteristics

Table 6.3 and Table 6.4 describe the characteristics of the entire sample (*n* = 243) and analytic sample (*n* = 216), respectively, at baseline. The analytic sample had an age range of 44 to 88 years, was predominantly male (87.0%) and overweight (BMI >25.0 = 80.1%). The majority of participants were retired (61.7%), three participants were registered disabled and nine participants were unemployed. The majority of the analytic sample had either no or only secondary educational qualifications (71.7%). Over 50% of the sample was a past-smoker, but only a minority were current smokers (7.5%). The majority of participants (91.4% of men and

96.4% of women) adhered to UK government guidelines[22] concerning alcohol consumption, which equate to a maximum of 28 units per week for men and 21 units per week for women.

TABLE 6.3: CHARACTERISTICS OF THE T1-T2 ENTIRE SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	243	67.97±8.84
Female	243	33 (13.6)
BMI (kg/m^2)	223	28.55±4.23
Married/cohabiting	243	184 (75.7)
Ethnicity – White British/other White	243	214 (87.7)
Tobacco smoking		
Never	223	82 (36.8)
Past		126 (56.5)
Current		15 (6.7)
Alcohol consumption (units/week)	242	8.75±12.77
Currently employed	241	74 (30.7)
Employment grade of current/last major occupation		
Unemployed	232	12 (5.2)
Managers, directors and senior officials		48 (20.7)
Professional		47 (20.3)
Associate professional and technical		26 (11.2)
Administrative and secretarial		17 (7.3)
Skilled trades		25 (10.8)
Caring, leisure and other service		12 (5.2)
Sales and customer service		12 (5.2)
Process, plant and machine operatives		19 (8.2)
Elementary		14 (6.0)
Yearly household income		
≤ 10,000 GBP	228	36 (15.8)
10,000 – 20,000 GBP		73 (32.0)
20,000 – 30,000 GBP		47 (20.6)
30,000 – 40,000 GBP		33 (14.5)
≥40,000		39 (17.1)
Education		
None	228	72 (31.6)
Secondary		92 (40.4)
Higher secondary		28 (12.3)
Degree		36 (15.8)

[22] http://www.drinkaware.co.uk

TABLE 6.4: CHARACTERISTICS OF THE T1-T2 ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	216	67.55±8.87
Female	216	28 (13.0)
BMI (kg/m^2)	211	28.55±4.21
Married/cohabiting	216	165 (76.4)
Ethnicity – White British/other White	216	190 (88.0)
Tobacco smoking		
Never	213	83 (39.0)
Past		115 (54.0)
Current		16 (7.5)
Alcohol consumption (units/week)	215	9.01±12.99
Currently employed	214	70 (32.7)
Employment grade of current/last major occupation		
Unemployed/disabled	205	12 (5.9)
Managers, directors and senior officials		44 (21.5)
Professional		41 (20.0)
Associate professional and technical		24 (11.7)
Administrative and secretarial		16 (7.8)
Skilled trades		20 (9.8)
Caring, leisure and other service		11 (5.4)
Sales and customer service		10 (4.9)
Process, plant and machine operatives		18 (8.8)
Elementary		9 (4.4)
Yearly household income		
≤ 10,000 GBP	204	29 (14.2)
10,000 – 20,000 GBP		66 (32.4)
20,000 – 30,000 GBP		45 (22.1)
30,000 – 40,000 GBP		28 (13.7)
≥40,000		36 (17.6)
Education		
None	205	63 (30.7)
Secondary		84 (41.0)
Higher secondary		27 (13.2)
Degree		31 (15.1)

TABLE 6.5: CLINICAL CHARACTERISTICS OF THE T1-T2 ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*n (%)*
*Co-morbidities**		
Diabetes	211	50 (23.7)
Renal failure (requiring dialysis)	211	3 (1.4)
Chronic respiratory disease	211	13 (6.2)
Cancer (self-reported)		
Colon	208	1 (0.5)
Prostate		4 (1.9)
Breast		1 (0.5)
Bladder		1 (0.5)
*Psychiatric history**		
History of depression	146	23 (15.8)
History of anxiety disorder	147	19 (12.9)
Current depression diagnosis	146	5 (3.4)
Current anxiety diagnosis	147	1 (0.7)
Cardiac morbidity		
Hypertension	211	163 (77.3)
Angina		
None	211	7 (3.3)
No limitation		46 (21.8)
Slight limitation		124 (58.8)
Marked limitation		33 (15.6)
Symptoms at rest		1 (0.5)
Dyspnoea		
None	211	50 (23.7)
Slight		129 (61.1)
Moderate		32 (15.2)
Previous MI		
None	211	145 (68.7)
1		61 (28.9)
2 or more		5 (2.4)
Disease severity		
Ejection fraction < 50	211	24 (11.4)
Logistic euroSCORE (%)		
<3.0	211	92 (43.6)
3.0-6.0		74 (35.1)
6.1-9.0		28 (13.3)
9.1-12.0		6 (2.8)
>12.0		11 (5.2)
Surgical details		
Off-pump	211	44 (20.9)
CABG in isolation	211	164 (77.7)
Graft sites		
1-2	211	64 (30.3)
3-4		130 (61.6)
5+		17 (8.1)

*Absolute number of cases in sample.

Clinical data for the analytic sample are displayed in Table 6.5. Clinical data collected from medical notes were only available for 223 participants of the entire sample and 211 participants of the analytic sample. Missing clinical data for the 20 participants was due to 14 of the participants who completed T1 not having had surgery at time of analysis and four participants having had surgery too recently for the notes to be released from the cardiac surgeon. In addition, clinical data were not available for the two participants who died during the study. It is important to note that this clinical information was missing at random, and does not reflect a selection bias; it therefore does not represent a confounder for analyses. Psychiatric history information was collected at T3, hence the reduced number of participants with information available for these items. Co-morbidities were prevalent in the analytic sample, with almost a quarter (23.7%) of participants having diabetes. In terms of psychiatric morbidity, 15.8% of participants reported a history of depression, but only 3.4% were being treated for depression symptoms within the four weeks prior to CABG. The association between baseline depression symptoms and current use of antidepressant medication was assessed in Pearson's correlations, but there were no significant associations between total BDI scores, somatic/affective depression symptom scores, cognitive affective depression symptom scores and use of antidepressant medications. Therefore, these participants were retained in analyses. The majority of participants had on-pump (cardiopulmonary bypass) surgery (79.1%) in isolation. All participants were alive on discharge.

Cross-tabulations were performed on age, total yearly household income, education and sex, to compare the characteristics of those who completed the first two time points (n = 216) to those who did not (n = 27). Age was converted to a categorical variable for chi-squared analysis (<50 years, 50-60 years, 60-70 years, 70-80 years, >80 years). There was no statistical difference between completers and non-completers in terms of age groups (χ^2 = 3.842, df = 4, n = 243, p = 0.428). However, the mean age, in years, was higher in the non-completers (Mean: 71.37 ± SD: 7.95) compared with the completers (Mean: 67.55 ± SD: 8.87) and this reached statistical significance (t = -2.135, p = 0.034). There was no significant difference between completers and non-completers in terms of income groups (χ^2 = 6.153, df = 4, n = 228, p = 0.188), or education groups (χ^2 = 2.543, df = 3, n = 228, p = 0.468), and sex (χ^2 = 0.631, df = 1, n = 243, p = 0.427). Markers of disease severity did also not significantly differ between completers and non-completers in terms of both euroSCORE groups (χ^2 = 6.211, df = 4, n = 223, p = 0.184) and LVEF (χ^2 = 0.105, df = 1, n = 223, p = 0.745); cut-offs for these variables are displayed in Table 4.5. In addition, an independent samples t-test for mean euroSCORE values confirmed this lack of difference between completers (Mean: 4.39, SD: 3.14) and non-completers (Mean: 5.96, SD: 3.73) (t = -1.679, p = 0.094).

Kolmogorov-Smirnov tests were performed revealing scores on all continuous questionnaire measures apart from the BIPQ to be non-normally distributed (p >0.05). Both non-parametric and parametric tests were performed on the data, but since results were similar the parametric results are presented here. Distribution of the biological data was also tested using Kolmogorov-Smirnov tests and raw data were assessed for log transformation, however in order to keep the full range of responses on the biological measures, and to retain those participants who had extreme responses, the raw data was used for both cortisol and inflammatory marker measures. In addition, this ensures the unit of measurement is preserved, maintaining the clinical relevance of the results. Again, both non-parametric and parametric tests were performed on the biological data, but since results were similar the parametric results are presented here. Correlation analyses were used throughout to assess the assumption of multicollinearity, prior to using regression analyses. Multicollinearity assumptions were not violated since correlation coefficients were <0.80 throughout.

6.4 Descriptive analyses of depression symptom and recovery measures

6.4.1 Depression symptoms at T1

TABLE 6.6: T1 DEPRESSION SYMPTOM SCORES

Depression symptom score	*N*	*T1* *Mean ± SD or n (%)*
Total BDI	213	8.38±6.31
Total cognitive/affective BDI	215	2.91±3.83
Total somatic/affective BDI	213	6.84±5.53
Normal (0-10)	212	150 (70.8)
Mild (11-16)	212	43 (20.3)
Borderline clinical (17-20)	212	11 (5.2)
Moderate (21-30)	212	6 (2.8)
Severe (31-40)	212	2 (0.9)
Extreme (41-63)	212	-

A summary of the depression symptom scores are displayed in Table 6.6. Total, somatic/affective and cognitive/affective scores on the BDI were used as predictor variables in analyses of the relationship between depression symptoms and early-term recovery over time. Please note that this table displays the values on the BDI in accordance with the BDI handbook severity cut-offs. Baseline values of the BDI, according to these guidelines, reveal the majority of participants were within the normal range for depression symptom scores (BDI >10 = 29.2%). However, as described in the method chapter (Chapter 3) a systematic review (Thombs

et al., 2008) of screening instruments used to detect depression symptoms in cardiac patients cites three studies using a BDI cut-off score of ≥10 with a mean sensitivity range between 82% and 88% and a mean specificity score range between 58% and 79% (Frasure-Smith et al., 1995; Freedland et al., 2003; Strik et al., 2001). One study used a BDI cut-off ≥13 finding a mean sensitivity value of 83% and a mean specificity value of 94% (Gutierrez & Davis, 1999). Therefore, to examine caseness on the BDI, a binary cut-off was implemented at a conservative ≥13, to maximise the specificity of this measure. Using this cut-off, 18.4% of participants were classified as depressed at baseline. Somatic/affective (range: 0-24) and cognitive/affective (range: 0-23) depression symptom scores are also displayed in this table (Table 6.6).

6.4.2 Early-term recovery outcome variables

Three different recovery outcomes at T2 were considered: emotional distress, physical symptoms and duration of participants' post-operative hospital stay. Anxiety was used as the measure of emotional distress at T2; descriptive analyses are displayed in Table 6.7. A paired samples *t*-test was performed on means scores for anxiety (see *p* in Table 6.7), revealing a significant decrease from before to after surgery. The majority of participants were free from anxiety at both time points, with only 10.6% of participants being clinically anxious (≥11) at T2. To examine borderline to caseness anxiety on the HADS, a binary cut-off was implemented in accordance with previous literature at ≥8. Four groups were created in order to examine the pattern of anxiety across time. Results from these analyses are shown in Table 6.8, revealing that 26 participants (12.2%) can be classified as having anxiety that persists to T2. A further 39 participants (18.3%) had anxiety that had resolved by T2.

Physical symptoms were measured using the MPQ-SF and the CROQ. The majority of participants experienced physical pain and discomfort at T2, with only 11.2% of participants reporting no sensory pain at T2 (Mean: 5.36, SD: 5.14). Affective pain (Mean: 1.37, SD: 1.98) was reported in just under half (47.4%) of participants. Scores on the numerical rating scale (Mean: 3.43, SD: 2.50) and the current pain descriptor (Mean: 1.53, SD: 1.03) items, reinforce the fact that pain was prevalent at T2. Physical symptoms, as measured by the CROQ, were also frequently reported following surgery (Table 6.9). In particular, feelings of pain around the surgical wound sites, bruising and swollen feet and ankles were commonly experienced by participants.

TABLE 6.7: ANXIETY AT T1 AND T2

Anxiety	*N*	*T1* *Mean ± SD or n (%)*	*T2* *Mean ± SD or n (%)*	*p*
Anxiety total	213	5.83±4.27	4.69±4.14	<0.001
Anxiety normal (≤7)	213	148 (69.5)	168 (77.8)*	-
Anxiety borderline (8-10)	213	33 (15.5)	25 (11.6)*	-
Anxiety caseness (≥11)	213	32 (15.0)	23 (10.6)*	-

**N* = 216

TABLE 6.8: ANXIETY TYPE ACCORDING TO TIME POINT

Anxiety type	*HADS ≥ 8*		*n (%)*
	T1	*T2*	
Never anxious	x	x	127 (59.6)
Post-CABG onset	x	✓	21 (9.9)
Persistent	✓	✓	26 (12.2)
Resolved	✓	x	39 (18.3)

TABLE 6.9: FREQUENCY OF CROQ PHYSICAL SYMPTOMS AT T2

Symptom severity (Moderate to A lot)	*T2*	
	N	*n (%)*
Pain in chest wound	216	133 (61.6)
Infection in chest wound	216	6 (2.8)
Tenderness around chest wound	216	115 (53.2)
Numbness/tingling around chest wound	214	16 (7.5)
Bruising around chest wound	216	23 (10.6)
Pain in arm/leg wound	208	81 (38.9)
Other pain in arm/leg due to operation	209	18 (8.6)
Infection in arm/leg wound	208	9 (4.3)
Numbness/tingling in arm/leg due to operation	208	25 (12.0)
Bruising arm/leg where vein was removed	208	49 (23.6)
Swollen feet/ankles	216	95 (44.0)
Mean ± SD	9.06±5.28	

Clinical outcome variables at T2 included length of ICU stay, ICU re-admission, reoperation, post-operative dialysis, new cerebrovascular accident, and length of post-operative hospital stay. However, since many of these outcomes occurred in just a handful of patients, only length of in-hospital stay was included in subsequent analyses. Descriptive

statistics of these outcomes are displayed in Table 6.10. One of the most policy relevant outcomes displayed in this table is length of post-operative hospital stay. This variable is a marker of clinical recovery, with those participants experiencing the poorest recovery and the greatest in-hospital complications, expected to have the longest hospital stays after CABG. Since data on length of post-operative hospital stay were skewed, this variable is presented here as a categorical variable, with participants coded as ≤7 days or >7 days. While other approaches were considered such as log-transformation of the data, this approach was deemed appropriate given it is a clinically pertinent indicator of recovery, with hospital guidelines aiming for all patients to be discharged within seven days of CABG surgery. A limitation of this approach is the fact that it reduces power, making it more difficult to demonstrate an effect. However, this binary variable was used in all further analyses.

TABLE 6.10: CLINICAL OUTCOMES

Post-operative recovery	*N*	*n (%)*
Intensive care stay > 2 days	211	25 (11.8)
Intensive care re-admission	211	5 (2.4)
Length of post-operative stay		
≤7 days	211	153 (72.5)
>7 days		58 (27.5)
Reoperation necessary	211	7 (3.3)
Post-operative complications		
Transient stroke	211	1 (0.5)
Post-operative dialysis		5 (2.4)

6.4.3 Covariates of the depression symptoms-recovery relationship

Covariates are factors associated with the predictor or outcome variable, which may spuriously account for the relationship the predictor variable has with the outcome of interest. Potential covariates of the depression symptoms-recovery relationship have been identified in the literature review. Thorough identification of covariates is necessary in order to identify the extent to which relationships are upheld after taking into account confounders; in other words the extent to which the relationship can be deemed causal. A limitation of ARCS is that some confounders have not been captured, whereas others may have been inadequately measured. An example is disease severity, where ARCS adequately captures coronary disease, but lacks data on cardiovascular disease severity more generally, including peripheral arterial and cerebrovascular disease. A full discussion of this is provided in Chapter 8 (Section 8.3.7).

Nevertheless, various potential demographic covariates have previously been described, but for ease of reference are presented again here in Table 6.11; they include age,

sex, and socioeconomic status as measured by education, occupation level and household income. Disease severity, including LVEF and euroSCORE, also need consideration as covariates, and are again presented in Table 6.11. To clarify, LVEF was used as a binary variable (<50 or ≥50) and logistic euroSCORE was used a continuous variable. Other clinical factors such as medication use and co-morbidities may also play a role in recovery and were also considered as potential covariates. Pre-operative medication usage is displayed in Table 6.12, demonstrating ACE inhibitors, aspirin, statins and beta-blockers were frequently prescribed.

TABLE 6.11: DEMOGRAPHIC AND DISEASE SEVERITY COVARIATES

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	216	67.55±8.87
Female	216	28 (13.0)
Employment grade of current/last major occupation		
Unemployed/disabled		12 (5.9)
Managers, directors and senior officials		44 (21.5)
Professional		41 (20.0)
Associate professional and technical		24 (11.7)
Administrative and secretarial	205	16 (7.8)
Skilled trades		20 (9.8)
Caring, leisure and other service		11 (5.4)
Sales and customer service		10 (4.9)
Process, plant and machine operatives		18 (8.8)
Elementary		9 (4.4)
Yearly household income		
≤ 10,000 GBP		29 (14.2)
10,000 – 20,000 GBP	204	66 (32.4)
20,000 – 30,000 GBP		45 (22.1)
30,000 – 40,000 GBP		28 (13.7)
≥40,000		36 (17.6)
Education		
None		63 (30.7)
Secondary	205	84 (41.0)
Higher secondary		27 (13.2)
Degree		31 (15.1)
Ejection fraction < 50	211	24 (11.4)
Logistic euroSCORE (%)	211	4.40±3.15

Although primary identification of covariates was theory driven, in order to create a parsimonious model of the depression symptoms-recovery relationship, some tailoring was required to identify those covariates applicable to recovery in my sample. This was necessary since the ARCS study was powered to include nine predictor variables, and some analyses were performed on a reduced sample size due to missing data. The potential covariates were

entered into correlation analyses in order to identify those variables which were strongly related to the predictor and outcome variables.

TABLE 6.12: PRE-OPERATIVE PRESCRIBED MEDICATION USE

Medication	*N*	*n (%)*
Symptom reduction drugs		
Anti-arrhythmia	195	4 (2.1)
Antibiotic	195	4 (2.1)
Calcium channel blocker	195	61 (31.3)
Nitrate	195	60 (30.8)
NSAID	195	24 (12.3)
Sleeping tablet	195	5 (2.6)
Risk reduction drugs		
ACE inhibitors	195	105 (53.8)
Angiotensin II receptor antagonist	195	26 (13.3)
Anticoagulant	195	15 (7.7)
Antiplatelet	195	62 (31.8)
Aspirin	200	162 (81.0)
Beta-blockers	195	128 (65.6)
Statins	195	173 (88.7)
Mood-enhancing drugs		
Antidepressants	146	5 (3.4)
Anxiolytics	147	1 (0.7)

Results of the correlation analyses offer some insight into the covariates applicable to the depression symptoms-recovery relationship in this sample. In correlation analyses, age (p = 0.049) and sex (p = 0.023) showed positive significant associations with length of hospital stay, such that older and female participants had a longer post-operative stay. Out of the three markers of socioeconomic position considered as potential covariates (education, occupation level and household income), total household income (p = 0.002) and occupation (p = 0.026) were significantly related to recovery, with those participants reporting lower socioeconomic position having a longer hospital stay. Similarly, euroSCORE (p = 0.001) was significantly associated with length of hospital stay, so that those with greater disease severity had a longer in-hospital recovery. This is an important finding given that euroSCORE was not originally designed as a specific measure of in-hospital recovery, but rather as mortality risk model. However, given that a significant association was found between euroSCORE and length of post-operative stay suggests that it is an appropriate marker of disease severity to include in analyses. Associations between use of medications and co-morbidities and recovery outcome

variables were also performed, with no significant associations found. Correlation analyses were also performed between the baseline depression scores (total, somatic/affective and cognitive/affective) and the potential covariates. The only significant associations observed were between depression symptoms and age, with a negative association such that younger participants had greater depression symptoms. The results of these analyses are shown in Table 6.13.

As a result of these analyses, household income was used as a proxy measure of socioeconomic status in analyses, rather than education or occupation level, since this produced the strongest association with length of hospital stay. Due to the fact that euroSCORE and LVEF were correlated (r = 0.181, p = 0.008) and euroSCORE actually takes into account LVEF, only euroSCORE was included in mediation models as a marker of disease severity.

TABLE 6.13: PEARSON'S CORRELATIONS TO IDENTIFY COVARIATES

Measure	*T1 BDI Total*	*T1BDI Somatic/ Affective*	*T1BDI Cognitive/ Affective*	*T2 Anxiety (HADS)*	*T2 Sensory pain*	*T2 Affective pain*	*T2 Physical symptoms (CROQ)*	*T2 Length of post-CABG stay (binary)*
Age								
r	-0.221	-0.149	-0.293	-0.066	-0.103	0.028	0.126	0.136
p	0.001	0.029	<0.001	0.335	0.132	0.688	0.065	0.049
Sex								
r	0.097	0.120	0.037	-0.073	-0.100	-0.016	0.072	0.157
p	0.159	0.079	0.585	0.287	0.143	0.812	0.292	0.023
Level of education								
r	0.017	0.008	0.076	-0.039	0.058	-0.026	-0.029	0.021
p	0.810	0.911	0.282	0.576	0.408	0.715	0.682	0.768
Occupation level								
r	-0.004	-0.001	-0.079	-0.085	-0.061	-0.091	-0.084	0.162
p	0.951	0.992	0.279	0.240	0.397	0.210	0.246	0.026
Household income								
r	-0.071	-0.083	0.008	-0.013	0.004	0.028	-0.077	-0.214
p	0.317	0.240	0.908	0.854	0.959	0.692	0.274	0.002
Logistic euroSCORE								
r	-0.029	0.041	-0.106	0.025	-0.096	0.079	0.039	0.236
p	0.680	0.561	0.125	0.722	0.166	0.251	0.575	0.001
LVEF								
r	0.068	0.062	0.062	0.024	0.031	-0.005	-0.054	0.114
p	0.331	0.374	0.371	0.725	0.660	0.947	0.433	0.099

6.5 T1 depression symptoms predicting early-term recovery

Regression models were built to assess depression symptoms as a predictor of anxiety, physical symptoms (CROQ and MPQ-SF) and length of post-operative hospital stay at T2. Multiple regression analyses were used for continuous outcomes (anxiety, CROQ symptoms, MPQ-SF pain) and a logistic regression model was used for the binary outcome, length of hospital stay. All models were adjusted for the covariates age, sex, household income and euroSCORE, and anxiety models controlled for baseline anxiety.

6.5.1 Emotional distress outcomes

Multiple regression analyses were performed using T2 anxiety, as measured on the HADS, as the outcome variable. Results showed that total and somatic/affective depression symptom scores on the BDI were both significant predictors of anxiety scores after controlling for covariates. The results of total BDI scores are displayed in Table 6.14 showing BDI total score (t = 2.249, p = 0.026) was a significant predictor of T2 anxiety after controlling for covariates. The only other significant predictor in the model was T1 anxiety (t = 3.855, p <0.001). The results of somatic/affective scores are displayed in Table 6.15 showing BDI somatic/affective depression symptom score (t = 3.075, p = 0.002) was a significant predictor of T2 anxiety after controlling for covariates. The only other significant predictors in the model were T1 anxiety (t = 3.596, p <0.001) and sex (t = -0.144, p = 0.044), with male sex being more strongly associated with T2 anxiety than female sex.

TABLE 6.14: MULTIPLE REGRESSION OF T2 ANXIETY ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.017	0.043	0.037	0.701
Sex	-1.725	0.930	-0.133	0.065
Household income	0.038	0.207	0.012	0.855
euroSCORE	0.050	0.134	0.037	0.709
T1 Anxiety	0.308	0.080	0.312	<0.001
T1 BDI total score	0.125	0.056	0.186	0.026

R^2 = 0.202, N = 194

Cognitive/affective depression symptom score (t = 1.860, p = 0.065) was not a significant predictor or T2 anxiety in adjusted regression models, with the only significant predictor in this model being T1 anxiety (t = 4.115, p <0.001). Overall, these regression models suggest that greater pre-operative depression symptoms were associated with greater emotional distress in the days following surgery, and that somatic/affective depression

symptom scores were particularly important for predicting anxiety outcomes. A moderate amount of variance in anxiety was explained in these models: 20.2% in the total BDI score model and 22.0% in the somatic/affective BDI score model.

TABLE 6.15: MULTIPLE REGRESSION OF T2 ANXIETY ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.015	0.042	0.033	0.726
Sex	-1.875	0.923	-0.144	0.044
Household income	0.041	0.205	0.014	0.841
euroSCORE	0.041	0.133	0.030	0.759
T1 Anxiety	0.280	0.078	0.283	<0.001
T1 BDI somatic	0.224	0.073	0.245	0.002

R^2 = 0.220, *N* = 194

6.5.2 Physical symptom outcomes

Pain

Multiple regression analyses were next performed using T2 pain symptoms, as measured on the MPQ-SF, as the outcome variables. Results showed that total and somatic/affective depression symptom scores on the BDI were both significant predictors of affective pain scores after controlling for demographic and disease severity covariates. The results of total BDI scores are displayed in Table 6.16 showing BDI total score (t = 1.995, p = 0.047) was a significant predictor of T2 affective pain score after controlling for covariates. None of the covariates were significant predictors in the final model. The results of somatic/affective scores are displayed in Table 6.17 showing BDI somatic/affective depression symptom score (t = 2.115, p = 0.036) was a significant predictor of T2 affective pain score after controlling for covariates. Again, none of the covariates were significant predictors in the final model. Cognitive/affective depression symptom score (t = 1.931, p = 0.055) approached statistical significance as a predictor or T2 affective pain scores in adjusted regression models. None of the depression symptom scores were significant predictors of sensory pain, pain numerical rating scale score or current pain descriptor in regression models adjusted for covariates.

TABLE 6.16: MULTIPLE REGRESSION OF T2 AFFECTIVE PAIN ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.002	0.024	0.009	0.932
Sex	-0.574	0.506	-0.088	0.257
Household income	0.077	0.113	0.051	0.495
euroSCORE	0.055	0.072	0.083	0.445
T1 BDI total score	0.050	0.025	0.148	0.047

R^2 = 0.029, *N* = 196

TABLE 6.17: MULTIPLE REGRESSION OF T2 AFFECTIVE PAIN ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	<0.001	0.023	0.001	0.990
Sex	-0.604	0.506	-0.093	0.234
Household income	0.077	0.112	0.051	0.497
euroSCORE	0.053	0.072	0.080	0.461
T1 BDI somatic	0.071	0.034	0.156	0.036

R^2 = 0.031, *N* = 196

Overall, these regression models suggest that pre-operative depression symptoms were positively associated with the distress component of physical pain in the days following surgery, and that somatic/affective depression symptom scores were particularly important for predicting affective pain outcomes. However, it should be noted that only a small amount of variance in affective pain was explained in these models: just 2.9% in the total BDI score model and 3.1% in the somatic/affective BDI score model.

Physical symptoms

Multiple regression analyses were also performed using T2 physical symptoms, as measured on the CROQ, as the outcome variable. Results showed that total, somatic/affective and cognitive/affective depression symptom scores on the BDI were all significant predictors of physical symptoms after controlling for demographic and disease severity covariates. The results of total BDI scores are displayed in Table 6.18 showing BDI total score (t = 2.279, p = 0.024) was a significant predictor of T2 physical symptom score after controlling for covariates. Age was the only other significant predictor in the model (t = 2.464, p = 0.015). The results of somatic/affective scores are displayed in Table 6.19 showing BDI somatic/affective depression symptom score (t = 2.661, p = 0.008) was a significant predictor of T2 physical symptom score

after controlling for demographic and disease severity variables. Age was the only other significant predictor in the model (t = 2.455, p = 0.015). The results of cognitive/affective scores are displayed in Table 6.20 showing BDI cognitive/affective depression symptom score (t = 2.476, p = 0.014) was a significant predictor of T2 physical symptoms after controlling for covariates. Age was the only other significant predictor in the model (t = 2.532, p = 0.012).

TABLE 6.18: MULTIPLE REGRESSION OF T2 PHYSICAL SYMPTOMS ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.147	0.060	0.257	0.015
Sex	0.340	1.279	0.020	0.791
Household income	-0.143	0.285	-0.037	0.616
euroSCORE	-0.264	0.181	-0.156	0.148
T1 BDI total score	0.144	0.063	0.167	0.024

R^2 = 0.051, N = 197

TABLE 6.19: MULTIPLE REGRESSION OF T2 PHYSICAL SYMPTOMS ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.145	0.059	0.253	0.015
Sex	0.219	1.276	0.013	0.864
Household income	-0.139	0.283	-0.036	0.624
euroSCORE	-0.273	0.181	-0.162	0.132
T1 BDI somatic	0.225	0.085	0.192	0.008

R^2 = 0.060, N = 197

TABLE 6.20: MULTIPLE REGRESSION OF T2 PHYSICAL SYMPTOMS ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.151	0.060	0.264	0.012
Sex	0.386	1.236	0.024	0.755
Household income	-0.190	0.282	-0.049	0.501
euroSCORE	-0.249	0.179	-0.147	0.167
T1 BDI cognitive	0.266	0.107	0.182	0.014

R^2 = 0.054, N = 199

As with the models predicting affective pain, these models accounted for a relatively small amount of variance in physical symptom scores on the CROQ, ranging from 5.1% using

the total depression symptom score to 6.0% using the somatic/affective depression symptom score. Overall, these regression models suggest baseline somatic/affective and cognitive/affective depression symptom scores were similarly predictive of T2 CROQ physical symptoms.

6.5.3 Length of hospital stay outcome

Logistic regression analyses were performed using T2 length of post-operative stay as the outcome variable. As previously described, this outcome is a binary variable, with participants split into two groups: ≤7 days and >7 days. Household income was also entered into models as a binary variable using a median split: ≤£20,000 days and >£20,000 per year. Results showed that total, somatic/affective and cognitive/affective depression symptom scores on the BDI were all significant predictors of length of hospital stay after controlling for demographic and disease severity covariates.

TABLE 6.21: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	1.030	0.974-1.090	0.298
Sex[a]	2.048	0.717-5.850	0.181
Household income[b]	0.405	0.202-0.811	0.011
euroSCORE	1.056	0.901-1.238	0.499
T1 BDI total	1.073	1.013-1.136	0.016

Reference groups are: [a]male; [b] <£20,000/year. *N* = 197. OR: Odds ratio; CI: Confidence interval.

The results of total BDI scores are displayed in Table 6.21 showing BDI total score (p = 0.016) was a significant predictor of length of hospital stay after controlling for covariates. These results show that for every unit increase in BDI score, there was a 7.3% greater odds of having a post-operative hospital stay of greater than one week. Household income was the only other significant predictor in the model (p = 0.011). The results of somatic/affective scores are displayed in Table 6.22 showing BDI somatic/affective depression symptom score (p = 0.030) was a significant predictor of T2 physical symptom score after controlling for demographic and disease severity variables. These results show that for every unit increase in BDI somatic/affective score, there was a 9.1% greater odds of having a post-operative hospital stay of greater than one week. Household income was again the only other significant predictor in the model (p = 0.009). The results of cognitive/affective scores are displayed in Table 6.23 showing BDI cognitive/affective depression symptom score (p = 0.008) was a significant predictor of T2 physical symptom score after controlling for covariates. These

results show that for every unit increase in BDI cognitive/affective score, there was a 13.9% greater odds of having a post-operative hospital stay of greater than one week. Household income was also a significant predictor in the model (p = 0.005). Overall, these regression models show that pre-operative cognitive/affective depression symptoms carry slightly greater risk of an extended post-operative hospital stay, compared with total BDI and somatic/affective depression symptom score.

TABLE 6.22: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	1.025	0.970-1.083	0.381
Sex[a]	1.992	0.695-5.707	0.200
Household income[b]	0.398	0.199-0.795	0.009
euroSCORE	1.056	0.901-1.238	0.502
T1 BDI somatic	1.091	1.008-1.180	0.030

Reference groups are: [a]male; [b] <£20,000/year. *N* = 197. OR: Odds ratio; CI: Confidence interval.

TABLE 6.23: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	1.034	0.977-1.095	0.250
Sex[a]	2.104	0.758-5.844	0.153
Household income[b]	0.372	0.185-0.745	0.005
euroSCORE	1.064	0.909-1.246	0.442
T1 BDI cognitive	1.139	1.034-1.255	0.008

Reference groups are: [a]male; [b] <£20,000/year. *N* = 199. OR: Odds ratio; CI: Confidence interval.

6.6 Mechanisms

Candidate mechanisms were identified in the literature review and the pilot results (Chapter 4) to involve several biopsychosocial pathways. This PhD tests the role of three possible mechanistic pathways, namely social-behavioural factors, cognitive factors and biological factors. These candidate mechanisms were based on measures taken at T1, with the exception of the inflammatory markers, where blood was also drawn at T2. Each of these mechanisms are described in turn below, followed by analyses of their association with depression symptoms and the outcome variables, before finally including them in multivariate regression models.

To restate the earlier discussion in Chapter 2 (see Section 2.5), the definition of mechanisms as mediators described by Skala and colleagues (Skala et al., 2006) was used in this PhD. They describe a mechanism to be a variable on the causal pathway between depression symptoms and cardiac prognosis. To be a valid mechanism, mediation must be upheld such that depression symptoms are associated with the candidate mechanism, and in turn the mechanism is associated with the cardiac outcome. In statistical analysis, partial mediation occurs when the addition of the mechanism to the model attenuates the association between depression symptoms and the cardiac outcome, whereas full mediation entirely removes this association.

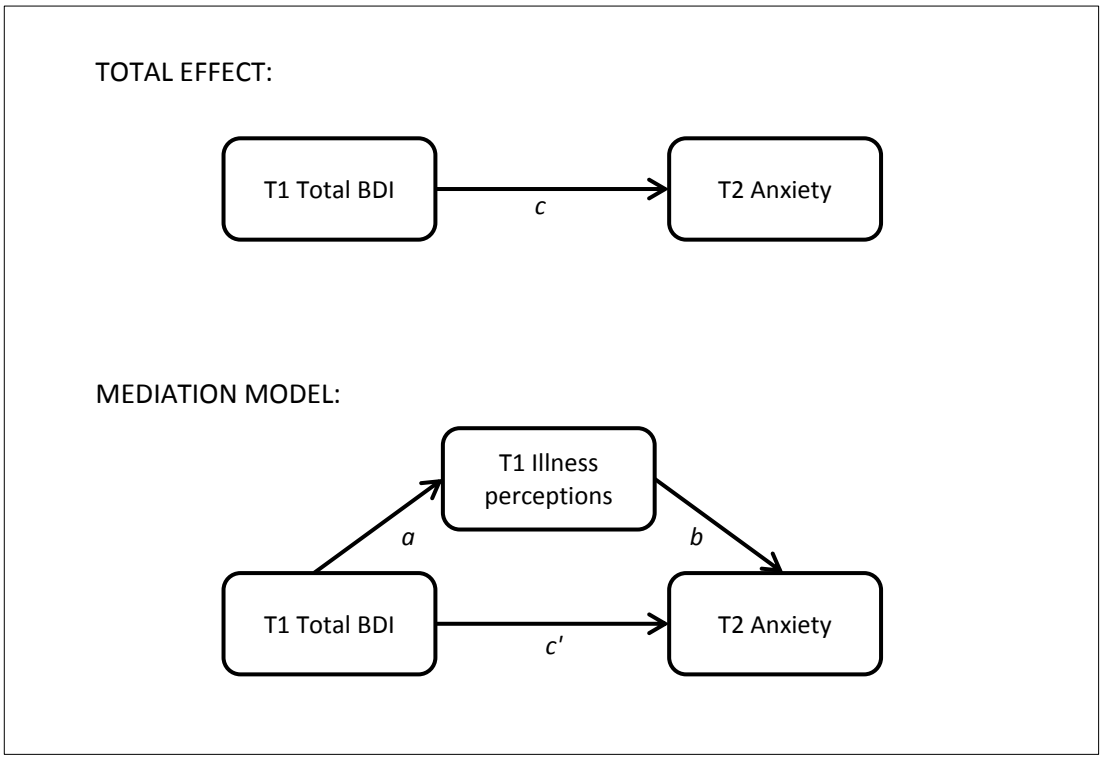

FIGURE 6.1: EXAMPLE SOBEL TEST MEDIATION MODEL

In order to directly test mediation, the Sobel test method was implemented for the outcomes with continuous scores, using the method set out by Preacher and Hayes (Preacher & Hayes, 2004, 2008). This method examines the mediation of the predictor and outcome variables, and tests the significance of the indirect effect in the model. The bootstrapping technique advocated in this method was also employed as a non-parametric approach to handle the non-normally distributed data. The model included T1 depression symptom score as the independent variable and the T2 recovery outcome as the dependent variable, with candidate mechanisms entered as the mediator. Covariates included age, sex, household

income, euroSCORE, and for models predicting T2 anxiety, T1 anxiety was also included. The resulting model is perhaps best illustrated, and an example is provided in Figure 6.2. Pathway *c* represents the total effect of the predictor on the outcome, pathway *c'* represents the direct effect after controlling for the mediator, and pathway *ab* represents the total indirect pathway of the mediator; the latter which can be expressed as c – c'. Since this method cannot be applied to the binary outcome data, a second approach was also taken to estimate the significance of the indirect effect. The change in the amount of variance explained by depression symptoms before and after the addition of the candidate mechanism in the models was estimated by calculating the percentage change: 1-(T2 β/ T1 β), or in the case of logistic regression models: 1-(T2 odds ratio/ T1 odds ratio).

One caution with regard to the interpretation of these models concerns the issue of causality. The direction of causality between depression symptoms and the candidate mechanisms is difficult to establish empirically in this study since depression symptoms and the candidate mechanisms were all measured at the same time point. For example, we cannot know whether depression symptoms cause negative illness perceptions or vice versa using this data. Nevertheless, these models provide an insight into the complex relationships occurring between depression symptoms and recovery after CABG surgery. Since depression symptoms were significant predictors of affective pain, CROQ physical symptoms and length of hospital stay, these outcomes were assessed for inclusion in analyses of mediation.

6.6.1 Behavioural and social mechanisms

6.6.1.1 Descriptive analyses

Social-behavioural factors such as physical activity, smoking, alcohol intake, sleep and social support were all discussed as important to both depression symptoms and cardiac outcomes in the literature review. Inclusion of these factors into mediation models would suggest that those participants with greater depression symptoms would also be more likely to have an unhealthy lifestyle, and this in turn would act to impede the recovery process. Importantly, sleep must be remembered as a symptom of depression, and therefore there are conceptual difficulties in describing sleep as a candidate mediator of the depression symptoms-recovery relationship. Given the interesting results from the pilot study, sleep was included in these analyses to assess its association with the recovery outcomes and for consideration in mediation analyses of cognitive/affective depression symptoms and recovery.

The descriptive statistics for the social-behavioural candidate mechanisms are displayed in Table 6.24. The majority of the sample was overweight with a mean BMI of 28.55 kg/m^2. The majority of the sample drank alcohol moderately, within the UK government recommended guidelines, and only 7.5% of participants were current smokers. On average,

participants walked for 3.5 hours per week. However, only 39.2% of participants walked for at least 10 minutes at a time, on every day of the previous week, and 15.9% of participants did not walk for 10 minutes at all during the week. Data from the Jenkins sleep questionnaire show that participants frequently experienced sleep disturbances prior to surgery, with the symptoms of waking several times during the night, trouble staying asleep and disturbed or restless sleep being most commonly reported. Social support scores ranged from the lowest (8) to highest (34) possible scores on the ESSI questionnaire, with a mean score of 28.94 indicating participants generally report high levels of support.

TABLE 6.24: T1 SOCIAL-BEHAVIOURAL MECHANISMS

Measure	*N*	*T1* *Mean ± SD or n (%)*
Health Behaviour		
BMI (kg/m^2)	211	28.55±4.21
Alcohol consumption (units/week)	215	9.01±12.99
Physical activity (hours/week)	201	3.58±4.92
Current smoker	213	16 (7.5)
Sleep total	214	9.22±6.85
Sleep items		
1. Trouble falling asleep	214	1.05±2.54
2. Waking during night	214	2.54±1.88
3. Trouble staying asleep	214	2.04±1.95
4. Waking feeling tired/ worn out	214	1.56±1.65
5. Disturbed/restless sleep	214	2.02±1.86
Social support		
Social support (ESSI)	213	28.94±5.56

6.6.1.2 Associations with depression symptom and recovery variables

Pearson's correlation analyses were performed to assess whether the candidate mechanisms were associated with depression symptoms (Table 6.25). To clarify, smoking was entered as a binary value (yes/no) to reflect current smoking status in these analyses. Results of these correlation analyses show smoking status, sleep problems and social support were all associated with depression symptoms. Independent *t*-tests confirmed the difference between depressed/non-depressed participants (BDI ≥13) on sleep scores ($t(209) = -5.090$, $p < 0.001$) and social support scores ($t(208) = 2.802$, $p = 0.006$). Chi-square tests found no difference in smoking status ($\chi^2 = 0.47$, df = 1, $p = 0.495$) between depressed and non-depressed groups. In addition, independent *t*-tests confirmed the lack of difference between depressed/non-

depressed participants in terms of BMI (t(205) = 0.614, p = 0.540), alcohol consumption (t(209) = 1.399, p = 0.163) and physical activity (t(196) = 0.578, p = 0.564).

Pearson's correlation analyses were also performed to assess the association of these social-behavioural factors with the recovery outcomes. These correlations found that smoking status was significantly associated with length of post-operative hospital stay (r = -0.152, p = 0.029), indicating that smoking was significantly associated with a post-operative stay of more than one week. Results also found sleep was significantly positively associated with T2 anxiety (r = 0.225, p = 0.001) and T2 CROQ physical symptoms (r = 0.138, p = 0.043), such that greater pre-operative sleep problems were related to greater anxiety and greater physical symptoms at T2.

TABLE 6.25: PEARSON'S CORRELATIONS OF T1 SOCIAL-BEHAVIOURAL FACTORS AND T1 DEPRESSION SYMPTOMS

Measure	*T1 BDI total*	*T1 BDI somatic*	*T1 BDI cognitive*
Health behaviour			
T1 BMI			
r	0.036	0.023	0.030
p	0.610	0.738	0.668
T1 Smoking			
r	-0.137	-0.158	-0.115
p	0.048	0.022	0.094
T1 Alcohol consumption			
r	-0.109	-0.113	-0.060
p	0.115	0.101	0.385
T1 Physical activity – walking			
r	0.075	0.021	0.094
p	0.294	0.770	0.186
T1 Sleep			
r	0.413	0.431	0.324
p	<0.001	<0.001	<0.001
Social support			
T1 Social support			
r	-0.317	-0.316	-0.310
p	<0.001	<0.001	<0.001

Regression analyses were also performed to assess whether the social-behavioural factors predicted any of the recovery outcomes after controlling for demographic and disease severity covariates. Anxiety models also controlled for baseline anxiety score. Statistically, the correlation coefficient represents the linear dependence between the predictor and outcome variable, but it does not control for the fact that other factors may also account for the

relationship, potentially producing a biased estimate. Interestingly, sleep was not a significant predictor of T2 anxiety (t = 1.047, p = 0.296), however sleep was a significant predictor of T2 CROQ physical symptoms (t = 2.211, p = 0.028) after controlling for covariates in these regression models. This association was positive such that those participants who reported greater sleep complaints prior to surgery also reported more physical symptoms post-CABG. In addition, physical activity (t = -2.182, p = 0.030) was significantly associated with T2 anxiety. This association was negative such that those participants who walked fewer hours per week had greater anxiety after CABG. Finally, smoking status at T1 (odds ratio = 0.177, 95% CI = 0.054-0.577, p = 0.004) was a significant predictor of length of post-operative hospital stay after controlling for covariates. This result suggests that compared with smokers, non-smokers had an 82.3% reduced odds of an extended post-operative stay. These significant predictors were examined as potential mediators of the depression symptoms-recovery relationship.

6.6.1.3 Mediation models of T2 emotional distress

TABLE 6.26: HIERARCHICAL REGRESSION OF T2 ANXIETY ON T1 PHYSICAL ACTIVITY AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.008	0.044	0.017	0.858
Sex	-1.952	0.926	-0.154	0.036
Household income	0.031	0.215	0.010	0.884
euroSCORE	0.052	0.135	0.039	0.701
T1 anxiety	0.275	0.082	0.273	0.001
T1 BDI total score	0.194	0.060	0.269	0.001
Step 2				
Age	0.007	0.044	0.016	0.869
Sex	-2.173	0.924	-0.171	0.020
Household income	0.050	0.213	0.016	0.816
euroSCORE	0.046	0.134	0.035	0.729
T1 anxiety	0.285	0.081	0.282	0.001
T1 BDI total score	0.188	0.059	0.261	0.002
T1 Physical activity - walking	-0.118	0.058	-0.137	0.041

Step 1 R^2 = 0.235; Step 2 R^2 = 0.253; N = 181

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of physical activity to the depression symptoms-T2 anxiety relationship (Table 6.26). The model shows that male sex (t = -2.109, p = 0.036), T1 anxiety (t = 3.353, p = 0.001) and total BDI score (t = 3.241, p = 0.001) were the only

significant predictors of T2 anxiety in step 1 adjusted for covariates. After adding T1 hours spent walking per week into the model, male sex (t = -2.352, p = 0.020), T1 anxiety (t = 3.497, p = 0.001) and depression symptoms (t = 3.162, p = 0.002) remained significant predictors. In addition T1 physical activity was also a significant predictor (t = -2.058, p = 0.041), with a negative association such that the least active participants at baseline, had greater anxiety following surgery. The final model accounted for 25.2% (R^2 = 0.252) of variance in T2 anxiety scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 physical activity in the model, the β for depression symptoms changed from 0.269 to 0.261. This indicates that when physical activity was included in the model, there was only a 3.0% reduction in the size of β. However, in a separate regression model using physical activity as the dependent variable to assess the association with T1 total BDI depression symptoms, after adjusting for disease severity and demographic covariates, total BDI depression symptoms (t = -0.247, p = 0.805) was not significant. Therefore, a Sobel test of mediation was not performed.

TABLE 6.27: HIERARCHICAL REGRESSION OF T2 ANXIETY ON T1 PHYSICAL ACTIVITY AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.001	0.044	0.003	0.976
Sex	-2.082	0.919	-0.164	0.025
Household income	0.036	0.213	0.012	0.867
euroSCORE	0.046	0.133	0.034	0.730
T1 anxiety	0.267	0.079	0.265	0.001
T1 BDI somatic	0.289	0.076	0.302	<0.001
Step 2				
Age	0.001	0.043	0.002	0.986
Sex	-2.284	0.917	-0.180	0.014
Household income	0.052	0.211	0.017	0.804
euroSCORE	0.041	0.132	0.031	0.755
T1 anxiety	0.278	0.078	0.275	0.001
T1 BDI somatic	0.278	0.076	0.291	<0.001
T1 Physical activity - walking	-0.112	0.057	-0.130	0.050

Step 1 R^2 = 0.251; Step 2 R^2 = 0.268; N = 181

Hierarchical regression analyses were also performed for somatic/affective and cognitive/affective depression symptom scores, using the same covariates. The model for somatic/affective depression symptoms is displayed in Table 6.27 and shows that male sex (t =

-2.267, p = 0.025), T1 anxiety (t = 3.390, p = 0.001) and somatic/affective BDI score (t = 3.800, p <0.001) were the only significant predictors of T2 anxiety in step 1 adjusted for covariates. After adding T1 hours spent walking per week into the model, male sex (t = -2.492, p = 0.014), T1 anxiety (t = 3.543, p = 0.001) and somatic/affective depression symptoms (t = 3.679, p <0.001) remained significant predictors. In addition, T1 physical activity was a borderline significant predictor (t = -1.971, p = 0.050), with a negative association such that the least active participants at baseline, had greater anxiety following surgery. The final model accounted for 26.8% (R^2 = 0.268) of variance in T2 anxiety scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 physical activity in the model, the β for depression symptoms changed from 0.302 to 0.291. This indicates that when physical activity was included in the model, there was only a 3.6% reduction in the size of β. However, in a separate regression model using physical activity as the dependent variable to assess the association with T1 somatic/affective depression symptoms, after adjusting for disease severity and demographic covariates, somatic/affective depression symptom score (t = -0.540, p = 0.590) was not significant. Therefore, a Sobel test of mediation was not performed.

TABLE 6.28: HIERARCHICAL REGRESSION OF T2 ANXIETY ON T1 PHYSICAL ACTIVITY AND T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.015	0.045	0.032	0.745
Sex	-1.610	0.897	-0.129	0.074
Household income	-0.035	0.214	-0.011	0.871
euroSCORE	0.055	0.134	0.041	0.681
T1 anxiety	0.281	0.083	0.279	0.001
T1 BDI cognitive	0.321	0.105	0.259	0.002
Step 2				
Age	0.013	0.044	0.028	0.772
Sex	-1.841	0.897	-0.148	0.042
Household income	-0.016	0.212	-0.005	0.941
euroSCORE	0.051	0.133	0.038	0.702
T1 anxiety	0.293	0.083	0.291	0.000
T1 BDI cognitive	0.304	0.104	0.245	0.004
T1 Physical activity - walking	-0.114	0.058	-0.132	0.049

Step 1 R^2 = 0.234; Step 2 R^2 = 0.250; N = 183

The model for cognitive/affective depression symptoms is displayed in Table 6.28 and shows that T1 anxiety (t = 3.387, p = 0.001) and cognitive/affective BDI score (t = 3.070, p = 0.002) were the only significant predictors of T2 anxiety in step 1 adjusted for covariates. After adding T1 hours spent walking per week into the model T1 anxiety (t = 3.555, p <0.001) and cognitive/affective depression symptoms (t = 2.922, p = 0.004) remained significant predictors. In addition, T1 physical activity was a significant predictor (t = -1.979, p = 0.049), with a negative association such that the least active participants at baseline, had greater anxiety following surgery. The final model accounted for 25.0% (R^2 = 0.250) of variance in T2 anxiety scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 physical activity in the model, the β for depression symptoms changed from 0.259 to 0.245. This indicates that when physical activity was included in the model, there was a 5.4% reduction in the size of β. However, in a separate regression model using physical activity as the dependent variable to assess the association with T1 cognitive/affective depression symptoms, after adjusting for disease severity and demographic covariates, cognitive/affective depression symptom score (t = -0.633, p = 0.528) was not significant. Therefore, a Sobel test of mediation was not performed.

In summary, these results suggest that even though physical activity is an independent predictor of T2 anxiety, it does not account for the association between pre-operative depression symptoms and later anxiety.

6.6.1.4 Mediation models of T2 physical symptoms

Since sleep is a symptom of depression, the Jenkins score was included in these analyses to assess its association with the recovery outcomes. Due to the fact that somatic/affective depression symptom scores include item 16 of the BDI, which relates to sleep disturbance, pre-operative Jenkins scores were only assessed as a potential mediator of the cognitive/affective depression symptoms and recovery relationship.

A regression model was built to assess the contribution of sleep in explaining T2 CROQ physical symptoms (Table 6.29). This model shows that T1 sleep was not a significant predictor (t = 1.433, p = 0.154) in the model after controlling for baseline depression symptoms and demographic and disease severity covariates. The only significant predictor in the final model was age (t = 2.048, p = 0.042) with a positive association, such that older participants had greater physical symptoms following surgery. The final model accounted for 5.1% (R^2 = 0.051) of variance in physical symptom scores.

TABLE 6.29: MULTIPLE REGRESSION OF T2 PHYSICAL SYMPTOMS ON T1 SLEEP

Model	*B*	*SE*	*ß*	*p*
Age	0.120	0.058	0.215	0.042
Sex	0.605	1.242	0.038	0.627
Household income	-0.041	0.278	-0.011	0.883
euroSCORE	-0.234	0.176	-0.144	0.185
T1 BDI total score	0.100	0.069	0.121	0.150
T1 Sleep	0.073	0.059	0.099	0.222

R^2 = 0.051; *N* = 196

Interestingly, using the cognitive/affective depression symptom score in the models did not change the results, with sleep still failing to predict T2 CROQ physical symptoms, with older age (*t* = 2.104, *p* = 0.037) being the only significant predictor in the final model. Therefore, contrary to the initial results from the pilot study, sleep was not associated with early-term recovery following CABG surgery nor was it a candidate mechanism of the cognitive/affective depression symptoms-recovery relationship.

6.6.1.5 Mediation models of T2 length of post-operative hospital stay

TABLE 6.30: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 SMOKING STATUS AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.029	0.973-1.089	0.318
Sex[a]	2.014	0.705-5.753	0.191
Household income[b]	0.393	0.196-0.788	0.009
euroSCORE	1.057	0.902-1.239	0.494
T1 BDI total	1.071	1.011-1.134	0.020
Step 2			
Age	1.048	0.987-1.113	0.127
Sex[a]	1.869	0.634-5.508	0.257
Household income[b]	0.394	0.193-0.804	0.010
euroSCORE	1.053	0.895-1.238	0.532
T1 BDI total	1.067	1.005-1.134	0.034
T1 Smoking[c]	0.195	0.059-0.645	0.007

Reference groups are: [a]male; [b] <£20,000/year; [c]smoker. *N* = 195. OR: Odds ratio; CI: Confidence interval.

Logistic regression models were built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of smoking status to the

depression symptoms-length of post-operative stay relationship. The model using T1 total BDI score is displayed in Table 6.30 and shows that depression symptoms (p = 0.020) and household income (p = 0.009) were the only significant predictors of length of hospital stay in step 1. After adding T1 smoking status into the model, depression symptoms (p = 0.034) and household income (p = 0.010) remained significant predictors. In addition, smoking (p = 0.007) was also a significant predictor of length of hospital stay after controlling for covariates. The final model showed that for every unit increase in total BDI score, there was a 6.7% greater odds of having a post-operative hospital stay of greater than one week. In addition, compared to smokers, non-smokers had 80.5% reduced odds of an extended post-operative stay. Looking at the odds ratio for depression symptoms shows that with the inclusion of T1 smoking status in the model, the odds changed from 1.071 to 1.067. This indicates that when smoking was included in the model, there was a 5.6% reduction in the size of the odds. As such, the addition of smoking to the model only had a limited effect on the association between depression symptoms and longer hospital stays.

TABLE 6.31: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 SMOKING STATUS AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.024	0.969-1.082	0.404
Sex[a]	1.962	0.685-5.621	0.210
Household income[b]	0.387	0.193-0.774	0.007
euroSCORE	1.057	0.901-1.239	0.496
T1 BDI somatic	1.087	1.005-1.176	0.038
Step 2			
Age	1.041	0.982-1.104	0.179
Sex[a]	1.839	0.626-5.407	0.268
Household income[b]	0.388	0.191-0.789	0.009
euroSCORE	1.054	0.897-1.239	0.524
T1 BDI somatic	1.075	0.990-1.167	0.087
T1 Smoking[c]	0.205	0.062-0.679	0.009

Reference groups are: [a]male; [b] <£20,000/year; [c]smoker. N = 195. OR: Odds ratio; CI: Confidence interval.

The models using somatic/affective and cognitive/affective depression symptom scores are shown in Table 6.31 and Table 6.32 respectively. Findings are in line with those using total BDI scores, whereby smoking status showed a significant relationship with length of post-operative stay in the final models. Interestingly, somatic/affective depression symptoms (p = 0.087) failed to be significant in the final model, while cognitive/affective depression

symptoms (p = 0.012) remained significant. Looking at the odds ratio for somatic/affective depression symptoms shows that with the inclusion of T1 smoking status in the model, the odds changed from 1.087 to 1.075. This indicates that when smoking was included in the model, there was a 13.8% reduction in the size of the odds. In the cognitive/affective model the odds changed from 1.135 to 1.138 suggesting a 2.2% increase with the addition of smoking to the model. As such, the addition of smoking status to the model accounted for a moderate amount of the association between somatic/affective depression symptoms and longer hospital stays, but not the association between cognitive/affective depression symptoms and longer hospital stays.

TABLE 6.32: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 SMOKING STATUS AND T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.033	0.975-1.093	0.271
Sex[a]	2.064	0.743-5.736	0.165
Household income[b]	0.362	0.180-0.725	0.004
euroSCORE	1.064	0.909-1.246	0.438
T1 BDI cognitive	1.135	1.031-1.251	0.010
Step 2			
Age	1.054	0.991-1.121	0.094
Sex[a]	1.915	0.661-5.549	0.231
Household income[b]	0.360	0.176-0.736	0.005
euroSCORE	1.060	0.902-1.245	0.482
T1 BDI cognitive	1.138	1.029-1.258	0.012
T1 Smoking[c]	0.178	0.991-1.121	0.005

Reference groups are: [a]male; [b] <£20,000/year; [c]smoker. *N* = 197. OR: Odds ratio; CI: Confidence interval.

6.6.2 Cognitive mechanisms

6.6.2.1 Descriptive analyses

Cognitive factors such as neurocognitive function and illness beliefs were discussed in the literature review as important to both depression symptoms and cardiac outcomes. Inclusion of these factors in mediation models was based on the premise that those participants with greater depression symptoms would also be more likely to have poor cognitive function and more negative illness perceptions, and this in turn would act to impede the recovery process.

Cognitive function, as measured by the MoCA, and illness perceptions, as measured by the BIPQ, were both considered as cognitive mechanisms of the depression symptoms-

recovery relationship. Descriptive analyses for these candidate mechanisms are displayed in Table 6.33. This table shows the mean score on the MoCA was below the cut-off of 26, with a lowest score of 8, ranging to 30, and 42.3% of the sample scoring ≤25. Scores on the individual items of the BIPQ are also displayed in Table 6.33. Please note that items 3, 4 and 7 have been reverse coded, so higher means reflect a more negative illness perception for all items. Individual item scores show that participants held most negative perceptions for the consequences of their illness, personal control over their illness and concern for their illness.

TABLE 6.33: T1 COGNITIVE MECHANISMS

Measure	*N*	*T1* *Mean ± SD*
Cognitive screen (MoCA)	201	25.45±3.36
Illness perceptions (BIPQ) total	215	35.97±11.24
Illness perceptions items		
1. Consequences	214	5.76±2.92
2. Timeline	212	4.45±2.99
3. Personal control	214	5.96±2.93
4. Treatment control	214	1.16±1.59
5. Identity	215	4.92±2.71
6. Concern	215	7.24±2.72
7. Understanding	212	1.61±1.96
8. Emotional response	212	4.80±3.11

6.6.2.2 Associations with depression symptom and recovery variables

Pearson's correlation analyses were performed to analyse the association between depression symptoms at T1 and the candidate cognitive mechanisms. Results are displayed in Table 6.34 and show illness perceptions were associated with all subtypes of depression symptoms, while MoCA scores were not significantly associated with any of the BDI scores. Independent *t*-tests confirmed the difference between depressed/non-depressed participants (BDI ≥13) on illness perceptions ($t(210) = -6.868$, $p < 0.001$), and confirmed the lack of difference in cognitive function scores on the MoCA ($t(195) = 0.111$, $p = 0.912$).

Next, Pearson's correlation analyses were performed to assess the association of the cognitive measures with the T2 recovery outcomes. These correlations are displayed in Table 6.35 and show that illness perceptions, but not cognitive function, were significantly associated with the recovery outcomes: anxiety, affective pain and physical symptoms. The relationship between illness perceptions and length of hospital stay approached statistical significance ($p = 0.056$). The null findings for the MoCA were also confirmed in regression

models controlling for covariates. As such, illness perception score was the only cognitive mechanism that was tested for mediation of the depression symptoms-early-term recovery relationship.

TABLE 6.34: PEARSON'S CORRELATIONS BETWEEN T1 COGNITIVE MECHANISMS AND T1 DEPRESSION

Cognition	*T1 BDI*	*T1 BDI somatic*	*T1 BDI cognitive*
T1 Cognitive function (MoCA)			
r	-0.002	-0.002	0049
p	0.974	0.982	0.489
T1 Illness perceptions (BIPQ)			
r	0.484	0.515	0.414
p	<0.001	<0.001	<0.001

TABLE 6.35: PEARSON'S CORRELATIONS BETWEEN T1 COGNITIVE MECHANISMS AND T2 RECOVERY OUTCOMES

Cognition	*T2 Anxiety (HADS)*	*T2 Affective pain*	*T2 Physical symptoms (CROQ)*	*T2 Length of post-CABG stay (binary)*
T1 Cognitive function				
r	-0.030	-0.085	-0.067	-0.103
p	0.673	0.234	0.346	0.149
T1 Illness perceptions				
r	0.339	0.149	0.228	0.132
p	<0.001	0.029	0.001	0.056

6.6.2.3 Mediation models of T2 emotional distress

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-T2 anxiety relationship (Table 6.36). The model shows that T1 anxiety (t = 3.855, p <0.001) and total BDI score (t = 2.249, p = 0.026) were the only significant predictors of T2 anxiety in step 1 adjusted for covariates. After adding T1 illness perceptions to the model, depression symptoms no longer remained a significant predictor (t = 1.709, p = 0.089). The only significant predictors in the final model were male sex (t = -1.990, p = 0.048), T1 anxiety (t = 2.754, p = 0.006) and T1 illness perceptions (t = 2.478, p = 0.014), both with a positive association such that more anxious participants at baseline who also held a more negative view of their illness, had greater anxiety following surgery. The final model accounted for 22.7% (R^2 = 0.227) of variance in T2 anxiety scores. Looking at the standardised regression

coefficient (β) for depression symptoms shows that with the inclusion of T1 illness perceptions in the model, the β for depression symptoms changed from 0.186 to 0.143. This indicates that when illness perceptions were included in the model, there was a 23.1% reduction in the size of β.

TABLE 6.36: HIERARCHICAL REGRESSION OF T2 ANXIETY ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.017	0.043	0.037	0.701
Sex	-1.725	0.930	-0.133	0.065
Household income	0.038	0.207	0.012	0.855
euroSCORE	0.050	0.134	0.037	0.709
T1 anxiety	0.308	0.080	0.312	<0.001
T1 BDI total score	0.125	0.056	0.186	0.026
Step 2				
Age	0.016	0.043	0.036	0.706
Sex	-1.828	0.919	-0.141	0.048
Household income	0.107	0.206	0.035	0.606
euroSCORE	0.074	0.133	0.054	0.579
T1 anxiety	0.233	0.085	0.235	0.006
T1 BDI total score	0.096	0.056	0.143	0.089
T1 Illness perceptions	0.070	0.028	0.196	0.014

Step 1 R^2 = 0.202; Step 2 R^2 = 0.227; *N* = 194

Next, a Sobel test was used on the data. Results are presented in Figure 6.3 with the total effect and mediation model confirming the multiple regression models already presented. The indirect pathway (pathway *ab*) was also significant in this model (B = 0.029, SE = 0.018, 95% CI = 0.005-0.080), confirming illness perceptions to be a significant mediator in this model. Full mediation was shown such that the direct effect, pathway *c*', was no longer significant after illness perceptions were taken into account.

Regression analyses were also built for somatic/affective and cognitive/affective depression symptoms. The results for somatic/affective depression symptoms are illustrated in Figure 6.4 using the Sobel test results, showing a significant total effect (pathway *c*) for the T1 somatic/affective depression symptoms and T2 anxiety relationship (B = 0.224, SE = 0.073, *p* = 0.002) and a significant direct pathway (pathway *c*') (B = 0.180, SE = 0.075, *p* = 0.018). The indirect pathway (pathway *ab*) was also significant in this model (B = 0.044, SE = 0.024, 95% CI = 0.009-0.107), confirming illness perceptions to be a significant mediator in this model. Partial

mediation was shown since the direct effect, pathway *c'*, was still significant after illness perceptions were taken into account.

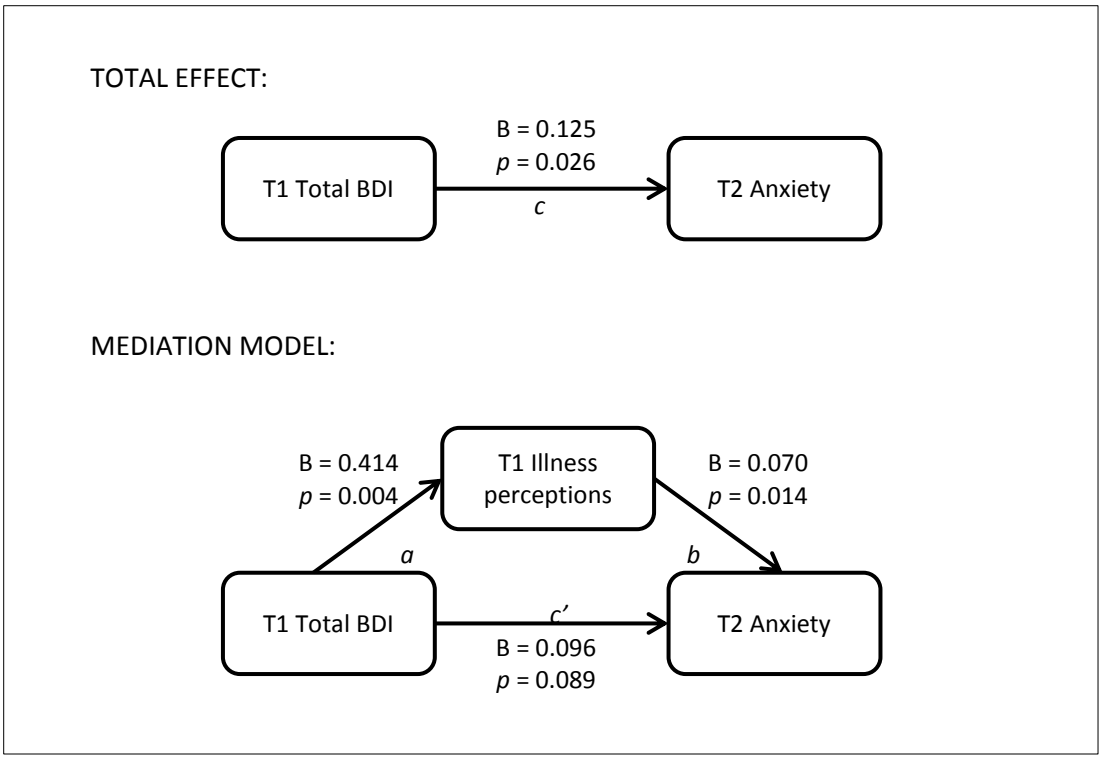

FIGURE 6.2: MEDIATION MODEL OF T1 TOTAL BDI SCORE AND T2 ANXIETY THROUGH T1 ILLNESS PERCEPTIONS

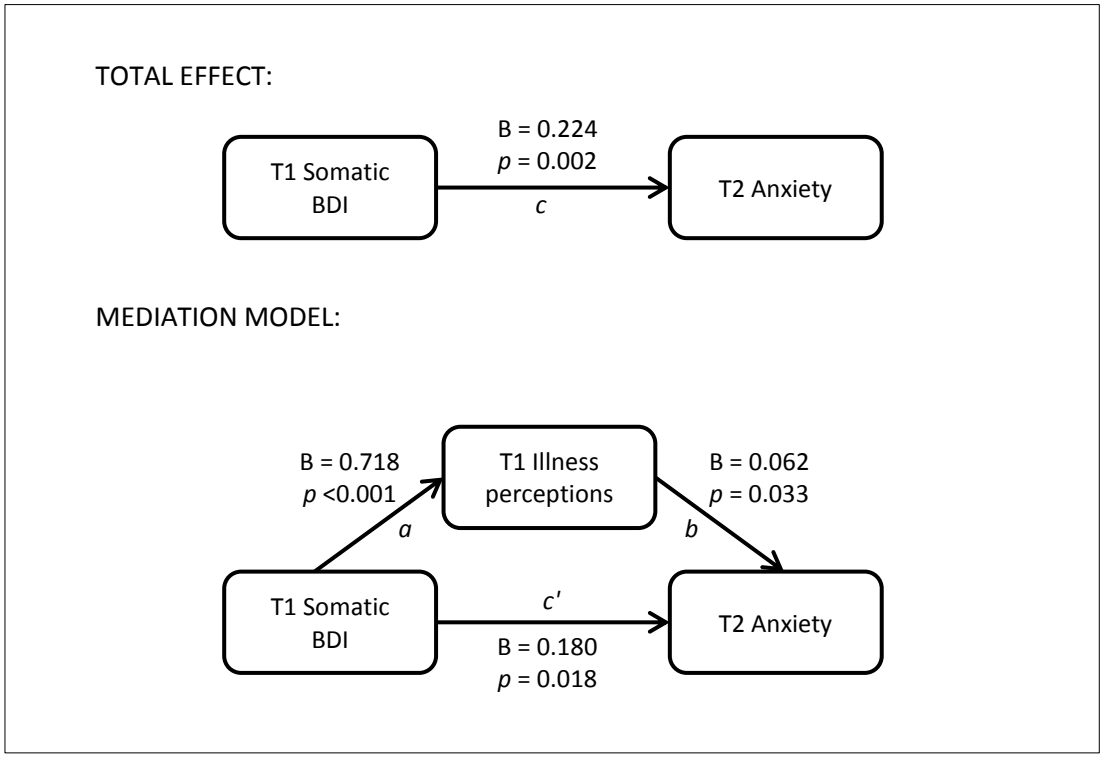

FIGURE 6.3: MEDIATION MODEL OF T1 SOMATIC/AFFECTIVE BDI SCORE AND T2 ANXIETY THROUGH T1 ILLNESS PERCEPTIONS

TABLE 6.37: HIERARCHICAL REGRESSION OF T2 ANXIETY AND T1 ILLNESS PERCEPTIONS AND T1 COGNITIVE/AFFECTIVE DEPRESSION BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.017	0.043	0.038	0.693
Sex	-1.478	0.904	-0.116	0.104
Household income	-0.000	0.206	0.000	1.000
euroSCORE	0.056	0.133	0.041	0.676
T1 anxiety	0.330	0.080	0.334	<0.001
T1 BDI cognitive	0.178	0.096	0.156	0.065
Step 2				
Age	0.017	0.043	0.038	0.687
Sex	-1.657	0.892	-0.130	0.065
Household income	0.076	0.205	0.025	0.710
euroSCORE	0.081	0.132	0.060	0.540
T1 anxiety	0.239	0.086	0.242	0.006
T1 BDI cognitive	0.152	0.095	0.133	0.111
T1 Illness perceptions	0.074	0.028	0.206	0.008

Step 1 R^2 = 0.198; Step 2 R^2 = 0.227; N = 196

The cognitive/affective depression symptoms regression model is displayed in Table 6.37 and shows that T1 anxiety (t = 4.115, p <0.001) was the only significant predictor of T2 anxiety in step 1 adjusted for covariates. After adding T1 illness perceptions into the model, the only significant predictors in the final model were T1 anxiety (t = 2.783, p = 0.006) and T1 illness perceptions (t = 2.669, p = 0.008), both with a positive association such that more anxious participants at baseline who held a more negative view of their illness, had greater anxiety following surgery. The final model accounted for 22.7% (R^2 = 0.227) of variance in T2 anxiety scores. However, since cognitive/affective depression symptoms were not a significant predictor in this model, a Sobel test of mediation was not performed.

In addition, in order to see whether any one illness perception was best associated with T2 anxiety, individual items on the BIPQ were entered into regression models to predict T2 anxiety, controlling for the demographic and disease severity covariates, baseline anxiety and T1 depression symptoms symptom score. In models using total BDI depression symptom score, the illness perceptions of consequences (t = 2.378, p = 0.018), concern (t = 3.744, p <0.001) and emotional response (t = 4.541, p <0.001) were the only significant illness perception predictors in the models. In models using somatic/affective depression symptom scores, again concern (t = 3.606, p <0.001) and emotional response (t = 4.363, p <0.001) were the only significant illness perception predictors in the models. In models using

cognitive/affective depression symptom scores, consequences (t = 2.217, p = 0.028), concern (t = 4.012, p <0.001) and emotional response (t = 4.755, p <0.001) were the only significant illness perception predictors. In summary, consequences, concern and emotional response were the only significant illness perception predictors of T2 anxiety. This suggests that those participants who felt their illness would have more severe consequences and were most emotionally distressed about their illness prior to surgery were more likely to have greater anxiety in the days following CABG.

6.6.2.4 Mediation models of T2 physical symptoms

Affective pain

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-affective pain relationship (Table 6.38). The model shows that T1 total BDI score was the only significant predictor of T2 physical symptoms in step 1 after controlling for demographic and disease severity (t = 1.995, p = 0.047). However, after adding T1 illness perceptions to the model, depression symptoms were no longer a significant predictor (t = 1.008, p = 0.315). In addition, illness perception score (t = 1.786, p = 0.076), was also non-significant in the model. The final model accounted for 4.5% (R^2 = 0.045) of variance in T2 affective pain scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 illness perceptions in the model, the β for depression symptoms changed from 0.148 to 0.083. This indicates that when illness perceptions were included in the model, there was a 43.9% reduction in the size of β. However, since illness perceptions were not a significant predictor in this model, a Sobel test was not performed.

The same regression analyses were also run using somatic/affective and cognitive affective depression symptom scores, finding the same pattern of results, such that neither depression symptom score (somatic/affective model: t = 1.054, p = 0.293; cognitive/affective model: t = 1.101, p = 0.272) nor illness perceptions (somatic/affective model: t = 1.673, p = 0.096; cognitive/affective model: t = 1.887, p = 0.061) were significant predictors of T2 affective pain in the final models. Since illness perceptions were not a significant predictor in these models, Sobel tests of mediation were not performed.

Despite total illness perceptions not mediating the depression symptoms-affective pain relationship, in order to see whether individual baseline illness perceptions were associated with pain, individual items on the BIPQ were entered into regression models to predict T2 affective pain, controlling for the demographic and disease severity covariates and

T1 depression symptoms symptom score. In models using total BDI depression symptom score, the illness perceptions of consequences (t = 2.001, p = 0.047) and emotional response (t = 2.131, p = 0.034) were the only significant illness perceptions predictors in the models. In models using somatic/affective depression symptom scores, only emotional response (t = 2.086, p = 0.038) was a significant illness perception predictor. In models using cognitive/affective depression symptom scores, both consequences (t = 2.146, p = 0.033) and emotional response (t = 2.217, p = 0.028) were significant illness perception predictors. In summary, consequences and emotional response were the only significant individual illness perception predictors of T2 affective pain. This suggests that those participants who viewed their illness as having more severe consequences and were most emotionally distressed about their illness prior to surgery, were more likely to have greater affective pain in the days following CABG.

TABLE 6.38: HIERARCHICAL REGRESSION OF T2 AFFECTIVE PAIN ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.002	0.024	0.009	0.932
Sex	-0.574	0.506	-0.088	0.257
Household income	0.077	0.113	0.051	0.495
euroSCORE	0.055	0.072	0.083	0.445
T1 BDI total score	0.050	0.025	0.148	0.047
Step 2				
Age	0.002	0.023	0.010	0.923
Sex	-0.597	0.503	-0.092	0.236
Household income	0.106	0.113	0.070	0.350
euroSCORE	0.063	0.071	0.095	0.382
T1 BDI total score	0.028	0.028	0.083	0.315
T1 Illness perceptions	0.026	0.015	0.145	0.076

Step 1 R^2 = 0.029; Step 2 R^2 = 0.045; N = 196

CROQ physical symptoms

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-physical symptom relationship (Table 6.39). The model shows that T1 total BDI score (t = 2.279, p = 0.024) and age (t = 2.464, p = 0.015) were the only significant predictors of T2 physical symptoms in step 1. However, after adding T1 illness perceptions to the model,

depression symptoms were no longer significant (t = 0.888, p = 0.376). The only significant predictors in the final model were age (t = 2.520, p = 0.013) and illness perceptions (t = 2.668, p = 0.008), both with a positive association such that older participants with a more negative view of their illness had greater physical symptoms following surgery. The final model accounted for 8.5% (R^2 = 0.085) of variance in physical symptom scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 illness perceptions in the model, the β for depression symptoms changed from 0.167 to 0.071. This indicates that when illness perceptions were included in the model, there was a 57.5% reduction in the size of β.

TABLE 6.39: HIERARCHICAL REGRESSION OF T2 PHYSICAL SYMPTOMS ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.147	0.060	0.257	0.015
Sex	0.340	1.279	0.020	0.791
Household income	-0.143	0.285	-0.037	0.616
euroSCORE	-0.264	0.181	-0.156	0.148
T1 BDI total score	0.144	0.063	0.167	0.024
Step 2				
Age	0.148	0.059	0.259	0.013
Sex	0.254	1.259	0.015	0.841
Household income	-0.035	0.283	-0.009	0.901
euroSCORE	-0.235	0.179	-0.139	0.191
T1 BDI total score	0.061	0.069	0.071	0.376
T1 Illness perceptions	0.097	0.036	0.212	0.008

Step 1 R^2 = 0.051; Step 2 R^2 = 0.085; N = 197

Next, a Sobel test was used on the data. The model included T1 total BDI score as the independent variable and T2 CROQ physical symptoms as the dependent variable, with illness perceptions entered as the mediator. Covariates included age, sex, household income and euroSCORE. The results are illustrated in Figure 6.5, showing a significant total effect (pathway *c*) for the T1 total BDI depression symptoms and T2 CROQ physical symptoms relationship (B = 0.144, SE = 0.063, p = 0.024). However, the direct pathway (pathway *c'*) (B = 0.062, SE = 0.069, p = 0.376) was not significant after taking the mediator into account. The indirect pathway (pathway *ab*) was significant in this model (B = 0.082, SE = 0.032, 95% CI = 0.019-0.169),

confirming illness perceptions to be a significant mediator. Full mediation was shown since the direct effect, pathway *c*', was not significant after illness perceptions were taken into account.

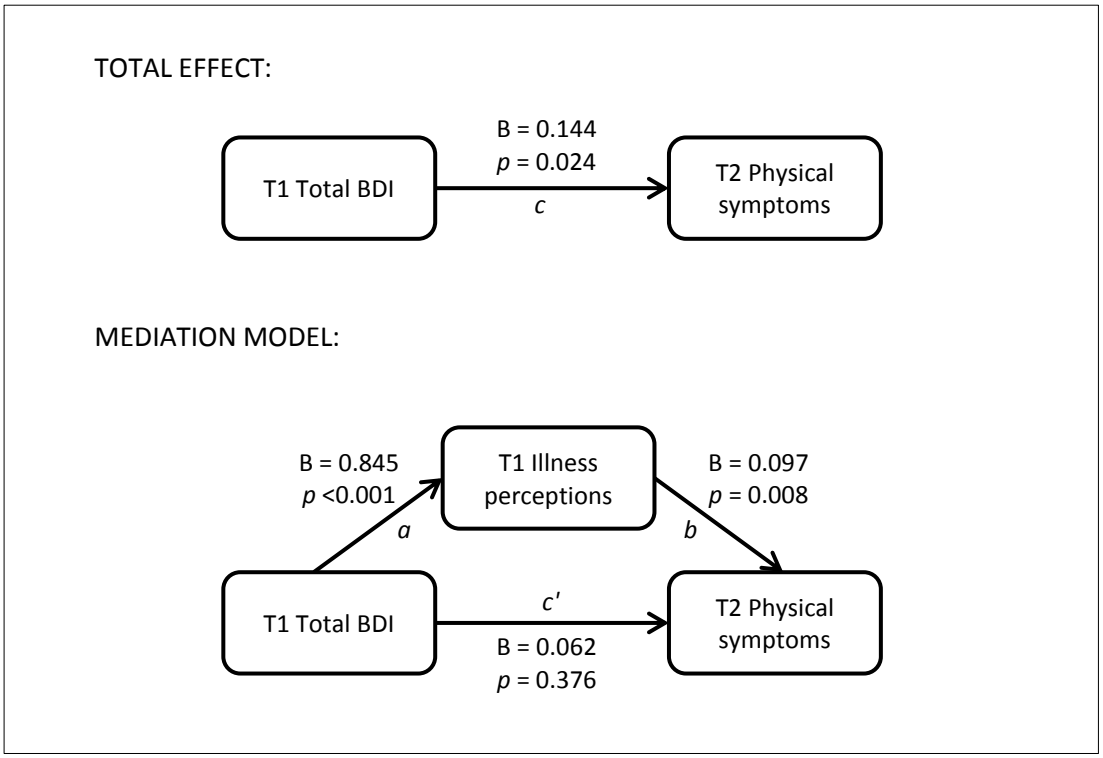

FIGURE 6.4: MEDIATION MODEL OF T1 TOTAL BDI SCORE AND T2 PHYSICAL SYMPTOMS THROUGH T1 ILLNESS PERCEPTIONS

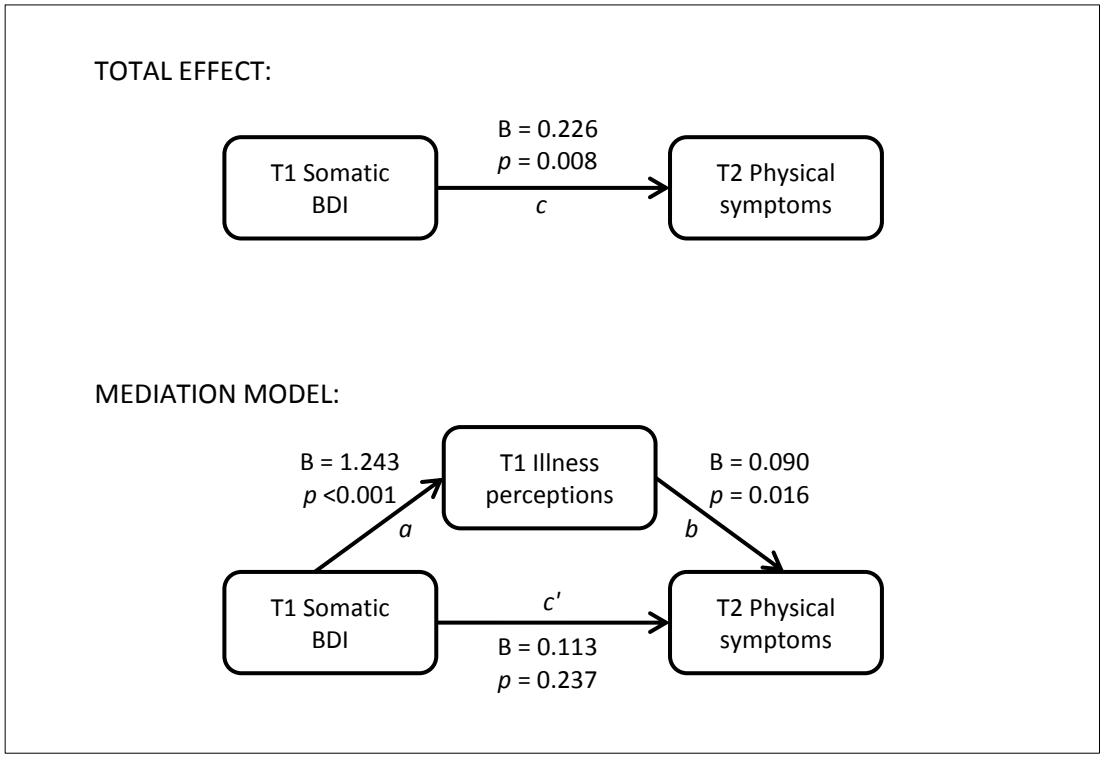

FIGURE 6.5: MEDIATION MODEL OF T1 SOMATIC/AFFECTIVE BDI SCORE AND T2 PHYSICAL SYMPTOMS THROUGH T1 ILLNESS PERCEPTIONS

Sobel tests of mediation were also performed for somatic/affective and cognitive/affective depression symptom scores, using the same covariates. The results for somatic/affective depression symptoms are illustrated in Figure 6.6, showing a significant total effect (pathway *c*) for the T1 somatic/affective depression symptoms and T2 CROQ physical symptom relationship (B = 0.226, SE = 0.085, *p* = 0.008). However, the direct pathway (pathway *c*') (B = 0.113, SE = 0.096, *p* = 0.237) was not significant after taking the mediator into account. The indirect pathway (pathway *ab*) was significant in this model (B = 0.112, SE = 0.052, 95% CI = 0.023-0.226), confirming illness perceptions to be a significant mediator. Full mediation was shown since the direct effect, pathway *c*', was not significant after illness perceptions were taken into account.

The results for cognitive/affective depression symptoms are illustrated in Figure 6.7, showing a significant total effect (pathway *c*) for the T1 cognitive/affective depression symptoms and T2 CROQ physical symptom relationship (B = 0.266, SE = 0.107, *p* = 0.014). However, the direct pathway (pathway *c*') (B = 0.153, SE = 0.114, *p* = 0.180) was not significant after taking the mediator into account. The indirect pathway (pathway *ab*) was significant in this model (B = 0.112, SE = 0.055, 95% CI = 0.029-0.250), confirming illness perceptions to be a significant mediator. Full mediation was shown since the direct effect, pathway *c*', was not significant after illness perceptions were taken into account.

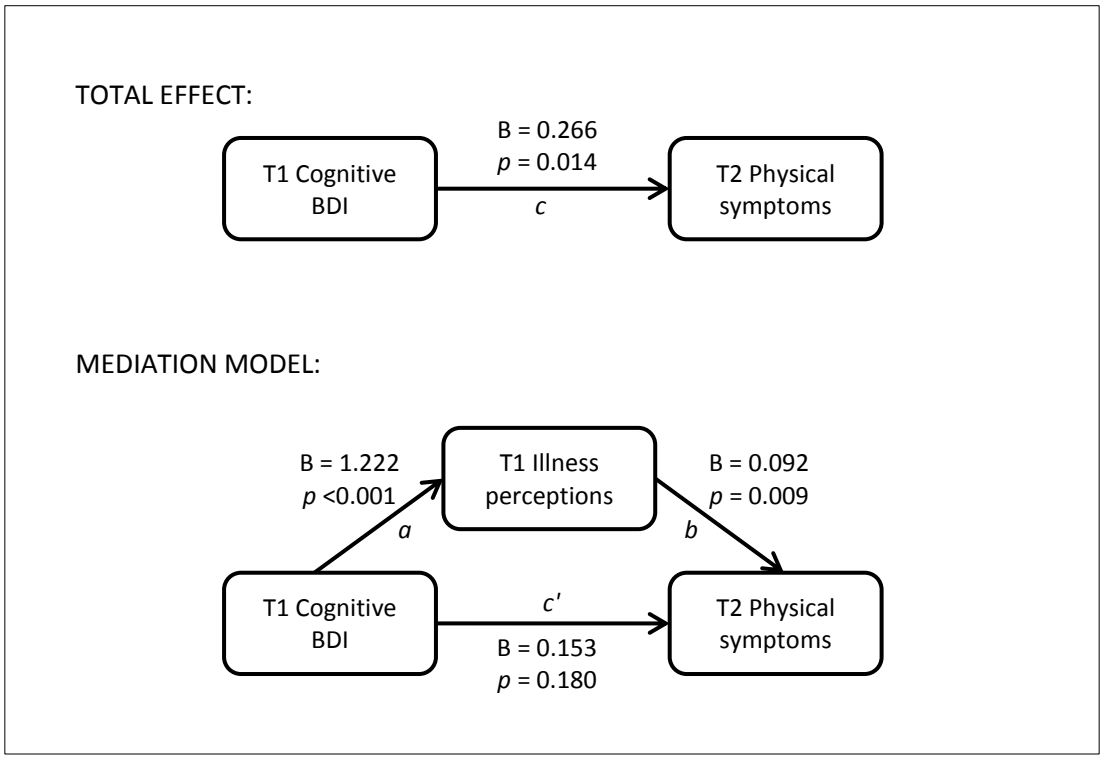

FIGURE 6.6: MEDIATION MODEL OF T1 COGNITIVE/AFFECTIVE BDI SCORE AND T2 PHYSICAL SYMPTOMS THROUGH T1 ILLNESS PERCEPTIONS

In addition, in order to see whether any one illness perception was best associated with T2 CROQ physical symptoms, individual items on the BIPQ were entered into regression models to predict T2 physical symptoms, controlling for the demographic and disease severity covariates and depression symptoms symptom scores. In models using total BDI depression symptom score, the illness perceptions of concern (t = 2.799, p = 0.006) and emotional response (t = 3.064, p = 0.003) were the only significant illness perceptions predictors in the models. In models using somatic/affective depression symptom scores, again concern (t = 2.698, p = 0.008) and emotional response (t = 2.902, p = 0.004) were the only significant illness perception predictors in the models. In models using cognitive/affective depression symptom scores, the same findings were found such that concern (t = 2.816, p = 0.005) and emotional response (t = 2.976, p = 0.003) were the only significant illness perception predictors. In summary, concern and emotional response were the only significant illness perception predictors of T2 physical symptoms. This suggests that those participants who were most emotionally distressed about their illness prior to surgery were more likely to have greater physical symptoms in the days following CABG surgery.

6.6.2.5 Mediation models of T2 length of post-operative hospital stay

Logistic regression models were built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-length of post-operative stay relationship. The model using T1 total BDI score is displayed in Table 6.40 and shows that depression symptoms (p = 0.016) and household income (p = 0.011) were the only significant predictors of length of hospital stay in step 1. Moreover, after adding T1 illness perceptions into the model, depression symptoms (p = 0.048) and household income (p = 0.012) remained significant predictors. Illness perceptions (p = 0.667) were not a significant predictor of length of hospital stay after controlling for covariates. The final model showed that for every unit increase in total BDI score, there was a 6.6% greater odds of having a post-operative hospital stay of greater than one week. Looking at the odds ratio for depression symptoms shows that with the inclusion of T1 illness perceptions in the model, the odds changed from 1.073 to 1.066. This indicates that when illness perceptions were included in the model, there was a 9.6% reduction in the size of the odds. As such, the addition of illness perceptions to the model accounted for a moderate amount of the association between depression symptoms and longer hospital stays.

TABLE 6.40: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.030	0.974-1.090	0.298
Sex[a]	2.048	0.717-5.850	0.181
Household income[b]	0.405	0.202-0.811	0.011
euroSCORE	1.056	0.901-1.238	0.499
T1 BDI total	1.073	1.013-1.136	0.016
Step 2			
Age	1.030	0.974-1.089	0.301
Sex[a]	2.029	0.711-5.788	0.186
Household income[b]	0.409	0.204-0.819	0.012
euroSCORE	1.059	0.903-1.242	0.477
T1 BDI total	1.066	1.001-1.137	0.048
T1 Illness perceptions	1.007	0.974-1.042	0.667

Reference groups are: [a]male; [b] <£20,000/year. *N* = 197.

TABLE 6.41: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 ILLNESS PERCEPTIONS AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.025	0.970-1.083	0.381
Sex[a]	1.992	0.695-5.707	0.200
Household income[b]	0.398	0.199-0.795	0.009
euroSCORE	1.056	0.901-1.238	0.502
T1 BDI somatic	1.091	1.008-1.180	0.030
Step 2			
Age	1.025	0.970-1.083	0.380
Sex[a]	1.984	0.694-5.669	0.201
Household income[b]	0.403	0.201-0.806	0.010
euroSCORE	1.060	0.903-1.243	0.477
T1 BDI somatic	1.080	0.987-1.182	0.095
T1 Illness perceptions	1.008	0.973-1.044	0.658

Reference groups are: [a]male; [b] <£20,000/year. *N* = 197.

TABLE 6.42: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T1 ILLNESS PERCEPTIONS AND T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*OR*	*95% CI*	*p*
Step 1			
Age	1.034	0.977-1.095	0.250
Sex[a]	2.104	0.758-5.844	0.153
Household income[b]	0.372	0.185-0.745	0.005
euroSCORE	1.064	0.909-1.246	0.442
T1 BDI cognitive	1.139	1.034-1.255	0.008
Step 2			
Age	1.034	0.976-1.094	0.256
Sex[a]	2.061	0.740-5.740	0.166
Household income[b]	0.377	0.187-0.756	0.006
euroSCORE	1.067	0.911-1.250	0.422
T1 BDI cognitive	1.129	1.018-1.253	0.022
T1 Illness perceptions	1.007	0.975-1.041	0.659

Reference groups are: [a]male; [b] <£20,000/year. *N* = 199.

The models using somatic/affective and cognitive/affective depression symptom scores are shown in Table 6.41 and Table 6.42 respectively. Findings are in line with those using total BDI scores, with illness perceptions failing to show a significant relationship with length of post-operative stay in the final models. Interestingly, somatic/affective depression symptoms (p = 0.095) failed to be significant in the final model, while cognitive/affective depression symptoms (p = 0.022) remained significant. Looking at the odds ratio for somatic/affective depression symptoms shows that with the inclusion of T1 illness perceptions in the model, the odds changed from 1.091 to 1.080. This indicates that when illness perceptions were included in the model, there was a 12.1% reduction in the size of the odds. In the cognitive/affective model the odds changed from 1.139 to 1.129 suggesting a 7.2% reduction in odds with the addition of illness perceptions to the model. As such, the addition of illness perceptions to the accounted for a moderate amount of the association between depression symptoms and longer hospital stays.

Despite the lack of association between total illness perception scores and length of hospital stay, the individual illness perceptions were entered into regression models controlling for demographic, disease severity and depression symptom score variables. Interestingly, none of the individual illness perceptions were able to predict length of hospital stay.

6.6.3 Biological mechanisms - Cortisol

6.6.3.1 Descriptive statistics

Biological mechanisms that were tested in this PhD include the neuroendocrine hormone, cortisol. Descriptive statistics for the non-transformed data for cortisol are displayed in Table 6.43. Missing cortisol data was due to some participants declining to provide samples and some outliers being removed. Figure 6.8 represents the mean cortisol data at the seven measurement points for participants across the course of the day, showing a peak in cortisol at 30 minutes after waking and a gradual decline throughout the rest of the day.

Use of pre-operative cardiac medication, including aspirin, beta-blockers, statins and antiplatelets, was not associated with T1 cortisol responses; multiple regression models supported these findings. Therefore, the regression models shown in the following sections adjust for the demographic and disease severity covariates only.

TABLE 6.43: T1 CORTISOL NON-TRANSFORMED DATA

Cortisol (nmol/l)	*N*	*Minimum*	*Maximum*	*Mean ± SD*
Waking	202	1.36	60.95	20.11±10.08
Waking + 30 minutes	204	1.67	71.32	24.67±11.95
10:00am	203	0.54	55.76	13.18±7.34
12:00noon	204	0.33	37.02	9.59±5.24
4:00 pm	206	0.55	22.38	6.49±3.22
8:00 pm	206	0.38	35.56	4.65±4.22
Bedtime	202	0.58	24.09	3.75±3.25
Slope	207	-0.06	0.07	0.02±0.01
CAR	208	-22.57	43.87	5.18±11.37
AUC	189	3644.24	20436.73	8988.54±2917.62
Waking-bedtime difference	196	-2.68	53.26	16.58±9.83

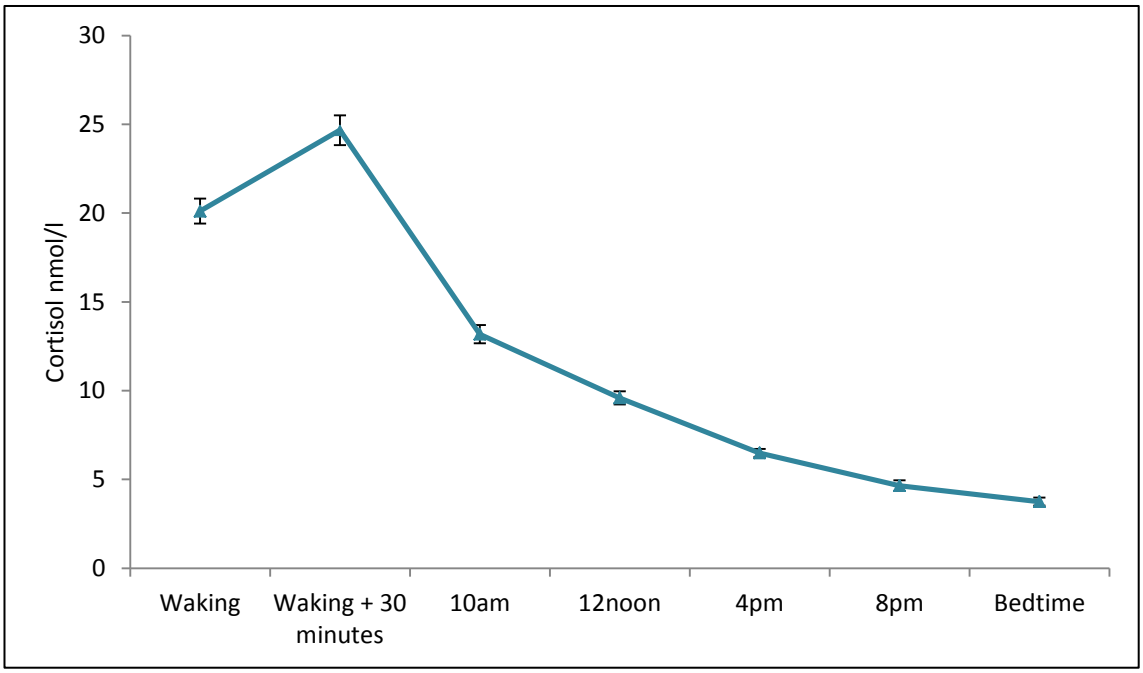

FIGURE 6.8: T1 MEAN SALIVARY CORTISOL ACROSS THE DAY

N.B. Bars represent standard error of the means.

6.6.3.2 Associations with depression symptoms and recovery variables

TABLE 6.44: T1 CORTISOL BY T1 DEPRESSION CASENESS

Cortisol (nmol/l)	*T1 Depression symptom score*	*N*	*Mean ± SD*	*t*	*p*
T1 AUC	<13	153	8773.83±2823.22	-2.299	0.023
	≥13	33	10055.34±3261.80		
T1 Waking-bedtime difference	<13	159	16.81±10.08	0.840	0.402
	≥13	34	15.24±8.96		
T1 CAR	<13	118	4.23±11.65	-1.064	0.289
	≥13	18	7.45±14.01		
T1 Cortisol slope	<13	168	0.02±0.01	0.516	0.607
	≥13	36	0.02±0.01		

Pearson's correlation analyses were performed to assess the relationship between the different cortisol scores (CAR, AUC, slope, waking-bedtime difference) and depression symptom scores and T2 recovery outcomes. Results showed AUC (r = 0.172, p = 0.019) was significantly correlated with depression symptoms caseness (BDI ≥13). The positive correlation coefficient for AUC suggests the presence of depression symptoms is associated with a higher

cortisol output across the day. No other significant correlations were found between cortisol and the predictor and outcome measures. These null findings were also confirmed in regression models controlling for covariates.

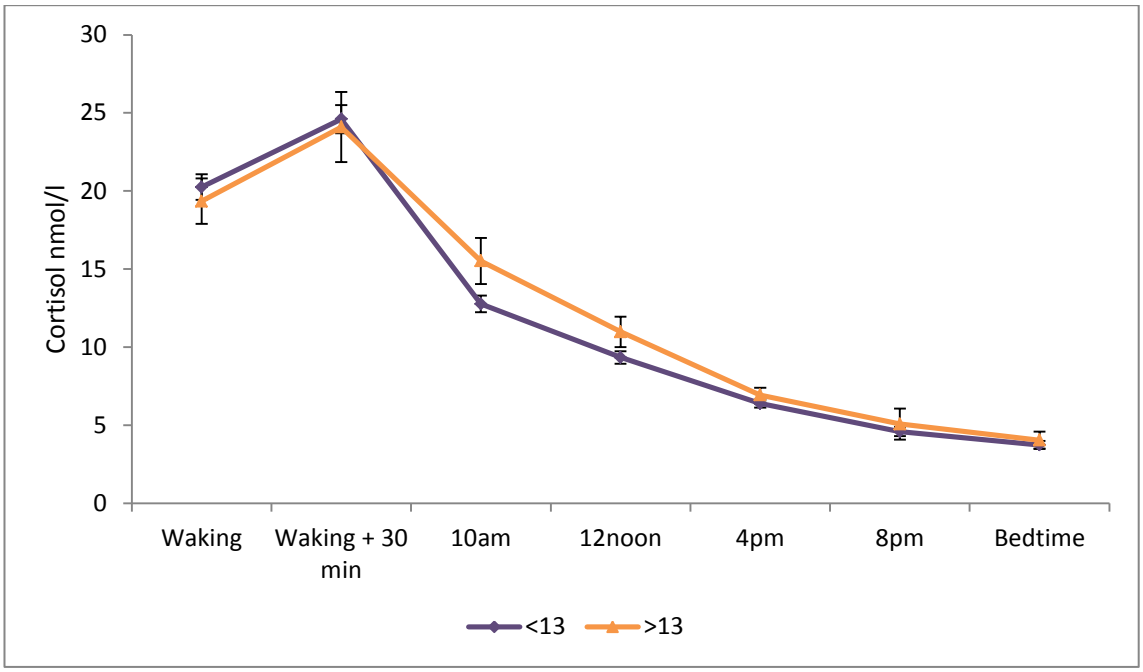

FIGURE 6.9: T1 CORTISOL ACROSS THE DAY BY T1 DEPRESSION CASENESS

Bars represent standard error of the means.

To investigate this significant finding further, independent *t*-tests were also performed to examine the difference in cortisol measures between non-depressed and depressed participants (BDI≥13). Results from these analyses are displayed in Table 6.44, confirming the significant difference between depression symptoms groups in terms of the AUC (p = 0.023). The cortisol output over the day is represented in Figure 6.9, illustrating the fact that depressed participants had a larger total cortisol output (AUC) over the day then non-depressed participants prior to surgery. This graph shows the 10am (t(198)= -2.025, p = 0.044) cortisol sample was higher in the depressed participants, suggesting a slower decline through the day.

A multiple regression (Table 6.45) was also performed to examine the association between caseness on the BDI (t = 2.832, p = 0.005) and T1 cortisol AUC, showing a significant result after controlling for covariates. These results suggest that the difference in total cortisol output across the day between depressed and non-depressed participants was not accounted for by differences in demographic or disease severity covariates. In total, this model accounted for 8.3% (R^2 = 0.083) of variance in cortisol AUC scores.

TABLE 6.45: MULTIPLE REGRESSION OF T1 CORTISOL AUC ON T1 DEPRESSION CASENESS

Model	*B*	*SE*	*ß*	*p*
Age	26.089	34.216	0.081	0.447
Sex	-1040.670	805.212	-0.103	0.198
Household income	306.356	172.254	0.139	0.077
euroSCORE	131.365	106.293	0.136	0.218
T1 BDI caseness	1694.841	598.488	0.214	0.005

R^2 = 0.083, *N* = 172

TABLE 6.46: PEARSON'S CORRELATIONS BETWEEN T1 CORTISOL AND T2 RECOVERY OUTCOMES

Cortisol (nmol/l)	*T2 Anxiety (HADS)*	*T2 Affective pain*	*T2 Physical symptoms (CROQ)*	*T2 Length of post-CABG stay (binary)*
T1 AUC				
r	0.099	0.018	-0.135	-0.023
p	0.175	0.805	0.064	0.754
T1 Waking-bedtime difference				
r	0.005	0.025	-0.038	-0.077
p	0.940	0.730	0.596	0.286
T1 CAR				
r	-0.097	-0.125	0.100	0.023
p	0.256	0.141	0.241	0.790
T1 Cortisol slope				
r	0.045	0.043	-0.020	-0.049
p	0.518	0.537	0.775	0.483

Pearson's correlations were also performed to assess the association between baseline cortisol responses and the T2 recovery outcomes. Results for the Pearson's correlations of cortisol with the outcome variables are displayed in Table 6.46. The results show that no significant associations were found between any of the cortisol responses and the recovery outcomes. These null findings were confirmed in regression models controlling for covariates. Since cortisol was not related to any of the recovery outcomes, mediation analyses were not performed.

6.6.4 Biological mechanisms – Inflammatory markers

6.6.4.1 Descriptive statistics

The second biological pathway tested in the PhD was the role of inflammation, including the inflammatory markers IL-6, hs-CRP and TNF-α. Inflammatory markers were measured both

pre-CABG and during the post-surgery hospital stay. Due to the variability in collection day for the post-operative bloods, two summary scores were created. The first summary score used the mean for the inflammatory marker values on day's one, two and three post-surgery and the second used the mean for the inflammatory marker values on day's four, five, six, seven and eight post-surgery. These scores were termed 'early' and 'late' T2 bloods. Change scores were also computed by deducting baseline from follow-up values; larger change scores indicate a greater response from T1 to T2.

Use of pre-operative cardiac medication, including aspirin, beta-blockers, statins and antiplatelets, was not associated with T1 or T2 early and late inflammatory responses; multiple regression models supported these findings. Therefore, the regression models shown in the following sections adjust for the demographic and disease severity covariates only.

TABLE 6.47: T1 INFLAMMATORY MARKER NON-TRANSFORMED DATA

Inflammatory marker	*Pair*	*N*	*Mean ± SD*	*t*	*p*
IL-6 (pg/mL)	T1 T2 Early	148	5.37±1.80 207.68±62.49	-39.528	<0.001
	T1 T2 Late	138	5.16±1.73 97.56±29.01	-37.896	<0.001
	T2 Early T2 Late	104	206.26±68.39 98.24±26.77	15.750	<0.001
hs-CRP (mg/mL)	T1 T2 Early	151	7.78±7.36 80.65±55.35	-16.098	<0.001
	T1 T2 Late	137	8.68±9.75 64.69±60.06	-11.336	<0.001
	T2 Early T2 Late	103	81.60±59.10 60.97±54.23	3.596	0.001
TNF-α (pg/mL)	T1 T2 Early	151	5.81±2.73 6.14±2.65	-1.100	0.273
	T1 T2 Early	139	5.74±2.77 6.03±2.63	-0.840	0.402
	T2 Early T2 Late	104	6.26±2.70 6.33±2.76	-0.167	0.868

Paired samples *t*-tests to assess change in the inflammatory markers over time are shown in Table 6.47. Data show that for IL-6 and hs-CRP there was a significant increase from T1 to T2, for both early and late samples. In addition, there was a significant decrease from T2 early to T2 late samples for these inflammatory markers. The TNF-α data reveals that no

significant changes occurred over time. The change in each of the inflammatory markers across time is also represented in Figure 6.10 illustrating the fact that IL-6 displayed the greatest increase from baseline to T2 early, compared to both CRP and TNF-α. At four to eight days following surgery, both IL-6 and CRP had not returned to baseline levels, suggesting a persistent heightened inflammatory response for these markers following surgery. In addition, the graph also shows how TNF-α was comparatively stable over time, with no change from pre- to post-surgery.

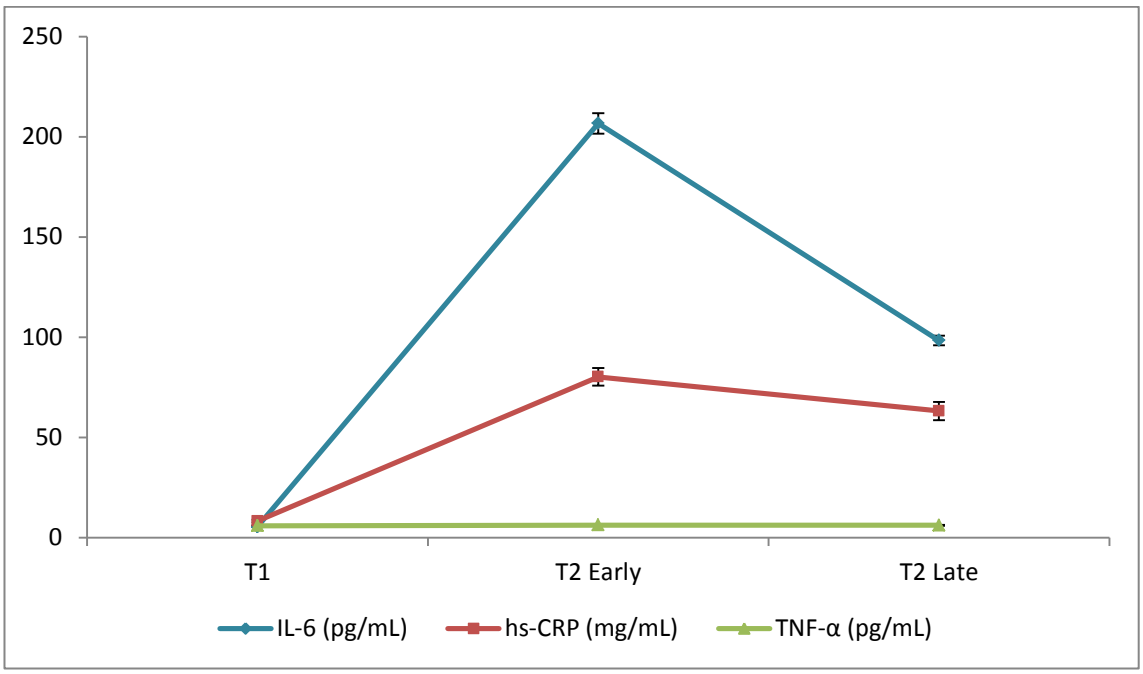

FIGURE 6.10: INFLAMMATORY MARKERS FROM PRE- TO POST-SURGERY

Bars represent standard error of the means. N.B. Standard errors of the mean for TNF-α are not perceptible on this graph but are: 0.19, 0.20, and 0.22 at T1, T2 early and T2 late respectively.

6.6.4.2 Associations with depression symptom variables

Pearson's correlation analyses were first performed to assess the relationship between the different inflammatory markers (IL-6, hs-CRP, TNF-α) and depression symptom scores. Results showed that baseline IL-6 was significantly associated with cognitive/affective depression symptoms (r = 0.152, p = 0.030); however after being entered into a regression model controlling for covariates, baseline IL-6 (t = 0.513, p = 0.609) was no longer significant. The results from the correlation analyses found all the other inflammatory marker variables were not related to T1 depression symptoms.

TABLE 6.48: MULTIPLE REGRESSION OF IL-6 T2 EARLY ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	1.913	0.943	0.257	0.045
Sex	36.227	19.174	0.167	0.061
Household income	0.004	4.173	<0.001	0.999
euroSCORE	-6.377	2.751	-0.305	0.022
T1 BDI total	2.479	0.940	0.223	0.009

R^2 = 0.094, *N* = 141

TABLE 6.49: MULTIPLE REGRESSION OF IL-6 T2 EARLY ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	1.749	0.943	0.235	0.066
Sex	34.938	19.376	0.161	0.074
Household income	-0.482	4.189	-0.010	0.908
euroSCORE	-6.369	2.771	-0.304	0.023
T1 BDI somatic	2.859	1.280	0.188	0.027

R^2 = 0.081, *N* = 141

TABLE 6.50: MULTIPLE REGRESSION OF IL-6 T2 EARLY ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	1.891	0.932	0.254	0.045
Sex	41.223	18.351	0.195	0.026
Household income	-0.585	4.121	-0.012	0.887
euroSCORE	-6.135	2.715	-0.292	0.025
T1 BDI cognitive	4.159	1.567	0.224	0.009

R^2 = 0.096, *N* = 143

Next, regression analyses were performed to assess whether depression symptoms predicted the inflammatory markers after controlling for covariates. The results of the multiple regression model using total BDI depression symptom score are displayed in Table 6.48 showing pre-operative depression symptoms (t = 2.637, p = 0.009) were a significant predictor of having a higher mean T2 early IL-6 response. The only other significant predictors in this model were age (t = 2.027, p = 0.045) and euroSCORE (t = -2.318, p = 0.022), such that older age and a lower euroSCORE value, or in other words a lower mortality risk, predicted greater IL-6 responses. This latter finding is counterintuitive and difficult to interpret, but is a result that was replicated for both the somatic/affective and cognitive/affective depression

symptoms models (see Table 6.49 and Table 6.50). These models also confirmed depression symptoms (somatic/affective: t = 2.233, p = 0.027; cognitive/affective: t = 2.654, p = 0.009) were a significant predictor of T2 early IL-6 response.

Figure 6.11 illustrates the change in IL-6 over time according to depression status (BDI ≥13). This graph shows there was no difference between depressed and non-depressed participants at baseline or four to eight days following CABG surgery. However, in the early term following surgery (T2 early) the depressed participants showed a greater IL-6 response compared to their non-depressed counterparts. This did not reach statistical significance in an independent t-test (t(154) = -1.431, p = 0.154), but illustrates the trend demonstrated using the continuous scores on the BDI in the covariate adjusted regression models.

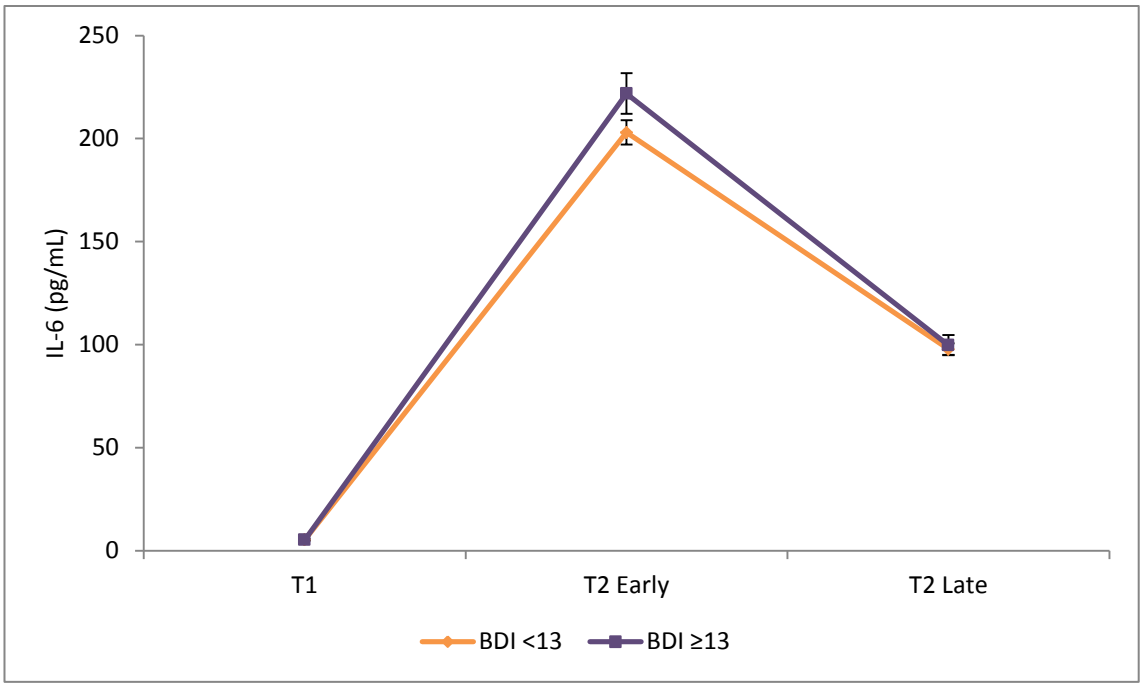

FIGURE 6.11: CHANGE IN IL-6 OVER TIME BY T1 DEPRESSION CASENESS

Bars represent standard error of the means.

Multiple regression analyses also showed that total BDI depression symptom score (t = 2.478, p = 0.015) was a significant predictor of having a higher change in IL-6 from T1 to T2 early (Table 6.51). There were no other significant predictors in this model. This finding was replicated for both the somatic/affective and cognitive/affective depression symptom models, such that depression symptoms (somatic/affective: t = 2.083, p = 0.039; cognitive/affective: t = 2.475, p = 0.015) were the only significant predictor of change in IL-6 response.

TABLE 6.51: MULTIPLE REGRESSION OF CHANGE IN IL-6 (T1 TO T2 EARLY) ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	1.716	0.969	0.238	0.079
Sex	34.642	20.267	0.158	0.090
Household income	1.077	4.191	0.023	0.798
euroSCORE	-4.671	2.827	-0.231	0.101
T1 BDI total	2.378	0.959	0.219	0.015

R^2 = 0.077, *N* = 132

6.6.4.3 Associations with recovery variables

Next, Pearson's correlations were performed to assess the association between inflammatory markers and the T2 recovery outcomes. Results for the Pearson's correlations of inflammatory markers with the outcome variables are displayed in Table 6.52. Please note that since no significant findings were observed between TNF-α and the recovery outcomes, the results are not displayed. This table shows that the mean T2 late IL-6 response was significantly associated with length of hospital stay (p = 0.005); this result was negative such that a lower response was associated with a stay of more than a week. This negative association was confirmed in change in IL-6 from T1 to T2 late samples (p = 0.011), again suggesting a smaller response was related to a longer hospital stay. In terms of the CRP response, hs-CRP at baseline was positively associated with anxiety at T2 (p = 0.018) and affective pain at T2 (p = 0.020), indicating a greater CRP level prior to surgery was related to poorer recovery after surgery. In addition, a higher T2 late hs-CRP level was associated with a longer hospital stay (p <0.001), and a greater change in hs-CRP was associated with a longer hospital stay (p <0.001).

Since none of the inflammatory markers correlating with the outcomes also correlated with depression, mediation analyses were not performed. However, each of these associations was further examined using regression models, controlling for demographic, disease severity and depression symptom covariates. These results are described in turn below. Regression analyses were also built for TNF-α, but no significant findings were found.

TABLE 6.52: PEARSON'S CORRELATIONS BETWEEN INFLAMMATORY MARKERS AND T2 RECOVERY OUTCOMES

Inflammatory marker	*T2 Anxiety (HADS)*	*T2 Affective pain*	*T2 Physical symptoms (CROQ)*	*T2 Length of post-CABG stay (binary)*
IL-6 (pg/mL)				
T1 IL-6				
r	-0.046	-0.073	-0.047	-0.118
p	0.512	0.299	0.503	0.096
T2 IL-6 Early				
r	0.121	0.098	0.073	0.026
p	0.130	0.222	0.361	0.752
T2 IL-6 Late				
r	0.084	0.114	0.084	-0.235
p	0.313	0.171	0.313	0.005
IL-6 Change T1 – T2 early				
r	0.102	0.088	0.072	0.014
p	0.216	0.286	0.387	0.869
IL-6 Change T1 – T2 late				
r	0.077	0.110	0.063	-0.219
p	0.368	0.201	0.463	0.011
hs-CRP (mg/mL)				
T1 hs-CRP				
r	0.165	0.162	-0.003	0.076
p	0.018	0.020	0.967	0.287
T2 hs-CRP Early				
r	-0.029	0.094	-0.027	0.105
p	0.713	0.236	0.735	0.190
T2 hs-CRP Late				
r	0.073	0.119	0.053	0.316
p	0.383	0.156	0.530	<0.001
hs-CRP Change T1 – T2 early				
r	-0.079	0.058	-0.039	0.121
p	0.337	0.484	0.633	0.144
hs-CRP Change T1 – T2 late				
r	0.039	0.118	0.090	0.308
p	0.654	0.170	0.296	<0.001

T2 emotional distress outcomes

A multiple regression model was built to assess the relative contribution of inflammation to T2 anxiety (Table 6.53). The model shows that T1 anxiety (t = 4.010, p <0.001), T1 total BDI score (t = 2.085, p = 0.039) and T1 hs-CRP (t = 2.746, p = 0.007) were significant predictors of T2 anxiety after adjusting for covariates. All these associations were positive such that more anxious and depressed participants at baseline, who had a higher level of CRP, had greater

anxiety following surgery. The model accounted for 24.0% (R^2 = 0.240) of variance in T2 anxiety scores. T1 hs-CRP was also a significant predictor of T2 anxiety in models using somatic/affective (*t* = 2.716, *p* = 0.007) and cognitive/affective (*t* = 2.695, *p* = 0.008) depression symptoms.

TABLE 6.53: MULTIPLE REGRESSION OF T2 ANXIETY ON T1 HS-CRP AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.002	0.043	0.004	0.964
Sex	-1.723	0.927	-0.134	0.065
Household income	0.039	0.206	0.013	0.848
euroSCORE	0.122	0.134	0.091	0.365
T1 Anxiety	0.318	0.079	0.329	<0.001
T1 BDI total	0.117	0.056	0.175	0.039
T1 hs-CRP (mg/mL)	0.078	0.028	0.181	0.007

R^2 = 0.240, *N* = 185

T2 physical symptom outcomes

TABLE 6.54: MULTIPLE REGRESSION OF T2 AFFECTIVE PAIN ON T1 HS-CRP AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.012	0.022	-0.058	0.592
Sex	-0.556	0.484	-0.091	0.252
Household income	0.041	0.107	0.029	0.704
euroSCORE	0.091	0.069	0.148	0.186
T1 BDI total	0.040	0.024	0.127	0.095
T1 hs-CRP (mg/mL)	0.035	0.015	0.172	0.019

R^2 = 0.053, *N* = 187

A multiple regression model was built to assess the relative contribution of inflammation to T2 affective pain (Table 6.54). The model shows that T1 hs-CRP (*t* = 2.357, *p* = 0.019) was the only significant predictor of T2 affective pain after adjusting for covariates. T1 total BDI score (*t* = 1.677, *p* = 0.095) was not a significant predictor in this model. CRP was positively associated with pain such that those participants who had a higher level of CRP at baseline also had greater affective pain following surgery. The model accounted for 5.3% (R^2 = 0.053) of variance in T2 affective pain scores. T1 hs-CRP was also a significant predictor of T2 affective pain in

models using somatic/affective (t = 2.290, p = 0.023) and cognitive/affective (t = 2.359, p = 0.019) depression symptoms.

T2 length of post-operative hospital stay outcome

IL-6 and CRP were both shown in the correlation analyses to relate to length of post-operative stay. Logistic regression models were built controlling for demographic and disease severity covariates as well as baseline total BDI score. The results using mean T2 late IL-6 scores are displayed in Table 6.55 showing that the IL-6 T2 late response was significantly associated with length of post-operative hospital stay (p = 0.003) after controlling for covariates. These results show that for every unit increase in IL-6, there was a 2.3% reduced odds of having a post-operative hospital stay of greater than one week. Household income (p = 0.018) and depression symptoms (p = 0.003) were the only other significant variables in the model. T2 late IL-6 was also significantly associated with of T2 length of hospital stay in models using somatic/affective (p = 0.004) and cognitive/affective (p = 0.003) depression. A similar pattern of results were also found for change in IL-6 from T1 to T2 late (see Table 6.56), with the change being significantly associated with length of post-operative stay after controlling for covariates (p = 0.008). These results suggest that for every unit increase in IL-6 change over time, there was a 2.1% reduction in the odds of having an extended hospital stay. Change in IL-6 was also significantly associated with T2 length of hospital stay in models using somatic/affective (p = 0.010) and cognitive/affective (p = 0.007) depression symptoms.

TABLE 6.55: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T2 LATE IL-6 AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	0.987	0.924-1.054	0.689
Sex[a]	1.568	0.415-5.927	0.508
Household income[b]	0.355	0.151-0.835	0.018
euroSCORE	1.190	0.978-1.447	0.082
T1 BDI total	1.071	1.000-1.148	0.050
T2 Late IL-6 (pg/mL)	0.977	0.962-0.992	0.003

Reference groups are: [a]male; [b] <£20,000/year. *N* = 130. OR: Odds ratio; CI: Confidence interval.

TABLE 6.56: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON CHANGE IN IL-6 (T1 TO T2 LATE) AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	0.989	0.926-1.056	0.744
Sex[a]	1.480	0.394-5.560	0.562
Household income[b]	0.387	0.164-0.913	0.030
euroSCORE	1.184	0.971-1.445	0.096
T1 BDI total	1.069	0.998-1.146	0.058
IL-6 Change T1 - T2 late (pg/mL)	0.979	0.964-0.994	0.008

Reference groups are: [a]male; [b] <£20,000/year. *N* = 123. OR: Odds ratio; CI: Confidence interval.

The results of the logistic regression models using mean T2 late hs-CRP scores are displayed in Table 6.57 showing that the CRP T2 late response was significantly associated with length of post-operative hospital stay (p = 0.002) after controlling for covariates. These results show that for every unit increase in CRP, there was a 1.1% greater odds of having a post-operative hospital stay of greater than one week. No other significant variables were found in this model. T2 late hs-CRP was also significantly associated with T2 length of hospital stay in models using somatic/affective (p = 0.002) and cognitive/affective (p = 0.001) depression symptoms. A similar pattern of results was also found for change in CRP from T1 to T2 late (see Table 6.58), with the change being significantly associated with length of post-operative stay after controlling for covariates (p = 0.003). Again, these results suggest that for every unit decrease in IL-6 change over time, there was a 1.1% increase in the odds of having an extended hospital stay. Change in hs-CRP was also significantly associated with T2 length of hospital stay in models using somatic/affective (p = 0.003) and cognitive/affective (p = 0.003) depression symptoms.

Due to the inconsistency of the direction of the IL-6 and CRP findings, Pearson's correlations were performed finding that IL-6 and CRP T2 late responses were not significantly associated, however IL-6 T2 early was significantly associated with CRP T2 late (r = 0.266, p = 0.007). This indicates differences with the association between inflammatory markers over time. In summary, the late post-operative markers of inflammation were the best inflammatory variables to show associations with length of hospital stay, with lower IL-6 values and higher CRP being related to the greatest odds of having a post-operative stay of more than one week. These associations were cross-sectional, showing inflammatory responses and recovery outcomes measured in the days following surgery were closely related.

TABLE 6.57: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON T2 LATE HS-CRP AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	0.997	0.932-1.065	0.924
Sex[a]	0.988	0.230-4.249	0.987
Household income[b]	0.420	0.180-0.977	0.044
euroSCORE	1.157	0.948-1.412	0.153
T1 BDI total	1.051	0.982-1.125	0.148
T2 Late hs-CRP (mg/mL)	1.011	1.004-1.018	0.002

Reference groups are: [a]male; [b] <£20,000/year. *N* = 129. OR: Odds ratio; CI: Confidence interval.

TABLE 6.58: LOGISTIC REGRESSION OF T2 LENGTH OF HOSPITAL STAY ON CHANGE IN HS-CRP (T1 TO T2 LATE) AND T1 TOTAL BDI SCORE

Model	*OR*	*95% CI*	*p*
Age	0.998	0.934-1.068	0.965
Sex[a]	0.933	0.218-3.991	0.926
Household income[b]	0.479	0.205-1.120	0.089
euroSCORE	1.155	0.942-1.417	0.165
T1 BDI total	1.052	0.982-1.127	0.149
hs-CRP Change T1 - T2 late (pg/mL)	1.011	1.004-1.018	0.003

Reference groups are: [a]male; [b] <£20,000/year. *N* = 122. OR: Odds ratio; CI: Confidence interval.

6.7 Discussion

6.7.1 Summary of results

The table (Table 6.59) displays a summary of the main findings presented in this chapter. Total and somatic/affective depression symptoms were related to all the recovery outcomes after controlling for covariates. However, cognitive/affective depression symptoms were only significantly associated with physical symptoms and length of post-operative hospital stay in covariate adjusted models.

Health behaviours were of limited importance in predicting recovery outcomes. Physical activity was an important predictor of T2 emotional distress, such that participants who walked for fewer hours per week prior to CABG were most anxious after surgery. Notably, depression symptoms were not related to physical activity and so physical activity had an independent effect on anxiety. The other health behaviour that was able to predict recovery was smoking status at baseline, which predicted length of post-operative stay. Participants who smoked were more likely to have a hospital stay of greater than one week. This effect was

also shown to be independent of depression symptom score, such that depression symptoms were not significantly related to smoking status.

TABLE 6.59: SUMMARY OF EARLY-TERM OUTCOME RESULTS

	Main findings using total BDI score	*Supported using depression symptom models?*
1.	Pre-operative total BDI score was able to predict: greater anxiety, greater affective pain, greater physical symptoms and longer hospital stays at T2.	• Somatic/affective depression symptoms showed the same relationship with recovery outcomes. • Cognitive/affective depression symptoms were only predictive of greater physical symptoms and a longer hospital stay.
2.	Baseline physical activity was associated with greater anxiety at T2, after adjusting for total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.
3.	Baseline smoking was associated with longer hospital stays, after adjusting for total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.
4.	Baseline illness perceptions mediated the relationship between total BDI score and greater anxiety and greater physical symptoms at T2.	• The same findings were found using somatic/affective depression. • Using cognitive/affective depression, baseline illness perceptions only mediated the relationship with greater physical symptoms.
5.	Baseline CRP was associated with greater anxiety and greater affective pain at T2, after adjusting for total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
6.	Lower IL-6 responses 4-8 days after surgery and a lower change in IL-6 from baseline to 4-8 days post-surgery were associated with longer hospital stays, after adjusting for total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
7.	Greater CRP responses 4-8 days after surgery were associated with longer hospital stays, after adjusting for total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.

Illness perceptions were broadly predictive of the self-reported recovery outcomes, but not length of hospital stay. In particular, the specific illness perceptions of consequence, concern and emotional representation were the most relevant. These perceptions capture the emotional distress element of illness cognitions and so suggest that illness-specific distress prior to surgery led to greater anxiety, greater affective pain and greater physical symptoms, but not a longer post-operative hospital stay. The relationship between depression symptoms and the recovery outcomes was in large part explained by these greater distress perceptions. However, the depression symptoms-length of hospital stay relationship was not explained by illness perceptions, suggesting that depression symptoms acted independently from illness perceptions.

Baseline levels of cortisol were not significantly related to the recovery outcomes. Depressed participants did however have a higher cortisol output over the course of the day, but this higher cortisol AUC did not mediate the relationship depression symptoms had with

the recovery outcomes. The inflammatory markers also produced interesting results, with baseline depression symptoms being significantly related to IL-6 in the days after surgery, such that those participants with greater depression symptoms had higher levels of IL-6 shortly after surgery. However, in terms of recovery it was the IL-6 and CRP responses that happened in the latter part of the post-operative hospital stay that were associated with poorer recovery outcomes. These results indicated that those participants who had the lowest IL-6 responses and the highest CRP responses four to eight days after surgery had the longest hospital stays after surgery. Prospective associations were also shown for baseline CRP and recovery, such that higher CRP levels prior to surgery predicted greater anxiety, affective pain and physical symptoms scores at T2.

6.7.2 Analysis of results

6.7.2.1 Hypothesis 1: Depression symptoms and recovery

Hypothesis 1 stated that depression symptoms would be associated with impaired adaptation following CABG surgery and in particular that pre-operative somatic/affective depression symptoms would carry greater risk than no depression symptoms or cognitive/affective depression symptoms for poor adaptation during the in-hospital recovery period. This hypothesis was supported for the emotional distress outcome, such that pre-operative somatic/affective depression symptoms were a significant predictor of T2 anxiety, after controlling for covariates, while cognitive/affective depression symptoms were not. In terms of surgical recovery there was only limited evidence to suggest that somatic/affective depression symptoms were a better predictor of recovery than cognitive/affective depression. Indeed, somatic/affective, but not cognitive/affective depression symptoms were predictive of affective pain following surgery, but neither predicted sensory pain and both predicted physical symptoms. In addition, with regards to the clinical outcomes, both somatic/affective and cognitive/affective depression symptoms were predictive of a post-operative hospital stay of greater than one week. No significant findings were found for any of the other clinical recovery indices, probably due to a lack of cases on these endpoints.

The rationale for this hypothesis was based on evidence from MI patients where studies have found some types of symptoms to be more “cardiotoxic” than others, with somatic symptoms being particularly damaging (de Jonge, Ormel, et al., 2006; Doyle et al., 2010; Hoen et al., 2010; Linke et al., 2009; Martens et al., 2010; McGowan et al., 2004). However, the work using CABG patients has not been congruent with these findings in MI patients. One of the few studies to date which has begun to address these issues in CABG patients has been published recently (Connerney, Sloan, Shapiro, Bagiella, & Seckman, 2010). In a 10-year follow-up study of the original cohort (Connerney et al., 2001), cognitive/affective

but not somatic symptoms were predictive of cardiac mortality in models adjusted for confounders. These results have been supported by another recent study of morbidity and mortality in CABG patients, which also found cognitive depressive symptoms to be particularly damaging (Tully et al., 2011).

The results from this PhD were not able to add to the discussion of the effect of symptom subtypes of depression symptoms having differential effects on mortality, however the results do add to the discussion on impaired adaptation outcomes. Pre-CABG somatic/affective depression symptoms were shown to be a better predictor of distress outcomes, including anxiety and the distress component of physical pain, but there was no or little difference between somatic/affective and cognitive/affective depression symptoms in predicting the more physical outcomes, such as physical symptom reporting and length of hospital stay. Therefore, in the short term, it seems there was little difference between the depression symptom subtypes on predicting the hard clinical outcome, length of post-operative hospital stay.

It is important to note that length of post-operative hospital stay, while arguably the most policy relevant outcome, is only a proxy measure of recovery. Longer hospital stay is taken as a marker of poorer recovery in these analyses, but it is not clear to what extent this was always the case. For example, some participants may have been given bed-space for an extended period due to social reasons preventing their discharge. Moreover, re-admittance is also not captured; for example some participants may have been discharged early only to be readmitted for complications shortly again afterwards.

6.7.2.2 Hypothesis 2: Social-behavioural mechanisms

Hypothesis 2 stated that social-behavioural factors would affect the depression symptoms-poor adaptation relationship, in particular that patients who showed more negative health behaviours and lower social support before surgery would be more likely to have poorer emotional adaptation and recovery during the in-hospital recovery period. This hypothesis was partially upheld, such that lower physical activity prior to surgery was a significant predictor of greater anxiety after surgery in models controlling for covariates and all depression symptoms subtypes. Moreover, smoking was shown to be predictive of longer hospital stays, again after controlling for covariates and depression symptoms subtypes. Physical activity and smoking did not significantly predict the physical symptom recovery outcomes including pain and physical symptom reporting on the CROQ. In addition, no other social-behavioural factors were found to be significant predictors of poor recovery at T2 after adjusting for covariates, including BMI, alcohol intake, sleep and social support.

Health behaviours were hypothesised to be important to recovery outcomes since they have been shown to be related to both depression symptoms and cardiac outcomes. Physical activity has been shown to be an important component of cardiac rehabilitation after surgery, being associated with reduced total and cardiovascular mortality and hospital readmission (Heran et al., 2011). A recent study showed that the relationship between depressive symptoms and future cardiac events in patients with CHD was largely accounted for by poor health behaviours, particularly physical inactivity (Whooley et al., 2008). This PhD has shown that levels of pre-surgical physical activity, as measured by hours spent walking per week, were important for the distress outcomes after surgery. However, the results did not support the findings by Whooley and colleagues (Whooley et al., 2008) that physical activity acted as a mediator, since pre-operative depression symptoms were not associated with time spent walking.

The effect of other health behaviours, such as smoking, is less clear in the literature. For example, smokers were found to be at greater risk of pulmonary complication following CABG surgery, but not of in-hospital mortality (Al-Sarraf et al., 2008). In an eight-year follow-up study, smokers were found to be at lower risk of arrhythmia than non-smokers (Al-Sarraf et al., 2010). The study by Whooley and colleagues (Whooley et al., 2008) did show current smoking to partially mediate the association between depression symptoms and future cardiac events in patients with stable CHD. This PhD has shown smokers to have a longer in-hospital recovery period after CABG surgery, but mediation was not found since depression symptoms prior to surgery were not related to smoking.

6.7.2.3 Hypothesis 3: Cognitive mechanisms

Hypothesis 3 stated that cognitive factors would affect the depression symptoms-poor adaptation relationship, with patients who showed lower cognitive function and more negative illness perceptions before surgery being more likely to have poorer emotional adaptation and recovery during the in-hospital recovery period. In fact, lower cognitive function was not found to produce any significant results in these analyses, neither with depression symptoms nor the recovery outcomes. Therefore, there was no evidence to suggest that those participants with depression symptoms had lower cognitive function, or those participants with lower cognitive function had poorer recovery.

Previous literature has shown low levels of cognitive function to be associated with greater all-cause (Bosworth & Siegler, 2002) and cardiac mortality (Batterham et al., 2012). The relationship between neurocognitive function and mortality was not assessed in this PhD. Nevertheless, low cognitive function was predominant in the ARCS sample, with the majority of participants scoring below the threshold for normal performance. Previous literature has

pointed to deterioration in various neurocognitive processes following CABG, such as memory loss and difficulties with concentration and problem-solving. Both short- and long-term deficits in neurocognition have been observed in CABG patients. In a systematic review of studies using CABG patients, van Dijk and colleagues (van Dijk et al., 2000) reported pooled estimates showing on average, 22.5% of CABG patients had a cognitive deficit two months following surgery. Longer-term effects have also been observed, with a study of 261 (171 available at five years) CABG patients by Newman and colleagues (Newman et al., 2001) reporting cognitive decline in 42% of patients at five-year follow-up. However, in the ARCS study it is not clear to what extent deterioration in cognitive function from before to after surgery would have affected outcomes, since the MoCA was only administered at baseline.

Negative illness perceptions were shown to be relevant to both depression symptoms and the recovery outcomes. Both somatic/affective and cognitive/affective depression symptoms were related to greater negative illness perceptions and in turn greater negative illness perceptions were predictive of greater anxiety following surgery and greater physical symptoms after controlling for covariates. Total illness perceptions were not a significant predictor of T2 affective pain or length of post-operative hospital stay; however, the individual perceptions of consequences and emotional response were significant predictors of affective pain. Overall, the individual illness perceptions that were predictive of anxiety, affective pain and physical symptoms were related to illness-specific distress, suggesting that those participants who were most emotionally affected by their illness had poorer recovery.

These findings support previous literature which has shown negative illness perceptions to be associated with an array of poorer outcomes in the cardiac population, including greater illness related disability at home and at work (Petrie et al., 1996), reduced quality of life (French et al., 2005; Stafford et al., 2009), later return to work (Maeland & Havik, 1987; Petrie et al., 1996), increased fatigue (Alsén et al., 2010), and greater risk of in-hospital complications (Cherrington et al., 2004). Only two studies to date have examined these effects in cardiac surgery patients, the first of these studies showed pre-surgical negative illness perceptions predicted depression symptoms three months after surgery (Juergens et al., 2010). The second study reported associations between negative illness perceptions and greater psychological distress in patients before CABG (Hermele et al., 2007).

More recent evidence has proposed a mediation model in which negative illness perceptions mediate the relationship between depression symptoms and cardiac outcomes. Such a model suggests that depression symptoms lead to negative illness perceptions, which in turn are capable of affecting health outcomes. For example, in a study of 201 (25 depression symptoms cases) stable CHD outpatients who completed baseline and six-month follow-up assessments, the negative illness perceptions of consequences, identity, illness concern and

emotional representation were shown to partly mediate the prospective, negative, relationship between baseline depression symptoms and follow-up health related quality of life (Dickens, Cherrington, & McGowan, 2011).

Notably, the ARCS study is the first study to test the mediation model in CABG surgery patients. While this study did find evidence to support a mediation model of illness perceptions for depression symptoms and the self-reported recovery outcomes, this effect did not extend to length of hospital stay, suggesting that while depressed mood prior to surgery was capturing elements of illness-specific distress, it was not limited to this. Depression symptoms were more important than illness perceptions for predicting the length of the in-hospital recovery period.

6.7.2.4 Hypothesis 4: Biological mechanisms

Hypothesis 4 stated that biological factors affect the depression symptoms-poor adaptation relationship, with patients who show flatter cortisol before surgery and greater inflammatory responses in the days after surgery being more likely to show poorer emotional and physical recovery during the in-hospital period. The results produced limited support for this hypothesis, since cortisol slope was not associated with depression or the T2 recovery outcomes. Results did support previous research which has shown alterations in the diurnal profile of cortisol to be associated with depressed mood in patients with CHD (Bhattacharyya et al., 2008), since this study found depression symptoms were associated with a greater cortisol AUC. Previous literature has also shown that HPA axis dysregulation is associated with greater cardiac-related mortality in depressed patients (Jokinen & Nordström, 2009). There are limited studies investigating cortisol in CABG surgery patients, although there is some evidence that there is heightened cortisol output in the post-operative period (Roth-Isigkeit & Schmucker, 1997; Tønnesen et al., 1987) and one study found this pattern to be associated with post-operative complications, in particular delirium (Mu et al., 2010). However, none of the cortisol responses were related to any of the early-term recovery outcomes in this study, including the AUC, the awakening response and slope of cortisol across the day.

In relation to the inflammatory markers, more promising results were found, but they were in an inconsistent direction, such that lower post-surgery IL-6, but higher post-surgery CRP was associated with poorer recovery. In particular, lower IL-6 responses four to eight days following CABG were associated with a longer post-operative stay, while higher CRP responses at the same time were also predictive of a longer hospital stay. Interestingly, IL-6 and CRP T2 late responses were not correlated, while IL-6 T2 early and CRP T2 late responses were significantly associated. This suggests that timing of assessment is an important indicator of the interrelationship between inflammatory markers. However, the reason for this discrepancy

in inflammatory responses on recovery outcomes is not clear and has not been supported in previous literature. For example, an observational study of 29 cardiopulmonary bypass patients by Holmes and colleagues (Holmes et al., 2002) used a median split to compare outcomes between those patients who showed a heightened inflammatory response at four hours post-CABG, to those who did not. Findings showed that hyper-responders in IL-8, IL-6 and CR3 (an anaphylatoxin) had greater risk of adverse clinical outcomes. In addition, Kaireviciute and colleagues (Kaireviciute et al., 2010) have shown that perioperative measures of hs-CRP and IL-6 are associated with greater risk of atrial fibrillation post-operatively. It will be necessary to corroborate the IL-6 findings reported in this chapter with results from the short-term follow-up data in Chapter 7.

More recently, pre-operative CRP has been shown to predict adverse outcomes in CABG patients (De Lorenzo et al., 2012). These authors studied 76 patients who had CRP assessed prior to surgery, with results showing that those with elevated CRP (≥3 mg/l) had significantly greater risk of post-operative mortality; other work has replicated this finding (Perry et al., 2010). In this study, findings were in line with these results such that baseline CRP was predictive of greater anxiety, greater affective pain and greater physical symptoms after surgery, independent of covariates. Therefore, those participants with greater inflammation prior to surgery were more likely to report poorer self-reported outcomes after surgery. This effect did not mediate the relationship between depression symptoms and the recovery outcomes, since depression symptoms were not associated with baseline CRP after controlling for covariates.

6.8 Chapter summary

This chapter has assessed the relationship between pre-operative depression, including somatic/affective and cognitive/affective symptom subtypes, and emotional distress, physical symptoms and length of post-operative hospital stay recovery outcomes. In addition, mechanisms accounting for this relationship were explored, finding little evidence of social-behavioural or biological mediation. Illness perceptions were found to mediate the relationship between pre-operative depression symptoms and greater anxiety, physical symptoms and affective pain after surgery, but not length of post-operative hospital stay. Therefore, it appears depression symptoms exert a unique influence on early-term recovery not entirely explained by the mechanisms explored in this PhD.

Chapter 7. Results: Short-term outcomes

7.1 Introduction

The ARCS study began in February 2011 and data collection is on-going. The data presented in this chapter comprise the 154 participants (Figure 6.1) who had completed all three time points by June 2012. To reiterate, the aim of the ARCS study was to characterise the progression of patients from the pre-operative to post-operative phases of recovery following cardiac surgery. This PhD focuses on the relationship between depression symptoms and adaptation over time, and the underlying mechanistic pathways. Two main mechanisms are explored here in detail: biological and psychosocial. Chapter 6 presented results pertaining to early-term outcomes, as measured at baseline and T2. This chapter focuses on predictors of short-term recovery outcomes, occurring up to two months following surgery at T3. In this chapter, the demographic statistics are described, followed by descriptive statistics of predictor and outcome variables, covariates, and candidate mechanisms. Lastly, mediation analyses of associations between depression symptoms and recovery are presented. In particular, this chapter assesses the role of three possible mechanistic pathways: social-behavioural factors, cognition, and biology.

The specific hypotheses to be tested in this chapter are:

(1) Depression symptoms are associated with impaired adaptation following CABG surgery

i. Somatic/affective depression, persistent depression and post-CABG onset depression will carry greater risk than no depression symptoms, cognitive/affective depression symptoms and resolved depression for poor adaptation up to two months following surgery, including:
   a) Short-term emotional recovery such as anxiety,
   b) Short-term surgical recovery such as pain, physical symptom reporting,
   c) Short-term physical and mental adaptation,

   and these associations will be independent of demographic and clinical factors.

(2) Social-behavioural factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more negative health behaviours and lower social support before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:
   a) Short-term emotional recovery,
   b) Short-term surgical recovery,
   c) Short-term physical and mental adaptation,

   and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show lower social support before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:

a) Short-term emotional recovery,

b) Short-term surgical recovery,

c) Short-term physical and mental adaptation,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(3) Cognitive factors affect the depression symptoms-poor adaptation relationship

i. Patients who show more neurocognitive impairment before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:

a) Short-term emotional recovery,

b) Short-term surgical recovery,

c) Short-term physical and mental adaptation,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show more negative illness perceptions before surgery will be more likely to have poorer emotional adaptation and recovery up to two months following surgery, including:

a) Short-term emotional recovery,

b) Short-term surgical recovery,

c) Short-term physical and mental adaptation,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

(4) Biological factors affect the depression symptoms-poor adaptation relationship

i. Patients who show a flatter diurnal cortisol profile before surgery will be more likely to show poorer emotional and physical recovery up to two months following surgery, including:

a) Short-term emotional recovery,

b) Short-term surgical recovery,

c) Short-term physical and mental adaptation,

and this will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

ii. Patients who show greater inflammatory responses in the days after surgery will be more likely to show poorer emotional and physical recovery up to two months following surgery, including:

a) Short-term emotional recovery;
b) Short-term surgical recovery;
c) Short-term physical and mental adaptation;

and these factors will partly mediate the association between baseline depression symptoms and adaptation following cardiac surgery.

iii. Patients who show greater inflammatory responses in the days after surgery will be more likely to display greater depression symptoms up to two months following surgery.

7.2 Uptake, attrition and missing data

Due to attrition, the final total of participants who completed the questionnaires at all three time points was 154. On average, participants completed their baseline questionnaire 27.55 (SD = 27.92) days prior to surgery, had their T2 assessment on the cardiac care ward 4.45 (SD = 4.94) days after surgery, and filled in their T3 questionnaire approximately two months (mean = 60.77 days, SD = 28.62) following surgery. The time delay variables were not associated with either depression symptoms or recovery outcomes in regression analyses. Missing data on questionnaires meant analyses were performed on a reduced number of participants for some measures.

Details of the types of missing questionnaire data are provided in Table 7.1. This table (Table 7.1) also displays the Cronbach's alphas for each questionnaire measure, as applicable. As in Chapter 6, in questionnaires where respondents had provided valid responses on at least half the questionnaire items, data were scaled up (see Table 7.1). All analyses in this chapter were performed using the scaled-up data, to increase power. As discussed in Chapter 6, questions that were sensitive in nature, such as household income and libido on the BDI, may partly account for high levels of missing data on these scales. High rates of missing data on the MPQ-SF may be due to participants having difficulty completing this measure.

TABLE 7.1 MISSING QUESTIONNAIRE DATA IN T1-T3 ANALYTIC SAMPLE

Measure	*T1*			*T2*			*T3*		
	n	*α*	*S**	*n*	*α*	*S**	*n*	*α*	*S**
Socio-demographics									
Education	2	-	-	-	-	-	-	-	-
Income	7	-	-	-	-	-	-	-	-
Emotional distress									
Depression symptoms (BDI)	16	0.82	2	-	-	-	14	0.85	1
Anxiety (HADS subscale)	7	0.88	2	1	0.76	0	7	0.87	0
Health status									
Health status (SF-12) – Physical	0	0.65	-	-	-	-	1	0.47	1
Health status (SF-12) – Mental	1	0.53	1	-	-	-	1	0.65	1
Health behaviour									
Physical activity (IPAQ – walking)	11	-	-	-	-	-	7	-	-
Sleep (Jenkins Scale)	1	0.81	1	-	-	-	3	0.88	1
Cognitive factors									
Illness perceptions (BIPQ)	5	0.64	0	-	-	-	1	0.81	0
Cognitive screen (MoCA)	8	0.57	8	-	-	-	-	-	-
Social support									
Social support (ESSI)	4	0.90	2	-	-	-	5	0.91	5
Physical symptoms									
Pain (MPQ-SF) - Sensory	-	-	-	3	0.73	1	29	0.93	10
Pain (MPQ-SF) - Affective	-	-	-	1	0.50	1	16	0.81	11
Symptoms (CROQ-CABG)	-	-	-	10	0.57	0	6	0.79	0

*S: Scaled-up data to account for missing values.

7.3 Sample characteristics

Table 7.2 describes the characteristics of the T1-T3 analytic sample (n = 154), respectively, at baseline. Please refer to Table 4.3 in Chapter 6 for details of the entire sample. The analytic sample had an age range between 44 to 88 years, was predominantly male (85.1%) and overweight (body mass index, BMI, >25.0 = 77.9%). The majority of participants were retired (63.4%), three participants were registered disabled and seven participants were unemployed. The majority of the analytic sample had either no or only secondary educational qualifications

(70.5%). Over 50% of participants were past-smokers, but only a minority were current smokers (7.2%). The majority of participants (90.0% of men and 95.7% of women) adhered to UK government guidelines concerning alcohol consumption which for men equates to a maximum of 28 units per week and for women are no more than 21 units per week.

TABLE 7.2: CHARACTERISTICS OF THE T1-T3 ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	154	68.31±9.11
Female	154	23 (14.9)
BMI (kg/m^2)	154	27.97±3.76
Married/cohabiting	154	118 (76.6)
Ethnicity – White British/other White	154	134 (87.0)
Tobacco smoking		
Never	153	55 (35.9)
Past		87 (56.9)
Current		11 (7.2)
Alcohol consumption (units/week)	153	9.63±13.86
Currently employed	153	46 (30.1)
Employment grade of current/last major occupation		
Unemployed/disabled	148	10 (6.8)
Managers, directors and senior officials		28 (18.9)
Professional		32 (21.6)
Associate professional and technical		19 (12.8)
Administrative and secretarial		9 (6.1)
Skilled trades		11 (7.4)
Caring, leisure and other service		8 (5.4)
Sales and customer service		8 (5.4)
Process, plant and machine operatives		14 (9.5)
Elementary		9 (6.1)
Yearly household income		
≤ 10,000 GBP	147	21 (14.3)
10,000 – 20,000 GBP		44 (29.9)
20,000 – 30,000 GBP		35 (23.8)
30,000 – 40,000 GBP		20 (13.6)
≥40,000		27 (18.4)
Education		
None	146	44 (30.1)
Secondary		59 (40.4)
Higher secondary		19 (13.0)
Degree		24 (16.4)

TABLE 7.3: CLINICAL CHARACTERISTICS OF THE T1-T3 ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*n (%)*
*Co-morbidities**		
Diabetes	154	36 (23.4)
Renal failure (requiring dialysis)	154	2 (1.3)
Chronic respiratory disease	154	9 (5.8)
Cancer (self-reported)		
Colon	149	1 (0.7)
Prostate		2 (1.3)
Breast		1 (0.7)
Bladder		1 (0.7)
*Psychiatric history**		
History of depression	145	23 (15.9)
History of anxiety disorder	146	19 (13.0)
Current treatment for depression	145	5 (3.4)
Current treatment for anxiety	146	1 (0.7)
Cardiac morbidity		
Hypertension	154	122 (79.2)
Angina		
None	154	5 (3.2)
No limitation		38 (24.7)
Slight limitation		84 (54.5)
Marked limitation		26 (16.9)
Symptoms at rest		1 (0.6)
Dyspnoea		
None	154	34 (22.1)
Slight		96 (62.3)
Moderate		24 (15.6)
Previous MI		
None	154	107 (69.5)
1		45 (29.2)
2 or more		2 (1.3)
Disease severity		
Ejection fraction < 50	154	18 (11.7)
Logistic euroSCORE (%)		
<3.0	154	63 (40.9)
3.0-6.0		55 (35.7)
6.1-9.0		24 (15.6)
9.1-12.0		5 (3.2)
>12.0		7 (4.5)

Surgical details		
Off-pump	154	33 (21.4)
CABG in isolation	154	118 (76.6)
Graft sites 1-2 3-4 5+	154	 52 (33.8) 88 (57.1) 14 (9.1)
Post-operative recovery		
Intensive care stay > 2 days	154	15 (9.7)
Intensive care re-admittance	154	2 (1.3)
Length of post-operative stay ≤7 days >7 days	154	 113 (73.4) 41 (26.6)
Reoperation necessary	154	6 (3.9)
Post-operative complications Post-operative dialysis	154	 3 (1.9)
Cardiac rehabilitation		
Attended cardiac rehabilitation	149	44 (29.5)

*Absolute number of cases in sample.

Clinical data of the analytic sample is displayed in Table 7.3. Co-morbidities were prevalent in the analytic sample, with almost a quarter (23.4%) of participants having a diagnosis of diabetes. In terms of psychiatric morbidity, 15.9% of participants reported a history of depression, but only 3.4% were being treated for depression symptoms in the four weeks prior to CABG surgery. The association between depression symptoms and use of antidepressant medication was checked in Pearson's correlations, but there were no significant associations between total BDI scores, somatic/affective depression symptom scores, cognitive affective depression symptom scores and use of antidepressant medications at T1 or T3. Therefore, these participants were retained in analyses. The majority of participants had on-pump (cardiopulmonary bypass) surgery (78.6%) in isolation. Three participants required dialysis post-operatively. All participants were alive on discharge. No deaths occurred between the in-hospital follow-up at T2 and the two-month post-surgery follow-up at T3.

Cross-tabulations were performed on age, total yearly household income, education and sex, to compare the characteristics of those who completed all three time points (n = 154) to those who did not (n = 89). Age was converted to a categorical variable for chi-squared analysis (<50 years, 50-60 years, 60-70 years, 70-80 years, >80 years). There was no statistical difference between completers and non-completers in terms of age groups (χ^2 = 3.847, df = 4, n = 243, p = 0.427). This was confirmed in an independent t-test of mean age (t = 0.789, p = 0.420). There was no significant difference between completers and non-completers in terms

of income groups (χ^2 = 3.805, df = 4, n = 228, p = 0.433), education groups (χ^2 = 0.554, df = 3, n = 228, p = 0.907), and sex (χ^2 = 0.658, df = 1, n = 243, p = 0.417). Markers of disease severity did also not significantly differ between completers and non-completers in terms of both euroSCORE groups (χ^2 = 2.331, df = 4, n = 223, p = 0.675) and LVEF (χ^2 = 0.114, df = 1, n = 223, p = 0.736); cut-offs for these variables are displayed in Table 7.3. In addition, an independent samples *t*-test for mean euroSCORE values, using the continuous score, confirmed this lack of difference between completers (M: 4.47, SD: 2.98) and non-completers (M: 4.47, SD: 3.61) (t = 0.008, p = 0.994).

Kolmogorov-Smirnov tests were performed revealing scores on all continuous measures apart from the BIPQ (T1 and T3) and the SF-12 physical (T1) to be non-normally distributed (p > 0.05). Both non-parametric and parametric tests were performed on the data, but since results were similar, the parametric results are presented here. Distribution of the biological data was also tested using Kolmogorov-Smirnov tests and raw data were assessed for log transformation, however in order to keep in the full range of responses on the biological measures, and to retain those participants who had extreme responses, the raw data was used for both cortisol and inflammatory marker measures. In addition, this ensures the unit of measurement is preserved, maintaining the clinical relevance of the results. Correlation analyses were used throughout to assess the assumption of multicollinearity, prior to using regression analyses. Multicollinearity assumptions were not violated since all correlation coefficients were <0.80.

7.4 Descriptive analyses of depression symptom and recovery measures

7.4.1 Depression symptoms at T1 and T3

A summary of the depression symptom scores are displayed in Table 7.4, with *p* representing the significance value of dependent *t*-tests. Total, somatic/affective and cognitive/affective scores on the BDI were used as predictor variables in analyses of the relationship between depression symptoms and recovery over time. Please note that this table displays the values on the BDI in accordance with the BDI handbook severity cut-offs. Baseline (>10 = 27.8%) and T3 (>10 = 20.4%) values of the BDI revealed the majority of participants were within the normal range for depression symptom scores. Dependent *t*-tests were performed to examine the change in depression symptom scores over time, with results showing a significant decrease in depression symptoms for BDI total, somatic/affective and cognitive/affective scores. However, as described in the method chapter (Chapter 3), to examine caseness on the BDI, a binary cut-off was implemented at a conservative ≥13 to maximise the specificity of this measure (Gutierrez & Davis, 1999). Using this cut-off, 18.4% of participants were classified as

depressed at baseline, and 15.0% of participants were depressed at T3. To examine caseness depression on the BDI over time, four groups were created in order to examine the pattern of depression symptoms from T1 to T3. Results from these analyses are shown in Table 7.5, revealing that 8.0% of participants can be classified as having depression that persists to T3. A further 10.0% of participants had depression that had resolved by T3, and 7.3% of participants had post-CABG onset depression.

In conjunction with scores on the BDI, self-reported history of depression was also examined, in order to assess the frequency of depression caseness on the BDI and a positive history of diagnosed depression. Fourteen participants (12.5%) who were never depressed according to the BDI reported a history of depression. In addition, three participants in each of the depressed groups, resolved (20.0%), persistent (25.0%), post-CABG onset (27.2%), had a positive depression history.

TABLE 7.4: T1 AND T3 DEPRESSION SYMPTOM SCORES

Measure	*N*	*T1* *Mean ± SD or n (%)*	*T3* *Mean ± SD or n (%)*	*p*
Total BDI	151	8.43±6.05	7.04±5.98	0.008
Total cognitive/affective BDI	153	2.78±3.75	2.21±3.33	0.043
Total somatic/affective BDI	150	6.91±4.40	5.48±4.55	<0.001
Normal (0-10)	151	109 (72.2)	121 (79.6)*	-
Mild (11-16)	151	29 (19.2)	19 (12.5)*	-
Borderline clinical (17-20)	151	7 (4.6)	6 (3.9)*	-
Moderate (21-30)	151	5 (3.3)	5 (3.3)*	-
Severe (31-40)	151	1 (0.7)	1 (0.7)*	-
Extreme (41-63)	151	-	-	-

**N* = 152

TABLE 7.5: DEPRESSION TYPE ACCORDING TO TIME POINT

Depression type	*BDI ≥ 13*		*n* (%)
	T1	*T3*	
Never depressed	x	x	112 (74.7)
Post-CABG onset	x	✓	11 (7.3)
Persistent	✓	✓	12 (8.0)
Resolved	✓	x	15 (10.0)

7.4.2 Short-term recovery outcome variables

Three different types of recovery were assessed at T3: emotional distress, physical symptom measures and health status. Descriptive analyses of these measures at T1, T2 and T3 are presented in Table 7.6. Although data are presented at each time point a measure was used, this is merely to describe these measures; only the T3 data were used as a recovery endpoint in this chapter. The in-hospital endpoints were included as early-term outcomes in Chapter 6, and will not be covered here. Dependent *t*-tests were performed to assess change in variables over time.

TABLE 7.6: RECOVERY OUTCOME MEASURES ACROSS TIME

Measure	*N*	*T1* *Mean ± SD*	*T2* *Mean ± SD*	*T3* *Mean ± SD*	*p*
Emotional distress					
Anxiety total (T1-T2)	152	5.83±4.22	4.53±3.86	-	<0.001
Anxiety total (T1-T3)	152	5.83±4.22	-	4.06±3.68	<0.001
Anxiety total (T2-T3)	154	-	4.51±3.84	4.03±3.66	0.159
Anxiety normal (≤7)	152	106 (69.7)	123 (79.9)*	133 (86.4)*	-
Anxiety borderline (8-10)	152	25 (16.4)	20 (13.0)*	8 (95.2)*	-
Anxiety caseness (≥11)	152	21 (13.8)	11 (7.1)*	13 (8.4)*	-
Physical symptoms					
Pain - Sensory	143	-	5.26±4.61	4.76±6.32	0.378
Pain - Affective	142	-	1.22±1.78	1.26±2.13	0.845
Pain – Numerical rating scale	152	-	3.44±2.47	2.41±2.23	<0.001
Pain – Current descriptor	151	-	1.55±0.96	1.00±0.94	<0.001
Symptoms (CROQ-CABG)	154	-	8.75±4.58	14.68±7.58	<0.001
Health status					
Health status (SF-12) – Physical	153	39.35±10.61	-	35.36±8.35	0.001
Health status (SF-12) – Mental	152	56.67±6.27	-	57.83±6.97	0.059

N = 154.

The emotional distress measure used in these analyses was anxiety. Dependent *t*-tests were performed on means scores for anxiety over time, revealing a significant decrease from T1 to T2 and from T1 to T3. T2 and T3 anxiety scores did not significantly differ. The majority of participants were free from anxiety at all three time points, with only 7.1% and 8.4% of participants being clinically anxious (≥11) at T2 and T3, respectively. To examine borderline to caseness anxiety on the HADS, a binary cut-off was implemented in accordance with previous

literature at ≥8. Four groups were created in order to examine the pattern of anxiety across time. Results from these analyses are shown in Table 7.7, revealing that 9.9% of participants can be classified as having anxiety that persists to T3. A further 20.4% of participants had anxiety that had resolved by T2. Only nine (3.9%) participants had post-CABG onset anxiety.

Physical symptoms were measured using the CROQ symptom subscale and the MPQ-SF. In terms of physical recovery, the majority of participants experienced physical pain and discomfort at T2, with only 10.5% of participants reporting no sensory pain at T2. Affective pain was reported in just under half (42.5%) of participants. At T3, mean pain scores were lower than at T2 on sensory measures, but this did not reach statistical significance. In addition, affective pain did not significantly change from T2 to T3. The reduction in pain over time was, however, reflected in scores on the numerical rating scale and the current pain descriptor score. Since the sensory and affective pain scores capture a wide array of pain symptoms, these scores were used in all further analyses, rather than the numerical rating scale and the current pain descriptor scores. Physical symptoms, as measured by the CROQ, were also frequently reported following surgery, with significantly higher mean scores at T3 than at T2 (Table 7.8). Feelings of pain around the surgical wound sites were frequently reported at both time points, and at T3 participants were likely to report bruising, infection and numbness and tingling. This observed increase in physical symptom reporting over time corroborates the findings from the pilot study.

Health status was measured using the SF-12 to generate mental and physical health status scores. These scores show that participants reported significantly poorer physical health status at T3, compared with T1. Mental health status slightly improved following surgery, but this was not significant. This latter finding is in line with the data showing a decrease in BDI mean score over time (see Table 7.4).

TABLE 7.7: ANXIETY TYPE ACCORDING TO TIME POINT

Anxiety type	*HADS ≥ 8*		*n* (%)
	T1	*T3*	
Never anxious	x	x	100 (65.8)
Post-CABG onset	x	✓	9 (3.9)
Persistent	✓	✓	15 (9.9)
Resolved	✓	x	31 (20.4)

TABLE 7.8: FREQUENCY OF CROQ PHYSICAL SYMPTOMS AT T2 AND T3

Symptom severity (*Moderate* to *A lot*)	*T2*		*T3*	
	N	*n (%)*	*N*	*n (%)*
Pain in chest wound	154	94 (61.0)	154	83 (53.9)
Infection in chest wound	154	4 (2.6)	154	15 (9.7)
Tenderness around chest wound	154	87 (56.5)	154	87 (56.5)
Numbness/tingling around chest wound	154	10 (6.5)	154	54 (35.1)
Bruising around chest wound	154	14 (9.1)	154	29 (18.8)
Pain in arm/leg wound	147	55 (37.4)	153	75 (49.0)
Other pain in arm/leg due to operation	147	8 (5.4)	153	52 (34.0)
Infection in arm/leg wound	147	1 (0.7)	153	42 (27.5)
Numbness/tingling in arm/leg due to operation	146	14 (9.6)	153	81 (52.9)
Bruising arm/leg where vein was removed	147	35 (23.8)	153	62 (40.5)
Swollen feet/ankles	154	66 (42.9)	149	82 (55.0)

7.4.3 Covariates of the depression symptoms-recovery relationship

Covariates are factors associated with the outcome variable, other than the predictor variable of interest. Potential covariates of the depression symptoms-recovery relationship were identified in the literature review and include both demographic and clinical factors. For ease of reference the demographic covariates are presented again here in Table 7.9; they include age, sex, and socioeconomic status as measured by education, occupation level and household income. Disease severity, including LVEF and euroSCORE were also considered as covariates, and are again presented in Table 7.9. To clarify, LVEF was used as a binary variable (<50 or ≥50) and logistic euroSCORE was used as a continuous variable. Other clinical factors such as medication use and co-morbidities may also play a role in recovery and were also considered as potential covariates. Pre- and post-operative medication usage is displayed in Table 7.10, demonstrating ACE inhibitors, aspirin, statins and beta-blockers were frequently prescribed both before and after CABG surgery. In addition, following surgery roughly one-third (30.7%) of patients were taking prescribed analgesic medication.

Although primary identification of covariates has been theory driven, in order to create a parsimonious model of the depression symptoms-recovery relationship, some tailoring was required to identify those covariates applicable to recovery in my sample. This was necessary since the ARCS study was powered to include nine predictor variables. The potential covariates were entered into correlation analyses in order to identify those variables which were strongly related to the T3 outcome variables.

TABLE 7.9: CHARACTERISTICS OF THE T1-T3 ANALYTIC SAMPLE AT BASELINE

Characteristic	*N*	*Mean ± SD or n (%)*
Age (years)	154	68.31±9.11
Female	154	23 (14.9)
Employment grade of current/last major occupation		
Unemployed/disabled		10 (6.8)
Managers, directors and senior officials		28 (18.9)
Professional		32 (21.6)
Associate professional and technical		19 (12.8)
Administrative and secretarial	148	9 (6.1)
Skilled trades		11 (7.4)
Caring, leisure and other service		8 (5.4)
Sales and customer service		8 (5.4)
Process, plant and machine operatives		14 (9.5)
Elementary		9 (6.1)
Yearly household income		
≤ 10,000 GBP		21 (14.3)
10,000 – 20,000 GBP	147	44 (29.9)
20,000 – 30,000 GBP		35 (23.8)
30,000 – 40,000 GBP		20 (13.6)
≥40,000		27 (18.4)
Education		
None		44 (30.1)
Secondary	146	59 (40.4)
Higher secondary		19 (13.0)
Degree		24 (16.4)
Ejection fraction < 50	154	18 (11.7)
Logistic euroSCORE (%)	154	4.49±3.00

Results of the correlation analyses offer some insight into the covariates applicable to the depression symptoms-recovery relationship in this sample. In correlation analyses, age, sex, occupation level, euroSCORE and LVEF failed to show any significant associations with T3 recovery. Out of the three markers of socioeconomic position considered as potential covariates (education, occupation level and household income), total household income (r = -0.227, p = 0.006) and education (r = -0.183, p = 0.027) were both significantly related to T3 physical symptoms; these associations were negative such that those participants with lower income/education had greater symptoms. Associations between use of medications and co-morbidities and outcome variables were also performed, with no significant associations found.

Household income was used as a proxy measure of socioeconomic status in analyses, rather than education or occupation level, since this produced the strongest significant association with T3 physical symptoms and because it was significantly correlated to both

education (r = 0.223, p = 0.008) and occupation (r = -0.357, p <0.001). Due to the fact that euroSCORE and LVEF were correlated (r = 0.247, p = 0.002) and euroSCORE actually takes into account LVEF, only euroSCORE was included in mediation models as a marker of disease severity.

TABLE 7.10: PRE- AND POST-OPERATIVE PRESCRIBED MEDICATION USE

Medication	*N*	*n (%)*
Pre-operative (T1)		
ACE inhibitors	142	76 (53.5)
Angiotensin II receptor antagonist	142	18 (12.7)
Anti-arrhythmia	142	3 (2.1)
Antibiotic	142	2 (1.4)
Anticoagulant	142	6 (4.2)
Antiplatelet	142	42 (29.6)
Aspirin	148	119 (80.4)
Beta-blockers	142	88 (62.0)
Calcium channel blocker	142	44 (31.0)
Nitrate	142	45 (31.7)
NSAID	142	22 (15.5)
Sleeping tablet	142	4 (2.8)
Statins	142	125 (88.0)
Post-operative (T3)		
ACE inhibitors	137	64 (46.7)
Angiotensin II receptor antagonist	137	16 (11.7)
Anti-arrhythmia	137	25 (18.2)
Antibiotic	137	13 (9.5)
Anticoagulant	137	24 (17.5)
Antiplatelet	137	13 (9.5)
Aspirin	141	118 (83.7)
Beta-blockers	137	111 (81.0)
Calcium channel blocker	137	11 (8.0)
Nitrate	137	3 (2.2)
NSAID	137	42 (30.7)
Sleeping tablet	137	1 (0.7)
Statins	137	120 (87.6)

7.5 Depression symptoms predicting short-term recovery

In order to examine the recovery outcomes in relation to depression, analyses were performed between depression symptom subtype scores at baseline and the emotional distress, health status and physical symptom recovery outcomes at T3. Depression symptoms were coded into three types: total BDI score, somatic/affective BDI symptom score and cognitive/affective BDI symptom score. Multiple regression analyses were performed in order to assess the relationship between depression symptom subtype and recovery outcomes after controlling for demographic and disease severity covariates, as well as baseline measures of the outcome variable for the anxiety and health status outcomes.

7.5.1 Emotional distress

Multiple regression analyses were performed using T3 anxiety (two months following surgery), as measured on the HADS, as the outcome variable. Total BDI (t = 1.202, p = 0.231) and cognitive/affective (t = 0.389, p = 0.698) depression symptom scores were not significant predictors of T3 anxiety after controlling for baseline anxiety and demographic and disease severity covariates. However, baseline somatic/affective depression symptoms (t = 1.953, p = 0.053) reached borderline statistical significance; results are displayed in Table 7.11. The significant predictors in this model were baseline anxiety (t = 5.213, p <0.001) and household income (t = -2.300, p = 0.023), such that those participants with greater pre-operative anxiety and a lower annual income, had greater anxiety two months after their surgery. The final model accounted for 35.3% of variance (R^2 = 0.353) in T3 anxiety scores. In summary, these results suggest that greater pre-operative somatic/affective depression symptoms were a borderline predictor of T3 emotional distress.

TABLE 7.11: MULTIPLE REGRESSION OF T3 ANXIETY ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.030	0.043	-0.076	0.486
Sex	-1.050	0.820	-0.099	0.203
Household income	-0.455	0.198	-0.167	0.023
euroSCORE	0.100	0.140	0.082	0.475
T1 Anxiety	0.386	0.074	0.443	<0.001
T1 BDI somatic	0.137	0.070	0.166	0.053

R^2 = 0.353, N = 143

7.5.2 Physical symptoms

Pain

Multiple regression analyses were performed using T3 sensory pain, as measured on the MPQ-SF, as the outcome variable. Total BDI (t = 1.838, p = 0.068) and cognitive/affective (t = 0.551, p = 0.582) depression symptom scores were not significant predictors of T3 sensory pain after controlling for demographic and disease severity covariates. However, baseline somatic/affective depression symptoms (t = 2.212, p = 0.029) reached statistical significance; results are displayed in Table 7.12. There were no other significant predictors in this model. The final model accounted for 6.3% of variance (R^2 = 0.063) in T3 sensory pain scores. In summary, these results suggest that only baseline somatic/affective depression symptom subtype was an important predictor of T3 sensory pain.

TABLE 7.12: MULTIPLE REGRESSION OF T3 SENSORY PAIN ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.032	0.098	0.046	0.744
Sex	2.192	1.823	0.111	0.232
Household income	-0.501	0.430	-0.104	0.246
euroSCORE	-0.115	0.310	-0.054	0.711
T1 BDI somatic	0.300	0.136	0.193	0.029

R^2 = 0.063, N = 136

Multiple regression analyses were also performed using T3 affective pain, as measured on the MPQ-SF, as the outcome variable. Total BDI (t = 1.870, p = 0.064) and cognitive/affective (t = 0.695, p = 0.488) depression symptom scores at baseline were not significant predictors of T3 affective pain after controlling for demographic and disease severity covariates. However, baseline somatic/affective depression symptoms (t = 2.672, p = 0.009) reached statistical significance; results are displayed in Table 7.13. There were no other significant predictors in this model. The final model accounted for a relatively small amount of variance (R^2 = 0.029) in T3 affective pain scores. In summary, these results suggest that only the somatic/affective depression symptom subtype was an important predictor of T3 affective pain.

TABLE 7.13: MULTIPLE REGRESSION OF T3 AFFECTIVE PAIN ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.000	0.033	0.002	0.991
Sex	-0.476	0.629	-0.069	0.451
Household income	-0.135	0.146	-0.083	0.355
euroSCORE	-0.023	0.106	-0.031	0.827
T1 BDI somatic	0.123	0.046	0.233	0.009

R^2 = 0.029, *N* = 135

Physical symptoms

Multiple regression analyses were also performed using T3 physical symptoms, as measured on the CROQ, as the outcome variable. Baseline total BDI (*t* = 1.846, *p* = 0.067) and cognitive/affective (*t* = 0.856, *p* = 0.393) depression symptom scores were not significant predictors of T3 physical symptoms after controlling for demographic and disease severity covariates. However, baseline somatic/affective depression symptoms (*t* = 2.352, *p* = 0.020) reached statistical significance; results are displayed in Table 7.14. The only other significant predictor in this model was household income (*t* = -2.477, *p* = 0.014), such that participants with a lower annual income had greater physical symptoms after surgery. The final model accounted for 9.1% of variance (R^2 = 0.091) in T3 CROQ physical symptom scores.

In summary, these results suggest that somatic/affective depression symptoms prior to surgery were the most important for predicting greater physical symptoms two months after surgery. Neither total BDI score, nor cognitive/affective depression symptom score were significant predictors of any of the physical symptom recovery endpoints at T3.

TABLE 7.14: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.068	0.108	0.081	0.528
Sex	0.351	2.046	0.015	0.864
Household income	-1.230	0.496	-0.212	0.014
euroSCORE	-0.126	0.340	-0.050	0.712
T1 BDI somatic	0.351	0.149	0.197	0.020

R^2 = 0.091, *N* = 145

7.5.3 Health status

Multiple regression analyses were performed using T3 physical health status, as measured on the SF-12, as the outcome variable. Total BDI (t = -1.939, p = 0.055) and cognitive/affective (t = -1.084, p = 0.280) depression symptom scores at baseline were not significant predictors of T3 physical health status after controlling for baseline physical health status and demographic and disease severity covariates. However, baseline somatic/affective depression symptoms (t = -2.511, p = 0.013) reached statistical significance; results are displayed in Table 7.15. This association was negative such that higher depression symptom scores predicted lower health status following surgery. Interestingly, there were no other significant predictors in this model, not even baseline SF-12 scores (t = 0.177, p = 0.860). The final model accounted for 9.8% of variance (R^2 = 0.098) in T3 physical health status scores. No significant associations were found between baseline depression symptoms and mental health status scores at T3, after controlling for covariates and baseline measures of these scales.

TABLE 7.15: MULTIPLE REGRESSION OF T3 PHYSICAL HEALTH STATUS ON T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.176	0.119	-0.195	0.144
Sex	-4.221	2.241	-0.174	0.062
Household income	0.132	0.536	0.021	0.806
euroSCORE	0.875	0.369	0.326	0.019
T1 Physical health status	0.013	0.071	0.016	0.860
T1 BDI somatic	-0.431	0.172	-0.227	0.013

R^2 = 0.098, N = 144

7.6 Depression onset predicting short-term recovery

In order to examine the recovery outcomes in relation to depression, analyses were also performed between depression onset subtypes and the emotional distress, health status and physical symptom recovery outcomes at T3. Depression caseness was categorised into binary variables (yes/no) based on the timing and recurrence of the depressive episode: resolved, persistent and post-CABG onset. To recapitulate, resolved depression participants were depressed at T1 (BDI ≥13), but not at T3, indicating a transient depressive episode. Persistent depressed participants were depressed at both T1 and T3 (BDI ≥13), indicating a persistent or chronic depressive episode. Finally, post-CABG depressed participants were depressed at T3 but not at T1. These were all coded as dummy variables based on the presence or absence of the depression subtype (yes/no).

Multiple regression analyses were performed in order to assess the relationship between depression symptoms onset subtype and recovery outcomes after controlling for demographic and disease severity covariates, as well as baseline measures of the outcome variable for the anxiety and health status outcomes. Importantly, each onset subtype was studied in turn; for example, in the resolved depression analyses, participants with persistent and post-CABG onset depression were excluded. This enabled comparisons to be made between the presence of each depression subtype and never depressed participants.

7.6.1 Emotional distress

Multiple regression analyses were performed using T3 anxiety, as measured on the HADS, as the outcome variable. Resolved depression (t = -1.177, p = 0.242) was not significantly associated with T3 anxiety after controlling for baseline anxiety and demographic and disease severity covariates. However, persistent depression (t = 5.952, p <0.001) was statistically significant; results are displayed in Table 7.16. This relationship was positive such that the presence of persistent depression was significantly associated with greater anxiety two months after surgery, compared to those who were never depressed. The only other significant predictors in this model were baseline anxiety (t = 6.863, p <0.001) and household income (t = -2.015, p = 0.046), such that those participants with greater pre-operative anxiety and a lower annual income had greater anxiety two months after their surgery. The model accounted for 59.0% of variance (R^2 = 0.590) in T3 anxiety scores.

TABLE 7.16: MULTIPLE REGRESSION OF T3 ANXIETY ON PERSISTENT DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.023	0.035	0.061	0.519
Sex	-0.358	0.651	-0.038	0.583
Household income	-0.326	0.162	-0.130	0.046
euroSCORE	-0.033	0.110	-0.030	0.766
T1 Anxiety	0.387	0.056	0.470	<0.001
Depression persistent	4.613	0.775	0.414	<0.001

R^2 = 0.590, N = 116

In addition, post-CABG onset depression (t = 8.921, p <0.001) was also statistically significant in regression models; results are displayed in Table 7.17. This relationship was positive such that the presence of post-CABG onset depression was significantly associated with greater anxiety two months after surgery, compared to those who were never depressed. The only other significant predictors in this model were baseline anxiety (t = 7.196, p <0.001) and household income (t = -2.751, p = 0.007), such that those participants with greater pre-

operative anxiety and a lower annual income had greater anxiety two months after their surgery. The model accounted for 58.3% of variance (R^2 = 0.583) in T3 anxiety scores.

TABLE 7.17: MULTIPLE REGRESSION OF T3 ANXIETY ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.009	0.034	0.024	0.796
Sex	-0.185	0.687	-0.019	0.788
Household income	-0.450	0.163	-0.179	0.007
euroSCORE	-0.055	0.109	-0.050	0.618
T1 Anxiety	0.417	0.058	0.452	<0.001
Depression post-CABG onset	6.175	0.692	0.558	<0.001

R^2 = 0.583, N = 116

7.6.2 Physical symptoms

Sensory pain

Multiple regression analyses were performed using T3 sensory pain, as measured on the MPQ-SF, as the outcome variable. Resolved depression (t = 1.161, p = 0.248) was not significantly associated with T3 sensory pain after controlling for demographic and disease severity covariates. However, persistent depression (t = 2.458, p = 0.016) was statistically significant; results are displayed in Table 7.18. This relationship was positive such that the presence of persistent depression was significantly associated with greater sensory pain two months after surgery, compared to those who were never depressed. There were no other significant predictors in this model. The model accounted for 10.0% of variance (R^2 = 0.100) in T3 sensory pain scores.

TABLE 7.18: MULTIPLE REGRESSION OF T3 SENSORY PAIN ON PERSISTENT DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.095	0.093	0.153	0.312
Sex	1.721	1.650	0.104	0.299
Household income	-0.592	0.411	-0.141	0.152
euroSCORE	-0.339	0.282	-0.186	0.231
Depression persistent	4.568	1.858	0.238	0.016

R^2 = 0.100, N = 112

In addition, post-CABG onset depression (t = 4.908, p <0.001) was also statistically significant in regression models; results are displayed in Table 7.19. This relationship was

positive such that the presence of post-CABG onset depression was significantly associated with greater sensory pain two months after surgery, compared to those who were never depressed. There were no other significant predictors in this model. The model accounted for 24.0% of variance (R^2 = 0.240) in T3 sensory pain scores.

TABLE 7.19: MULTIPLE REGRESSION OF T3 SENSORY PAIN ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.118	0.093	0.170	0.206
Sex	4.090	1.751	0.220	0.021
Household income	-0.797	0.428	-0.167	0.065
euroSCORE	-0.553	0.286	-0.271	0.056
Depression post-CABG onset	9.055	1.845	0.420	<0.001

R^2 = 0.240, *N* = 112

Affective pain

Multiple regression analyses were performed using T3 affective pain, as measured on the MPQ-SF, as the outcome variable. Resolved depression (t = 0.841, p = 0.402) was not significantly associated with T3 affective pain after controlling for demographic and disease severity covariates. However, persistent depression (t = 3.628, p <0.001) was statistically significant; results are displayed in Table 7.20. This relationship was positive such that the presence of persistent depression was significantly associated with greater affective pain two months after surgery, compared to those who were never depressed. There were no other significant predictors in this model. The model accounted for 13.7% of variance (R^2 = 0.137) in T3 affective pain scores.

In addition, post-CABG onset depression (t = 5.782, p <0.001) was also statistically significant in regression models; results are displayed in Table 7.21. This relationship was positive such that the presence of post-CABG onset depression was significantly associated with greater affective pain two months after surgery, compared to those who were never depressed. There were no other significant predictors in this model. The model accounted for 26.1% of variance (R^2 = 0.261) in T3 affective pain scores.

TABLE 7.20: MULTIPLE REGRESSION OF T3 AFFECTIVE PAIN ON PERSISTENT DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.003	0.032	0.014	0.923
Sex	-0.155	0.574	-0.026	0.788
Household income	-0.132	0.143	-0.088	0.359
euroSCORE	-0.016	0.098	-0.025	0.868
Depression persistent	2.347	0.647	0.344	<0.001

R^2 = 0.137, *N* = 112

TABLE 7.21: MULTIPLE REGRESSION OF T3 AFFECTIVE PAIN ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.025	0.030	0.112	0.401
Sex	0.222	0.568	0.036	0.698
Household income	-0.176	0.136	-0.115	0.198
euroSCORE	-0.143	0.091	-0.216	0.120
Depression post-CABG onset	3.560	0.616	0.492	<0.001

R^2 = 0.261, *N* = 111

Physical symptoms

Next, multiple regression analyses were performed using T3 physical symptoms, as measured on the CROQ, as the outcome variable. Resolved depression (t = 0.030, p = 0.976) was not significantly associated with T3 physical symptoms after controlling for demographic and disease severity covariates. However, persistent depression (t = 0.191, p = 0.042) was statistically significant; results are displayed in Table 7.22. This relationship was positive such that the presence of persistent depression was significantly associated with greater physical symptoms two months after surgery, compared to those who were never depressed. Household income (t = -2.526, p = 0.013) was the only other significant predictor in this model, with a negative association such that those participants with a lower annual income reported greater physical symptoms. The model accounted for 11.2% of variance (R^2 = 0.112) in T3 physical symptom scores.

In addition, post-CABG onset depression (t = 3.084, p = 0.003) was also statistically significant in regression models; results are displayed in Table 7.23. This relationship was positive such that the presence of post-CABG onset depression was significantly associated with greater physical symptoms two months after surgery, compared to those who were never depressed. Household income (t = -2.765, p = 0.013) was the only other significant predictor in

this model, with a negative association such that those participants with a lower annual income reported greater physical symptoms. The model accounted for 14.9% of variance (R^2 = 0.149) in T3 physical symptom scores.

TABLE 7.22: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON PERSISTENT DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.114	0.115	0.137	0.322
Sex	0.560	2.128	0.026	0.793
Household income	-1.346	0.533	-0.238	0.013
euroSCORE	-0.235	0.346	-0.098	0.498
Depression persistent	4.872	2.372	0.191	0.042

R^2 = 0.112, N = 118

TABLE 7.23: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	0.116	0.112	0.135	0.301
Sex	1.521	2.246	0.067	0.500
Household income	-1.489	0.539	-0.254	0.007
euroSCORE	-0.258	0.345	-0.105	0.455
Depression post-CABG onset	7.084	2.297	0.271	0.003

R^2 = 0.149, N = 118

7.6.3 Health status

Physical health status

Multiple regression analyses were next performed using T3 physical health status, as measured on the SF-12, as the outcome variable. Both resolved depression (t = 0.465, p = 0.643) and persistent depression (t = -0.759, p = 0.450) were not significantly associated with T3 physical health status after controlling for demographic and disease severity covariates and baseline SF-12 physical scores. However, post-CABG onset depression (t = -3.598, p <0.001) was statistically significant in a regression model; results are displayed in Table 7.24. This relationship was negative such that the presence of post-CABG onset depression was significantly associated with lower physical health status two months after surgery, compared to those who were never depressed. Interestingly, baseline SF-12 physical score (t = 0.750, p =

0.455) was not a significant predictor in this model. The model accounted for 15.5% of variance (R^2 = 0.155) in T3 physical health status scores.

TABLE 7.24: MULTIPLE REGRESSION OF T3 PHYSICAL HEALTH STATUS ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	-0.204	0.130	-0.212	0.120
Sex	-5.391	2.602	-0.213	0.041
Household income	0.082	0.610	0.013	0.893
euroSCORE	1.052	0.394	0.386	0.009
T1 Physical health status	0.056	0.074	0.069	0.455
Depression post-CABG onset	-9.250	2.571	-0.319	<0.001

R^2 = 0.155, N = 117

Mental health status

Multiple regression analyses were performed using T3 mental health status, as measured on the SF-12, as the outcome variable. Resolved depression (t = 0.798, p = 0.427) was not significantly associated with T3 mental health status after controlling for demographic and disease severity covariates and baseline SF-12 mental scores. However, persistent depression (t = -3.419, p = 0.001) was statistically significant; results are displayed in Table 7.25. This relationship was negative such that the presence of persistent depression was significantly associated with lower mental health status two months after surgery, compared to those who were never depressed. Baseline SF-12 mental score (t = 4.198, p <0.001) was the only other significant predictor in this model, with a positive association such that those participants with higher mental health status prior to surgery also had higher mental health status after surgery. The model accounted for 29.3% of variance (R^2 = 0.293) in T3 mental health status scores.

In addition, post-CABG onset depression (t = 4.226, p <0.001) was also statistically significant in regression models; results are displayed in Table 7.26. This relationship was negative such that the presence of post-CABG onset depression was significantly associated with lower mental health status two months after surgery, compared to those who were never depressed. Baseline SF-12 mental health status score (t = 3.823, p <0.001) was the only other significant predictor in this model, with a positive association such that those participants with higher mental health status prior to surgery also had higher mental health status after surgery. The final model accounted for 24.7% of variance (R^2 = 0.247) in T3 mental health status scores.

TABLE 7.25: MULTIPLE REGRESSION OF T3 MENTAL HEALTH STATUS ON PERSISTENT DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	-0.081	0.102	-0.103	0.428
Sex	-1.119	1.813	-0.055	0.538
Household income	-0.276	0.458	-0.052	0.548
euroSCORE	0.004	0.303	0.002	0.989
T1 Mental health status	0.430	0.103	0.369	<0.001
Depression persistent	-7.226	2.113	-0.302	0.001

R^2 = 0.293, *N* = 117

TABLE 7.26: MULTIPLE REGRESSION OF T3 MENTAL HEALTH STATUS ON POST-CABG ONSET DEPRESSION

Model	*B*	*SE*	*ß*	*p*
Age	-0.078	0.102	-0.099	0.449
Sex	-1.476	1.952	-0.071	0.451
Household income	-0.282	0.472	-0.053	0.552
euroSCORE	-0.017	0.311	-0.008	0.957
T1 Mental health status	0.405	0.106	0.328	<0.001
Depression post-CABG onset	-8.355	1.977	-0.353	<0.001

R^2 = 0.247, *N* = 117

7.6.4 Summary

The results using depression onset subtypes have consistently shown that persistent and post-CABG onset depression subtypes were significantly associated with poorer recovery outcomes at T3. In contrast, resolved depression cases were not significantly associated with recovery following CABG surgery. However, several caveats need to be borne in mind in summarising these results. Firstly, these analyses involved only a small number of depression cases, for each of the subtypes respectively. Therefore, these results only indicate preliminary findings and warrant further investigation when the full sample becomes available. Secondly, these analyses do not demonstrate a prospective relationship between depression and recovery, but rather reveal the importance of the cross-sectional association between T3 depression symptoms and T3 recovery outcomes. These analyses will benefit from the 12-month follow-up data to test the effect of depression onset on physical and mental adaptation up to one year post-CABG. As such, while these analyses have produced some interesting findings, depression onset subtypes will not be investigated in the analyses of mediation. Instead the

mediation analyses will be limited to the prospective association between depression symptom subtypes, as measured at baseline, and later recovery.

7.7 Mechanisms

Candidate mechanisms were identified in the literature review and in Chapter 6 to involve several biopsychosocial pathways. This PhD tests the role of three possible mechanistic pathways: social-behavioural factors, cognitive factors and biology. All of these candidate mechanisms were based on measures taken at T1, except for inflammatory markers which were assessed at T1 and T2. Although descriptive data are presented at each time point a measure was used, this is merely to characterise these measures; only the T1 (and T2 for inflammatory markers) measurement point was used as a mechanism variable in this chapter. Each of the mechanisms are described in turn below, followed by analyses of their association with depression symptoms and the outcome variables, before finally including them in multivariate regression models.

In order to directly test mediation, the Sobel test method was implemented using the method set out by Preacher and Hayes (Preacher & Hayes, 2004, 2008). This method has previously been described in Chapter 6 (Section 6.6). The models included depression symptoms subtype score as the independent variable and the T3 recovery outcome as the dependent variable, with candidate mechanisms entered as the mediator. Covariates included age, sex, household income, euroSCORE, and for models predicting T2 anxiety and health status, baseline scores on these measures were also controlled for. A second approach was also taken to estimate the significance of the indirect effect. The change in the amount of variance explained by depression symptoms before and after the addition of the candidate mechanism in the models was estimated by calculating the percentage change: 1-(T3 β/ T1 β). Since depression symptoms were significant predictors of affective and sensory pain, physical symptoms and health status, these outcomes were used in analyses of mediation.

7.7.1 Behavioural and social mechanisms

7.7.1.1 Descriptive statistics

As shown in Chapter 6, social-behavioural factors were relevant to both depression symptoms and poorer recovery outcomes. In particular, physical activity and smoking were identified as important predictors of poorer early-term recovery. Therefore, this chapter will again examine the role of social-behavioural factors to include: physical activity, smoking, alcohol intake, sleep and social support. Importantly, sleep must be remembered as a symptom of depression, and therefore there are conceptual difficulties in describing sleep as a candidate mediator of the depression symptoms-recovery relationship. Given that cognitive/affective depression

symptoms were not a significant predictor of any of the T3 recovery outcomes, sleep was not assessed as a mediator, but instead has been included here to show associations with the recovery outcomes.

TABLE 7.27: SOCIAL-BEHAVIOURAL MECHANSIMS AT T1 AND T3

Measures	*N*	*T1* *Mean ± SD or n (%)*	*T3* *Mean ± SD or n (%)*	*p*
Health behaviour				
BMI (kg/m^2)	154	27.97±3.76	-	-
Current smoker	151	11 (7.3)	3 (2.0)	<0.001*
Alcohol consumption (units/week)	153	9.63±13.86	6.61±14.52	<0.001
Physical activity (hours/week)	138	3.30±4.02	3.43±3.06	0.700
Sleep total	152	9.61±6.87	10.39±7.11	0.166
Sleep items				
1. Trouble falling asleep	152	1.16±1.59	1.39±1.61	0.070
2. Waking during night	152	2.65±1.87	2.88±1.79	0.146
3. Trouble staying asleep	152	2.16±1.99	2.24±1.83	0.562
4. Waking feeling tired/ worn out	152	1.55±1.69	1.59±1.55	0.787
5. Disturbed/restless sleep	152	2.11±1.88	2.30±1.80	0.223
Social support				
Social support (ESSI)	152	28.99±5.58	29.78±5.22	0.024

*Chi-square statistic

The descriptive statistics for the social-behavioural candidate mechanisms are displayed in Table 7.27; dependent *t*-tests were performed to compare mean baseline and follow-up scores, with chi-square analysis for frequency comparisons. The majority of the sample was overweight at baseline, with a mean BMI of 27.97 kg/m^2. The majority of the sample drank alcohol moderately, within the UK government recommended guidelines, however one participant reported drinking heavily with an estimated 148 units of alcohol per week. Overall, there was a significant decline in mean alcohol intake from T1 to T3. Only 7.3% of participants were current smokers prior to surgery and this fell to just 2.0% after surgery; a chi-square analysis showed this to be a significant decline (χ^2 = 38.956, df = 1, n = 151, *p* <0.001). On average, participants walked for 3.30 hours per week at T1 and this did not significantly change following surgery. Data from the Jenkins sleep questionnaire show that participants frequently experienced sleep disturbances prior to surgery, with the symptoms of waking several times during the night, trouble staying asleep and disturbed or restless sleep being most commonly reported. Sleep symptom reporting did not significantly differ following

surgery compared to before. Finally, social support scores significantly increased over time, suggesting participants generally perceived higher levels of social support after surgery than before.

7.7.1.2 Associations with depression symptoms and recovery variables

Pearson's correlation analyses were performed to assess whether the candidate mechanisms were associated with depression symptoms (Table 7.28). To clarify, smoking was entered as a binary value (yes/no) to reflect current smoking status in these analyses. Although only somatic/affective depression symptoms were associated with T3 recovery outcomes, associations between social-behavioural factors and all the depression symptom scores on the BDI and recovery outcomes were tested to explore the data in detail. Results of these correlation analyses show smoking status, sleep problems and social support were all associated with depression symptom subtypes. However, physical activity, alcohol intake and BMI were not significantly associated with depression symptoms. Independent *t*-tests confirmed the difference between depressed/non-depressed participants (BDI ≥13) on sleep scores ($t(136) = -3.519$, $p = 0.001$), and social support scores ($t(135) = 2.265$, $p = 0.025$), but chi-square tests found no difference in smoking status ($\chi^2 = 2.66$, df = 1, $p = 0.103$). In addition, independent *t*-tests found no difference between depressed/non-depressed participants in terms of BMI ($t(136) = 0.091$, $p = 0.927$) and weekly alcohol intake ($t(135)= 0.998$, $p = 0.320$), but did find a significant difference in physical activity levels ($t(128)= 2.270$, $p = 0.025$). The latter finding shows that non-depressed participants were more physically active than depressed participants.

Pearson's correlation analyses were also performed to assess the association of these social-behavioural factors with the recovery outcomes. However, no significant associations were found for any of the social-behavioural factors. Regression analyses were also performed to assess whether the social-behavioural factors predicted any of the recovery outcomes after controlling for demographic and disease severity covariates. Anxiety and health status models also controlled for baseline scores on these measures. Statistically, the correlation coefficient represents the linear dependence between the predictor and outcome variable, but it does not control for the fact that other factors may also account for the relationship, potentially producing a biased estimate.

TABLE 7.28: PEARSON'S CORRELATIONS OF T1 SOCIAL-BEHAVIOURAL FACTORS AND T1 DEPRESSION SYMPTOMS

Measure	*T1 BDI total*	*T1 BDI somatic*	*T1 BDI cognitive*
Health behaviour			
T1 BMI			
r	0.112	0.101	0.069
p	0.168	0.215	0.394
T1 Smoking			
r	-0.210	-0.239	-0.184
p	0.010	0.003	0.023
T1 Alcohol consumption			
r	-0.126	-0.140	-0.046
p	0.122	0.086	0.572
T1 Physical activity – walking			
r	-0.130	-0.141	-0.143
p	0.123	0.096	0.089
T1 Sleep			
r	0.396	0.422	0.290
p	<0.001	<0.001	<0.001
Social support			
T1 Social support			
r	-0.378	-0.369	-0.369
p	<0.001	<0.001	<0.001

Results found that baseline BMI was a significant predictor of T3 sensory pain (t = 2.450, p = 0.016) after controlling for covariates, with a positive relationship such that a higher BMI was associated with greater pain following surgery. Physical activity was significantly associated with anxiety at T3 (t = 2.149, p = 0.034) and was borderline significantly associated with affective pain at T3 (t = 1.963, p = 0.052), with greater time spent walking per week being predictive of greater anxiety and more affective pain. This is an interesting finding and not easy to interpret, given lower physical activity was related to greater emotional distress at T2 (Chapter 6). Finally, baseline sleep problems were a significant predictor of CROQ physical symptoms at T3 (t = 3.120, p = 0.002) and physical health status at T3 (t = -3.175, p = 0.002). The association with physical symptoms was positive such that greater sleep problems were associated with more physical symptoms, while the association with health status was negative such that greater sleep problems were predictive of poorer physical health status. No other significant predictors of recovery were found. These significant predictors were examined as potential mediators of the depression symptoms-recovery relationship.

7.7.1.3 Mediation models of T3 emotional distress

TABLE 7.29: HIERARCHICAL REGRESSION OF T3 ANXIETY ON T1 PHYSICAL ACTIVITY AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	-0.038	0.047	-0.093	0.422
Sex	-0.969	0.855	-0.093	0.259
Household income	-0.373	0.213	-0.134	0.082
euroSCORE	0.125	0.148	0.103	0.400
T1 anxiety	0.398	0.081	0.443	<0.001
T1 BDI total score	0.090	0.058	0.140	0.125
Step 2				
Age	-0.028	0.046	-0.070	0.542
Sex	-0.700	0.847	-0.067	0.410
Household income	-0.372	0.209	-0.134	0.077
euroSCORE	0.116	0.145	0.095	0.427
T1 anxiety	0.398	0.080	0.443	<0.001
T1 BDI total score	0.104	0.057	0.163	0.072
T1 Physical activity - walking	0.161	0.068	0.173	0.019

Step 1 R^2 = 0.336; Step 2 R^2 = 0.365; N = 134

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of physical activity to the depression symptoms-T3 anxiety relationship. Depression symptom subtypes were used in separate models. The final model using total BDI score, is displayed in Table 7.29 confirming the earlier presented results that T1 total BDI score (t = 1.814, p = 0.072) was not a significant predictor of T3 anxiety. However, T1 physical activity was a significant predictor (t = 2.374, p = 0.019), with a positive association such that the most active participants at baseline, had greater anxiety following surgery. This is counterintuitive and does not support the findings demonstrated in Chapter 6 whereby greater physical activity at T1 was predictive of lower anxiety levels at T2. Similar findings were also found using T1 cognitive/affective depression symptom scores as a predictor of T3 anxiety, such that baseline physical activity (t = 2.275, p = 0.025) was a significant predictor in the final model, but not T1 cognitive/affective depression symptoms (t = 1.814, p = 0.311). Since baseline total BDI and cognitive/affective depression symptoms were not significant predictors of T3 anxiety, Sobel tests of mediation were not conducted.

TABLE 7.30: HIERARCHICAL REGRESSION OF T3 ANXIETY ON T1 PHYSICAL ACTIVITY AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	-0.040	0.046	-0.099	0.386
Sex	-1.044	0.847	-0.100	0.220
Household income	-0.359	0.210	-0.129	0.090
euroSCORE	0.118	0.146	0.097	0.423
T1 anxiety	0.374	0.078	0.416	<0.001
T1 BDI somatic	0.172	0.076	0.198	0.025
Step 2				
Age	-0.031	0.045	-0.077	0.494
Sex	-0.771	0.838	-0.074	0.359
Household income	-0.359	0.206	-0.129	0.084
euroSCORE	0.108	0.144	0.089	0.454
T1 anxiety	0.374	0.077	0.417	<0.001
T1 BDI somatic	0.190	0.074	0.219	0.012
T1 Physical activity - walking	0.165	0.067	0.177	0.015

Step 1 R^2 = 0.350; Step 2 R^2 = 0.380; N = 134

Next, a hierarchical regression model was built adjusting for somatic/affective depression symptoms (Table 7.30). The model shows that T1 anxiety (t = 4.760, p <0.001) and T1 somatic/affective depression symptoms (t = 2.276, p = 0.025) were the only significant predictors of T3 anxiety in step 1 adjusted for covariates. After adding T1 hours spent walking per week into the model, T1 anxiety (t = 4.864, p <0.001) and T1 somatic/affective depression symptoms (t = 2.552, p = 0.012) remained significant predictors. In addition, T1 physical activity was also a significant predictor (t = 2.464, p = 0.015), with a positive association such that the most active participants at baseline, had greater anxiety following surgery. This is in line with results using baseline total BDI and cognitive/affective depression symptom scores. The final model accounted for 38.0% (R^2 = 0.380) of variance in T3 anxiety scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of T1 physical activity in the model, the β for depression symptoms changed from 0.198 to 0.219. This indicates that when physical activity was included in the model, there was a 10.6% increase in the size of β for T1 somatic/affective depression symptoms. However, since T1 somatic/affective depression symptoms (t = -1.116, p = 0.266) were not significantly associated with T1 physical activity in a covariate adjusted model, a Sobel test was not conducted.

7.7.1.4 Mediation models of T3 physical symptoms

BMI

TABLE 7.31: HIERARCHICAL REGRESSION OF T3 SENSORY PAIN ON T1 BMI AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.033	0.100	0.048	0.738
Sex	2.193	1.834	0.111	0.234
Household income	-0.508	0.432	-0.106	0.241
euroSCORE	-0.091	0.311	-0.042	0.770
T1 BDI total score	0.185	0.100	0.164	0.068
Step 2				
Age	0.024	0.098	0.034	0.808
Sex	1.136	1.865	0.057	0.544
Household income	-0.627	0.429	-0.130	0.146
euroSCORE	0.024	0.311	0.011	0.939
T1 BDI total score	0.166	0.099	0.147	0.096
T1 BMI	0.339	0.150	0.201	0.025

Step 1 R^2 = 0.052; Step 2 R^2 = 0.089; N = 136

The next regression model to be built used the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of baseline BMI to the depression symptoms-T3 sensory pain relationship. Depression symptom subtypes were used in separate models. The final model using T1 total BDI score is displayed in Table 7.31 and confirms the earlier presented results that T1 total BDI score (t = 1.675, p = 0.096) was not a significant predictor of T3 sensory pain. However, T1 BMI was a significant predictor (t = 2.266, p = 0.025), with a positive association such that the participants with higher BMIs, had greater sensory pain after surgery. There were no other significant predictors in this model. Similar findings were also found using T1 cognitive/affective depression symptom scores as a predictor of T3 sensory pain, such that BMI (t = 2.432, p = 0.016) was a significant predictor in the final model, but not cognitive/affective depression symptoms (t = 0.510, p = 0.611). Since, baseline total BDI and cognitive/affective depression symptoms were not significant predictors of sensory pain, Sobel tests of mediation were not conducted.

TABLE 7.32: HIERARCHICAL REGRESSION OF T3 SENSORY PAIN ON T1 BMI AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.032	0.098	0.046	0.744
Sex	2.192	1.823	0.111	0.232
Household income	-0.501	0.430	-0.104	0.246
euroSCORE	-0.115	0.310	-0.054	0.711
T1 BDI somatic	0.300	0.136	0.193	0.029
Step 2				
Age	0.024	0.096	0.034	0.805
Sex	1.145	1.854	0.058	0.538
Household income	-0.618	0.426	-0.129	0.149
euroSCORE	-0.001	0.309	-0.001	0.996
T1 BDI somatic	0.278	0.134	0.178	0.040
T1 BMI	0.336	0.149	0.199	0.025

Step 1 R^2 = 0.063; Step 2 R^2 = 0.099; N = 136

A hierarchical regression model was also built adjusting for baseline somatic/affective depression symptoms (Table 7.32). The model shows that T1 somatic/affective depression symptoms (t = 2.212, p = 0.029) were the only significant predictor of T3 sensory pain in step 1 adjusted for covariates. After adding BMI into the model, T1 somatic/affective depression symptoms (t = 2.071, p = 0.040) remained a significant predictor. In addition, BMI was also a significant predictor (t = 2.263, p = 0.025), with a positive association such that the most overweight participants at baseline, had greater sensory pain following surgery. The final model accounted for 9.9% (R^2 = 0.099) of variance in T3 sensory pain scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of BMI in the model, the β for depression symptoms changed from 0.193 to 0.178. This indicates that when T1 physical activity was included in the model, there was a 7.8% reduction in the size of β for T1 somatic/affective depression symptoms. However, in a separate regression model using baseline BMI as the dependent variable to assess the association with T1 somatic/affective depression symptoms, after adjusting for disease severity and demographic covariates, T1 somatic/affective depression symptom score (t = 0.930, p = 0.350) was not significant. Therefore, a Sobel test of mediation was not performed.

TABLE 7.33: HIERARCHICAL REGRESSION OF T3 AFFECTIVE PAIN ON T1 PHYSICAL ACTIVITY AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.001	0.035	0.004	0.977
Sex	-0.529	0.652	-0.077	0.419
Household income	-0.136	0.156	-0.082	0.385
euroSCORE	-0.015	0.110	-0.020	0.892
T1 BDI total score	0.074	0.038	0.177	0.057
Step 2				
Age	0.009	0.035	0.036	0.805
Sex	-0.345	0.647	-0.050	0.595
Household income	-0.137	0.153	-0.082	0.373
euroSCORE	-0.024	0.108	-0.032	0.825
T1 BDI total score	0.084	0.038	0.202	0.028
T1 Physical activity	0.111	0.049	0.201	0.026

Step 1 R^2 = 0.045; Step 2 R^2 = 0.083; N = 127

The hierarchical regression method was again used to assess the relative contribution of physical activity to the depression symptoms-T3 affective pain relationship. Depression symptom subtypes were used in separate models. First, total BDI score was used; results are displayed in Table 7.33. Step 1 of the model confirms the earlier presented results that total BDI score was not a significant predictor of affective pain (t = 1.924, p = 0.057). However, in step 2, after the addition of physical activity to the model, total BDI score (t = 2.217, p = 0.028) was a significant predictor of T3 affective pain. In addition, T1 hours spent walking per week was a significant predictor (t = 2.250, p = 0.026), with a positive association such that the most active participants had greater affective pain two months after surgery. Although counterintuitive, this finding is in line with the results previously presented which showed greater physical activity at T1 was associated with greater anxiety at T3 (Section 7.7.1.3). There were no other significant predictors in this model. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of physical activity in the model, the β for depression symptoms changed from 0.177 to 0.202. This indicates that when physical activity was included in the model, there was a 14.1% increase in the size of β for total BDI depression symptom score. However, in a separate regression model using baseline physical activity as the dependent variable to assess the association with T1 total BDI depression symptoms, after adjusting for disease severity and demographic covariates, total

BDI depression symptoms (t = -1.401, p = 0.163) were not significant. Therefore, a Sobel test of mediation was not performed.

Next, a hierarchical regression model was built adjusting for somatic/affective depression symptoms (Table 7.34). The model shows that T1 somatic/affective depression symptoms (t = 2.633, p = 0.010) were the only significant predictor of T3 sensory pain in step 1 adjusted for covariates. After adding T1 physical activity into the model, T1 somatic/affective depression symptoms (t = 2.949, p = 0.004) remained a significant predictor. In addition, physical activity was also a significant predictor (t = 2.365, p = 0.020), again with a positive association such that the most active participants at baseline, had greater affective pain following surgery. The final model accounted for 11.0% (R^2 = 0.110) of variance in T3 affective pain scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of physical activity in the model, the β for depression symptoms changed from 0.236 to 0.261. This indicates that when physical activity was included in the model, there was a 10.6% increase in the size of β for T1 somatic/affective BDI depression. However, in a separate regression model using baseline physical activity as the dependent variable to assess the association with T1 somatic/affective depression symptoms, after adjusting for disease severity and demographic covariates, T1 somatic/affective depression symptoms (t = -1.369, p = 0.173) were not significant. Therefore, a Sobel test of mediation was not performed.

TABLE 7.34: HIERARCHICAL REGRESSION OF T3 AFFECTIVE PAIN ON T1 PHYSICAL ACTIVITY AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.001	0.034	0.006	0.968
Sex	-0.518	0.644	-0.076	0.423
Household income	-0.124	0.154	-0.074	0.422
euroSCORE	-0.027	0.109	-0.036	0.806
T1 BDI somatic	0.133	0.051	0.236	0.010
Step 2				
Age	0.009	0.034	0.036	0.798
Sex	-0.328	0.637	-0.048	0.607
Household income	-0.125	0.151	-0.075	0.408
euroSCORE	-0.036	0.107	-0.049	0.734
T1 BDI somatic	0.148	0.050	0.261	0.004
T1 Physical activity	0.115	0.049	0.208	0.020

Step 1 R^2 = 0.069; Step 2 R^2 = 0.110; N = 127

Findings using T1 cognitive/affective depression symptom scores as a predictor of T3 affective pain, showed that T1 physical activity (t = 2.123, p = 0.036) was a significant predictor in the final model, but not cognitive/affective depression symptoms (t = 1.105, p = 0.271). Since, T1 cognitive/affective depression symptoms were not a significant predictor of affective pain, a Sobel test was not conducted.

Sleep

To reiterate, since sleep is a symptom of depression, the Jenkins score was only included in these analyses to assess its association with the recovery outcomes. A regression model was built to assess the contribution of baseline self-reported sleep problems in explaining T3 physical symptoms (Table 7.35). The model shows that T1 sleep was a significant predictor (t = 2.493, p = 0.014) after controlling for baseline depression symptoms and demographic and disease severity covariates. The only other significant predictor in the final model was household income (t = -2.206, p = 0.029). This model suggests that those participants with poorer T1 sleep and lower annual income had greater physical symptoms two months after surgery. The final model accounted for 11.2% (R^2 = 0.112) of variance in CROQ physical symptom scores. Individual regression models were also built entering each of the T1 Jenkins items individually to predict physical symptoms at T3. In these analyses, after controlling for demographic and disease severity covariates as well as baseline total BDI score, only items 3 (trouble staying asleep) (t = 2.141, p = 0.034) and 5 (disturbed or restless sleep) (t = 2.988, p = 0.003) were significant independent predictors of greater physical symptoms after surgery.

Similar results were also found using T1 somatic/affective depression symptoms, such that T1 sleep (t = 2.228, p = 0.028) and household income (t = -2.206, p = 0.029) were significant predictors after controlling for baseline depression symptoms and demographic and disease severity covariates. The model using T1 cognitive/affective depression symptoms was also in line with these results, such that T1 sleep (t = 3.008, p = 0.003) and household income (t = -2.240, p = 0.027) were significant predictors after controlling for baseline depression symptoms and demographic and disease severity covariates. Interestingly, using the individual T1 Jenkins items in separate regression models found only item 5 (disturbed or restless sleep) (t = 2.769, p = 0.006) to be a significant independent predictor of greater physical symptoms at T3, after adjusting for demographic, disease severity and T1 somatic/affective BDI score covariates. In contrast, in the models adjusting for demographic and disease severity covariates and T1 cognitive/affective BDI score, all the items except item 1 (trouble falling asleep) were significant predictors of greater physical symptoms at T3: item 2 (waking during the night) (t = 2.136, p = 0.034), item 3 (trouble staying asleep) (t = 2.491, p = 0.014), item 4 (waking feeling tired/worn out) (t = 2.394, p = 0.018), and item 5 (disturbed or restless sleep) (t

= 3.428, p = 0.001). In summary, greater sleep problems at T1 were significantly associated with greater physical symptoms two months after surgery in models controlling for covariates and baseline total BDI, somatic/affective, cognitive/affective depression symptom scores. In particular, the individual sleep problems specifically related to physical symptoms varied according to the depression subtype included in the model. Nevertheless, it appeared that items related to difficulty in maintaining sleep were the best predictors of physical symptoms, as opposed to problems initiating sleep.

TABLE 7.35: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T1 SLEEP PROBLEMS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.056	0.108	0.066	0.607
Sex	1.159	2.032	0.051	0.569
Household income	-1.090	0.494	-0.188	0.029
euroSCORE	-0.127	0.336	-0.051	0.705
T1 BDI total score	0.072	0.120	0.056	0.546
T1 Sleep	0.253	0.102	0.225	0.014

R^2 = 0.112; N = 144

7.7.1.5 Mediation models of T3 health status

Sleep was next assessed as an independent predictor of T3 physical health status (Table 7.36). The model shows that T1 sleep was a significant predictor (t = -2.330, p = 0.021) after controlling for baseline depression symptoms and demographic and disease severity covariates. The only other significant predictors in the final model were sex (t = -2.242, p = 0.027) and euroSCORE (t = 2.476, p = 0.015). This model suggests that those participants with poorer sleep, female sex and lower mortality risk had lower physical health status two months after surgery. The final model accounted for 11.7% (R^2 = 0.117) of variance in physical health status scores. Separate regression analyses were also performed entering each of the baseline Jenkins items individually to predict T3 physical health status, controlling for demographic and disease severity covariates and baseline total BDI score. These analyses showed that item 2 (waking during the night) (t = -2.737, p = 0.007) was a significant predictor, and item 3 (trouble staying sleep) (t = -1.967, p = 0.051) approached being a significant predictor, of lower physical health status following CABG.

Similar results were also found using T1 somatic/affective depression symptoms, such that T1 sleep (t = -2.082, p = 0.039) and euroSCORE (t = 2.557, p = 0.012) were significant predictors after controlling for baseline depression symptoms and demographic and disease

severity covariates. Again, the euroSCORE relationship was positive suggesting those participants with lower mortality risk had poorer physical health status. The model using T1 cognitive/affective depression symptoms were also in line with these results, such that T1 sleep (t = -2.968, p = 0.004), sex (t = -2.763, p <0.001) and euroSCORE (t = 2.443, p = 0.016) were significant predictors after controlling for baseline depression symptoms and demographic and disease severity covariates. Separate regression analyses using the individual items of the T1 Jenkins questionnaire in covariate adjusted models were also performed. These analyses showed that the baseline score on item 2 (waking during the night) (t = -2.737, p = 0.007) was the only significant predictor of lower physical health status following CABG in models using somatic/affective depression symptoms. However, in the models using cognitive/affective depression symptoms, both items 2 (waking during the night) (t = -3.291, p = 0.001) and 3 (trouble staying sleep) (t = -2.421, p = 0.017) at T1 were significant predictors of lower physical health status at T3. In summary, these results suggest that poorer pre-CABG sleep was a significant independent predictor of lower T3 physical health status, in models adjusting for all depression symptom subtypes. In particular, problems maintaining sleep prior to surgery were particularly important for predicting poorer physical health status after surgery.

TABLE 7.36: MULTIPLE REGRESSION OF T3 PHYSICAL HEALTH STATUS ON T1 SLEEP PROBLEMS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.192	0.122	-0.211	0.116
Sex	-5.079	2.265	-0.210	0.027
Household income	0.066	0.539	0.011	0.902
euroSCORE	0.915	0.369	0.340	0.015
T1 BDI total score	-0.003	0.071	-0.004	0.963
T1 Physical health status	-0.131	0.132	-0.095	0.323
T1 Sleep	-0.263	0.113	-0.218	0.021

R^2 = 0.117; N = 143

7.7.2 Cognitive mechanisms

7.7.2.1 Descriptive statistics

Chapter 6 identified the importance of negative illness perceptions for mediating the relationship between greater pre-operative depression symptoms and poorer early-term recovery. The following analyses sought to replicate these findings using the two month post-surgery recovery endpoints.

Cognitive function and illness perceptions were considered as cognitive mechanisms of the depression symptoms-recovery relationship; descriptive statistics of these measures are displayed in Table 7.37, *p* represents the significance value in dependent *t*-tests for total BIPQ scores and individual BIPQ items. The mean score on the MoCA was below the cut-off of 26, with 43.2% of the sample scoring ≤25. Scores on the individual items of the BIPQ are also displayed in Table 7.37. Please note that items 3, 4 and 7 have been reverse coded, so higher means reflect a more negative illness perception for all items. Total scores on the BIPQ reveal that participants held a less negative view of their illness over time, with significant decreases in items 3 (personal control), 5 (identity), 6 (concern) and 8 (emotional response). These items reflect that participants perceived more control over their illness experienced less symptoms from their illness, were less concerned about their illness, and were less emotionally affected by their illness, two months after surgery than before. Interestingly, a significant increase was found for item 4 (treatment control), suggesting participants had a more negative view of treatment for their illness after surgery than before.

TABLE 7.37: COGNITIVE MECHANISMS AT T1 AND T3

Cognitive factors	*N*	*T1* *Mean ± SD*	*T3* *Mean ± SD*	*p*
Cognitive screen (MoCA)	146	25.20±3.43	-	-
Illness perceptions total	154	34.88±11.18	27.85±14.01	<0.001
Illness perceptions items				
1. Consequences	153	5.58±2.91	5.19±2.91	0.182
2. Timeline	153	4.22±2.90	4.36±3.00	0.623
3. Personal control	154	5.86±2.87	4.31±2.81	<0.001
4. Treatment control	154	1.11±1.45	1.56±1.74	0.005
5. Identity	154	4.81±2.73	3.49±2.81	<0.001
6. Concern	153	7.08±2.79	4.38±3.15	<0.001
7. Understanding	151	1.48±1.91	1.79±2.07	0.072
8. Emotional response	152	4.66±3.05	2.86±2.82	<0.001

7.7.2.2 Associations with depression symptoms and recovery variables

Pearson's correlation analyses were performed to analyse the association between depression symptoms subtypes and the candidate cognitive mechanisms. Results are displayed in Table 7.38 and show illness perceptions were associated with all depression symptom subtypes, while MoCA scores were not significantly associated with any of the depression subtype scores. Independent *t*-tests confirmed the difference between depressed/non-depressed

participants (BDI ≥13) on illness perceptions (t(136) = -4.618, p <0.001), and confirmed the lack of difference in cognitive function scores on the MoCA (t(129) = -0.261, p = 0.794).

TABLE 7.38: PEARSON'S CORRELATIONS BETWEEN T1 COGNITIVE MECHANISMS AND T1 DEPRESSION SYMPTOMS

Cognition	*T1 BDI*	*T1 BDI somatic*	*T1 BDI cognitive*
T1 Cognitive function (MoCA)			
r	-0.080	-0.076	-0.020
p	0.339	0.363	0.811
T1 Illness perceptions(BIPQ)			
r	0.452	0.499	0.365
p	<0.001	<0.001	<0.001

Next, Pearson's correlation analyses were performed to assess the association of the cognitive measures with the T3 recovery outcomes. These correlations are displayed in Table 7.39 and show that illness perception score was significantly associated with all outcomes except sensory pain. Cognitive function on the other hand was not associated with any of the T3 recovery outcomes. These null findings for the MoCA were also confirmed in regression models controlling for covariates. As such, illness perception score was the only cognitive mechanism that was assessed for mediation of the depression symptoms-short-term recovery relationship.

TABLE 7.39: PEARSON'S CORRELATIONS BETWEEN T1 COGNITIVE MECHANISMS AND T3 RECOVERY OUTCOMES

Cognition	*T3 Anxiety*	*T3 Affective pain*	*T3 Sensory pain*	*T3 Physical symptoms*	*T3 Physical health status*	*T3 Mental health status*
T1 Cognitive function						
r	-0.154	-0.068	-0.135	-0.089	0.018	-0.005
p	0.064	0.427	0.114	0.284	0.829	0.954
T1 Illness perceptions						
r	0.420	0.317	0.159	0.236	-0.222	-0.341
p	<0.001	<0.001	0.057	0.003	0.006	<0.001

7.7.2.3 Mediation models of T3 emotional distress

The first regression model was built using the hierarchical method to assess the relative contribution of illness perceptions to the depression symptoms-T3 anxiety relationship.

Depression symptom subtypes were used in separate models. The final model using baseline total BDI score, confirmed the earlier presented results that T1 total BDI score (t = 0.853, p = 0.395) was not a significant predictor of T3 anxiety. In addition, T1 illness perceptions were also not a significant predictor (t = 1.830, p = 0.069). Similar findings were also found using T1 somatic/affective depression symptom scores as a predictor of T3 anxiety, such that neither somatic/affective depression symptoms (t = 1.466, p = 0.145) nor illness perceptions (t = 1.558, p = 0.122) were a significant predictor in the final model. This lack of association was confirmed in individual covariate adjusted models using each of the BIPQ items entered separately to predict T3 anxiety. Since illness perceptions were not a significant predictor of T3 anxiety, Sobel tests of mediation were not conducted.

TABLE 7.40: HIERARCHICAL REGRESSION OF T3 ANXIETY ON T1 ILLNESS PERCEPTIONS AND T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	-0.032	0.044	-0.081	0.464
Sex	-0.713	0.803	-0.069	0.376
Household income	-0.467	0.199	-0.171	0.020
euroSCORE	0.106	0.140	0.086	0.450
T1 anxiety	0.451	0.076	0.518	<0.001
T1 BDI cognitive	0.034	0.088	0.035	0.698
Step 2				
Age	-0.039	0.043	-0.097	0.375
Sex	-0.861	0.797	-.083	0.282
Household income	-0.427	0.198	-0.156	0.033
euroSCORE	0.140	0.139	0.114	0.317
T1 anxiety	0.371	0.085	0.426	<0.001
T1 BDI cognitive	0.029	0.087	0.030	0.736
T1 Illness perceptions	0.054	0.027	0.169	0.044

Step 1 R^2 = 0.339; Step 2 R^2 = 0.358; N = 145

A hierarchical regression model using T1 cognitive/affective depression symptoms (Table 7.40) showed that in step 2, lower household income (t = -2.157, p = 0.033) and greater T1 anxiety (t = 4.347, p <0.001) were significant predictors of anxiety. In addition, T1 illness perception score was also a significant predictor (t = 2.030, p = 0.044), with a positive association such that the participants with the most negative view of their illness at baseline, had greater anxiety following surgery. However, in separate covariate adjusted analyses entering each of the BIPQ items individually to predict T3 anxiety, none were significant. In

summary, these results suggest that baseline illness perceptions were not consistently related to T3 anxiety and none of the baseline depression symptom subtypes were significant predictors of T3 anxiety after including illness perceptions in the models.

7.7.2.4 Mediation models of T3 physical symptoms

Sensory pain

Regression models were built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-T3 sensory pain relationship, controlling for covariates. Baseline depression symptom subtypes were used in separate models, however no significant findings were found. Illness perceptions were not a significant predictor in models using T1 total BDI, cognitive/affective and somatic/affective depression symptom scores. Baseline somatic/affective depression symptom score (t = 2.212, p = 0.029) was a significant predictor in step 1 controlling for covariates, but not in step 2 (t = 1.546, p = 0.125) when illness perceptions were added to the model. Furthermore, the lack of association between baseline illness perceptions and T3 sensory pain was confirmed in covariate adjusted models using each of the BIPQ items individually.

Affective pain

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of illness perceptions to the depression symptoms-T3 affective pain relationship. Depression symptom subtypes were used in separate models. The final model using baseline total BDI score, confirmed the earlier presented results that total BDI score (t = 0.211, p = 0.833) was not a significant predictor of T3 affective pain. However, T1 illness perceptions were a significant predictor (t = 3.386, p = 0.001). The individual items of the BIPQ that were found to be significant predictors of T3 affective pain when entered into separate covariate adjusted regression models were: item 1 (consequences) (t = 2.133, p = 0.035), item 2 (timeline) (t = 1.980, p = 0.050), item 5 (identity) (t = 2.197, p = 0.030) and item 6 (concern) (t = 2.025, p = 0.045). Similar findings were also found using T1 cognitive/affective depression symptom scores in the model, such that cognitive/affective depression symptoms (t = 0.615, p = 0.540) were not a significant predictor, but T1 illness perceptions (t = 3.888, p <0.001) were. In individual item analyses of the baseline BIPQ, item 1 (consequences) (t = 2.532, p = 0.013), item 2 (timeline) (t = 2.268, p = 0.025), item 5 (identity) (t = 2.522, p = 0.013) and item 6 (concern) (t = 2.323, p = 0.022) and item 8 (emotional response) (t = 2.321, p = 0.022) were all significant independent predictors of

greater affective pain after adjusting for covariates. These results suggest that those participants prior to surgery who saw their illness as having more severe consequences, a longer duration, and greater symptoms, as well as having greater concern about their illness, were more likely to experience greater distress from physical pain following surgery. However, since baseline total depression symptoms and cognitive/affective depression symptoms were not a significant predictor of T3 affective pain in step 1 of these models, Sobel tests of mediation were not conducted.

TABLE 7.41: HIERARCHICAL REGRESSION OF T3 AFFECTIVE PAIN ON T1 ILLNESS PERCEPTIONS AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.000	0.033	0.002	0.991
Sex	-0.476	0.629	-0.069	0.451
Household income	-0.135	0.146	-0.083	0.355
euroSCORE	-0.023	0.106	-0.031	0.827
T1 BDI somatic	0.123	0.046	0.233	0.009
Step 2				
Age	0.004	0.032	0.016	0.906
Sex	-0.590	0.613	-0.086	0.337
Household income	-0.079	0.143	-0.048	0.583
euroSCORE	-0.018	0.103	-0.025	0.861
T1 BDI somatic	0.045	0.052	0.086	0.386
T1 Illness perceptions	0.055	0.019	0.287	0.004

Step 1 R^2 = 0.066; Step 2 R^2 = 0.124; N = 135

A hierarchical regression model was also built adjusting for T1 somatic/affective depression symptoms (Table 7.41). The model shows that T1 somatic/affective depression symptom score (t = 2.672, p = 0.009) was the only significant predictor of T3 affective pain in step 1 adjusted for covariates. After adding T1 illness perception total score into the model, T1 somatic/affective depression symptoms were no longer a significant predictor (t = 0.870, p = 0.386). However, T1 illness perception score was a significant predictor (t = 2.914, p = 0.004), with a positive association such that the participants with the most negative view of their illness at baseline, had greater affective pain following surgery. The final model accounted for 12.4% (R^2 = 0.124) of variance in T3 affective pain scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of illness perceptions in the model, the β for depression symptoms changed from 0.233 to 0.086. This indicates that when illness perceptions were included in the model, there was a 63.1%

reduction in the size of β for somatic/affective depression symptoms. In regression models using the individual illness perceptions as predictors of T3 affective pain, adjusting for covariates and T1 somatic/affective depression symptoms, none of the individual perceptions were significant predictors, suggesting that having a general negative perception of the illness was more important than any individual cognition.

A Sobel test was used on these data to assess the significance of the indirect effect. The model included T1 somatic/affective BDI score as the independent variable and T3 affective pain as the dependent variable, with illness perceptions entered as the mediator. Covariates included age, sex, household income and euroSCORE. The results of this Sobel test are illustrated in Figure 7.1, showing a significant total effect (pathway *c*) for the T1 somatic/affective depression symptoms and T3 affective pain relationship (B = 0.123, SE = 0.046, *p* = 0.009). However, the direct pathway (pathway *c*') (B = 0.045, SE = 0.052, *p* = 0.386) was not significant after taking the mediator into account. The indirect pathway (pathway *ab*) was significant in this model (B = 0.078, SE = 0.033, 95% CI = 0.022-0.154), confirming illness perceptions to be a significant mediator. Full mediation was shown since the direct effect, pathway *c*', was not significant after illness perceptions were taken into account.

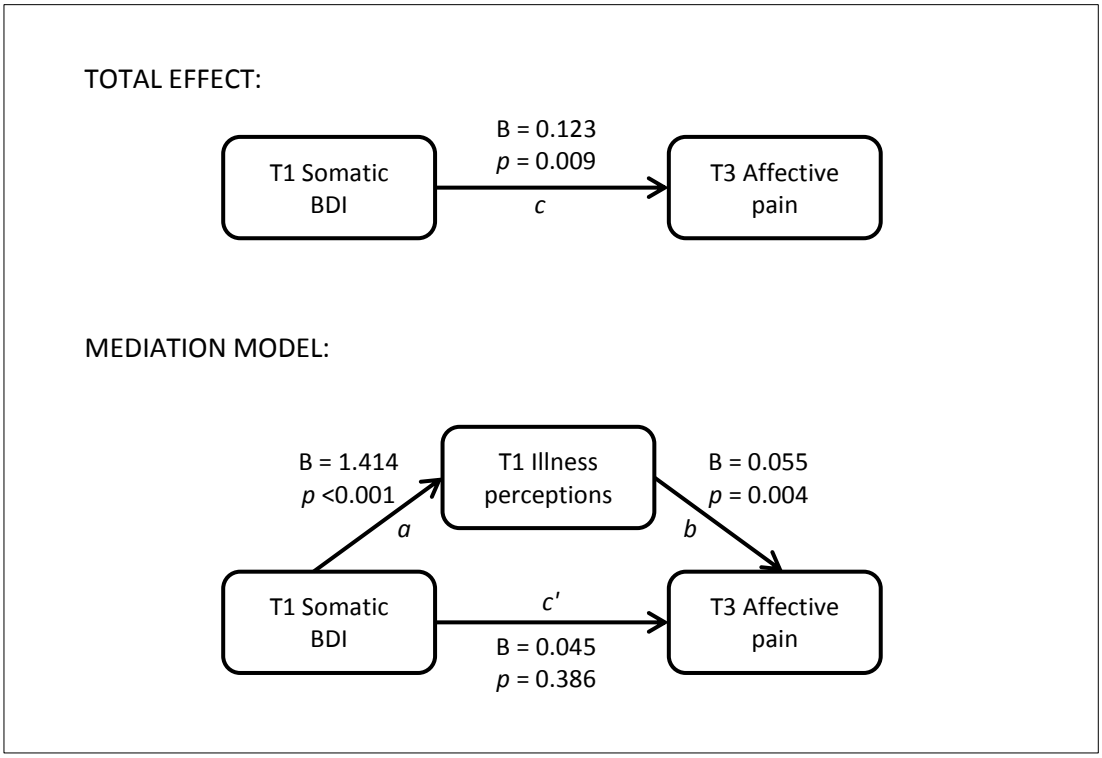

FIGURE 7.1: MEDIATION MODEL OF T1 SOMATIC/AFFECTIVE DEPRESSION SYMPTOMS AND T3 AFFECTIVE PAIN THROUGH T1 ILLNESS PERCEPTIONS

In summary, these results suggest that illness perceptions were a significant mediator of the somatic/affective depression symptoms-affective pain relationship, with full mediation found. Interestingly none of the individual illness perceptions were found to be significant in this model. Illness perceptions were also a significant predictor of T3 affective pain in models using baseline total BDI and cognitive/affective depression symptom scores, with the T1 individual negative perceptions being widely predictive of greater affective pain following surgery.

Physical symptoms

The next regression model built used the hierarchical method to assess the relative contribution of baseline illness perceptions to the depression symptoms-T3 physical symptoms relationship. Depression symptom subtypes were used in separate models. The final model using baseline total BDI score is displayed in Table 7.42, confirming the earlier presented results that baseline total BDI score (t = 0.592, p = 0.555) was not a significant predictor of T3 CROQ physical symptoms. However, T1 illness perceptions were a significant predictor (t = 2.546, p = 0.012), with a positive relationship, which meant the participants with the most negative view of their illness reported the most physical symptoms after surgery. The only other significant predictor in this model was household income (t = -2.245, p = 0.026), with a negative association such that those participants with the lowest income reported the most physical symptoms. In separate regression models, entering each of the T1 illness perception items individually to predict T3 physical symptoms, item 5 (symptoms) (t = 2.055, p = 0.042) and item 6 (concern) (t = 2.911, p = 0.004) were both significant predictors. Similar findings were also found using T1 cognitive/affective depression symptom scores as a predictor of T3 physical symptoms, such that T1 cognitive/affective depression symptom score (t = -0.186, p = 0.852) was not a significant predictor of T3 physical symptoms, but T1 illness perceptions (t = 2.976, p = 0.003) were. Again this association was positive, such that those participants who held a more negative view of their illness prior to surgery had greater physical symptoms up to two months after surgery. Separate regression models were also used to enter each of the T1 illness perception items individually to predict T3 physical symptoms, finding item 1 (consequences) (t = 2.108, p = 0.037), item 5 (symptoms) (t = 2.308, p = 0.022) and item 6 (concern) (t = 3.103, p = 0.002) were all significant predictors. These results suggest that those participants, prior to surgery, who saw their illness as having more severe consequences and greater symptoms, and who felt most concerned by their illness, experienced greater physical symptoms up to two months after surgery. However, since total BDI and cognitive/affective depression symptoms were not significant predictors of T3 physical symptoms, Sobel tests of mediation were not conducted.

TABLE 7.42: HIERARCHICAL REGRESSION OF T3 PHYSICAL SYMPTOMS ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.067	0.110	0.079	0.543
Sex	0.485	2.060	0.021	0.814
Household income	-1.246	0.500	-0.214	0.014
euroSCORE	-0.096	0.342	-0.038	0.780
T1 BDI total score	0.204	0.110	0.157	0.067
Step 2				
Age	0.059	0.108	0.069	0.588
Sex	0.282	2.022	0.012	0.889
Household income	-1.108	0.494	-0.191	0.026
euroSCORE	-0.033	0.336	-0.013	0.923
T1 BDI total score	0.071	0.120	0.055	0.555
T1 Illness perceptions	0.158	0.062	0.230	0.012

Step 1 R^2 = 0.078; Step 2 R^2 = 0.119; N = 145

The succeeding hierarchical regression analyses used baseline somatic/affective depression symptoms (Table 7.43). The model shows that household income (t = -2.477, p = 0.014) and T1 somatic/affective depression symptoms (t = 2.352, p = 0.020) were the only significant predictors of T3 CROQ physical symptoms in step 1 adjusted for covariates. After adding T1 illness perception total score into the model, household income (t = -2.254, p = 0.026) remained a significant predictor, but not T1 somatic/affective depression symptoms (t = 0.979, p = 0.329). T1 illness perception score was also a significant predictor (t = 2.232, p = 0.027), with a positive association such that the participants with the most negative view of their illness at baseline, had greater physical symptoms following surgery. The final model accounted for 12.3% (R^2 = 0.123) of variance in T3 physical symptom scores. Looking at the standardised regression coefficient (β) for depression symptoms shows that with the inclusion of illness perceptions in the model, the β for depression symptoms changed from 0.197 to 0.093. This indicates that when physical activity was included in the model, there was a 52.8% reduction in the size of β for somatic/affective BDI depression. In regression models using the individual illness perceptions as predictors of T3 physical symptoms, adjusting for covariates and T1 somatic/affective depression, only the T1 illness perception of concern (t = 2.812, p = 0.006) was a significant predictor, such that those participants who were most concerned about their illness prior to surgery had greater physical symptoms after surgery.

TABLE 7.43: HIERARCHICAL REGRESSION OF T3 PHYSICAL SYMPTOMS ON T1 ILLNESS PERCEPTIONS AND T1 SOMATIC/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.068	0.108	0.081	0.528
Sex	0.351	2.046	0.015	0.864
Household income	-1.230	0.496	-0.212	0.014
euroSCORE	-0.126	0.340	-0.050	0.712
T1 BDI somatic	0.351	0.149	0.197	0.020
Step 2				
Age	0.063	0.106	0.075	0.553
Sex	0.225	2.019	0.010	0.911
Household income	-1.110	0.492	-0.191	0.026
euroSCORE	-0.058	0.336	-0.023	0.864
T1 BDI somatic	0.165	0.169	0.093	0.329
T1 Illness perceptions	0.143	0.064	0.208	0.027

Step 1 R^2 = 0.091; Step 2 R^2 = 0.123; N = 145

Mediation was assessed by using a Sobel test on the data. The model included T1 somatic/affective BDI score as the independent variable and T3 CROQ physical symptoms as the dependent variable, with T1 illness perceptions entered as the mediator. Covariates included age, sex, household income and euroSCORE. The results of this Sobel test are illustrated in Figure 7.2, showing a significant total effect (pathway *c*) for the T1 somatic/affective depression symptoms and T3 CROQ physical symptom relationship (B = 0.351, SE = 0.149, *p* = 0.020). However, the direct pathway (pathway *c*') (B = 0.165, SE = 0.169, *p* = 0.330) was not significant after taking the mediator into account. The indirect pathway (pathway *ab*) was significant in this model (B = 0.185, SE = 0.091, 95% CI = 0.028-0.391), confirming baseline illness perceptions to be a significant mediator. Full mediation was shown since the direct effect, pathway *c*', was not significant after illness perceptions were taken into account.

In summary, baseline illness perceptions were a significant predictor of T3 physical symptoms in models using all depression symptom subtypes. Moreover, the association between somatic/affective depression symptoms and T3 physical symptoms was mediated by illness perceptions. The individual illness perception that was of particular importance in this relationship was concern.

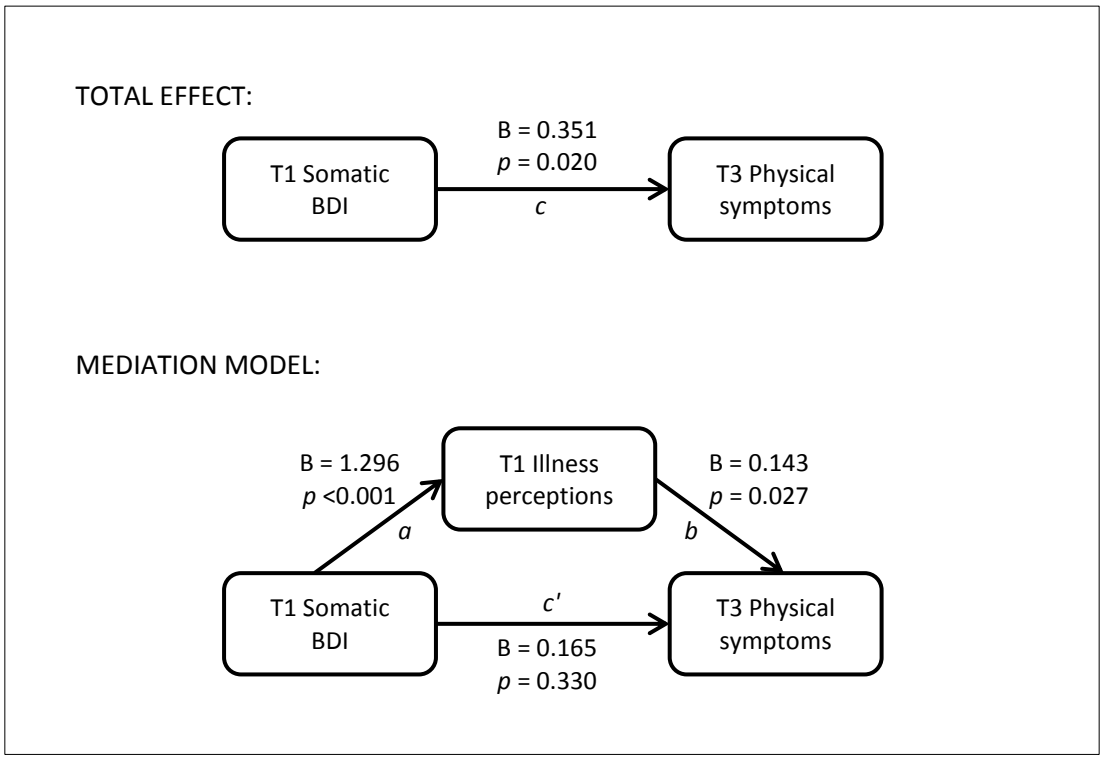

FIGURE 7.2: MEDIATION MODEL OF T1 SOMATIC/AFFECTIVE DEPRESSION SYMPTOMS AND T3 PHYSICAL SYMPTOMS THROUGH T1 ILLNESS PERCEPTIONS

7.7.2.5 Mediation models of T3 health status

Physical health status

A hierarchical regression model was built to assess the relative contribution of baseline illness perceptions to the depression symptoms-T3 physical health status relationship. Depression symptom subtypes were used in separate models. The final model using T1 total BDI score, confirmed the earlier presented results that T1 total BDI score (t = -1.203, p = 0.231) was not a significant predictor of T3 physical health status. T1 total illness perceptions were also not a significant predictor (t = -1.906, p = 0.059) in this model. However, in separate regression models using each of the BIPQ items entered individually to predict physical health status at T3, item 3 (personal control) (t = -1.906, p = 0.059) and item 5 (identity) (t = -1.906, p = 0.059) were both significant. These results suggest that those participants prior to surgery who felt least control over their illness and experienced most physical symptoms, had poorer physical health status at T3. In models using somatic/affective depression symptom scores as a predictor of T3 physical health status, somatic/affective depression symptoms (t = -1.716, p = 0.088) and total illness perceptions (t = -1.627, p = 0.106) were both not significant predictors of T3 physical health status. Moreover, none of the individual illness perceptions were found to be significant when entered into separate regression models. Since illness perceptions were

not significant predictors of T3 physical health status, Sobel tests of mediation were not conducted.

TABLE 7.44: HIERARCHICAL REGRESSION OF T3 PHYSICAL HEALTH STATUS ON T1 ILLNESS PERCEPTIONS AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	-0.137	0.124	-0.148	0.269
Sex	-5.189	2.240	-0.213	0.022
Household income	0.225	0.554	.035	0.686
euroSCORE	0.787	0.378	0.285	0.039
T1 Physical health status	0.046	0.067	0.060	0.491
T1 BDI cognitive	-0.217	0.200	-0.095	0.280
Step 2				
Age	-0.147	0.122	-0.159	0.230
Sex	-5.186	2.204	-0.213	0.020
Household income	0.102	0.548	0.016	0.852
euroSCORE	0.734	0.373	0.266	0.051
T1 Physical health status	-0.030	0.074	-0.039	0.682
T1 BDI cognitive	-0.066	0.207	-0.029	0.751
T1 Illness perceptions	-0.171	0.073	-0.229	0.020

Step 1 R^2 = 0.069; Step 2 R^2 = 0.104; N = 146

A hierarchical regression model was subsequently built adjusting for cognitive/affective depression symptoms (Table 7.44). The model shows that sex (t = -2.317, p = 0.022) and euroSCORE (t = 2.081, p = 0.039) were the only significant predictors of T3 physical health status in step 1 adjusted for covariates, such that female sex and greater mortality risk were associated with poorer physical health status. After adding T1 illness perception total score into the model, female sex (t = -2.352, p = 0.020) remained a significant predictor. In addition, T1 illness perception score was also a significant predictor (t = -2.349, p = 0.044), with a negative association such that the participants with the most negative view of their illness at baseline, had poorer physical health status following surgery. In particular, in individual analyses entering each of the T1 BIPQ items separately to predict physical health status at T3, item 2 (timeline) (t = -2.102, p = 0.037), item 3 (personal control) (t = -2.071, p = 0.040) and item 5 (concern) (t = -2.139, p = 0.034) were significant independent predictors. These results suggest that those participants who felt their illness would last longer and who perceived less personal control and greater concern prior to surgery, experienced lower physical health status two months after surgery. In summary, these results suggest that

baseline illness perceptions were inconsistently associated with physical health status at T3, after taking baseline depression scores into account.

Mental health status

A regression model was built using the hierarchical method to assess the relative contribution of illness perceptions to the depression symptoms-T3 mental health status relationship. Depression symptom subtypes were used in separate models. The final model using T1 total BDI score, confirmed the earlier presented results that baseline total BDI score (t = -0.554, p = 0.581) was not a significant predictor of T3 mental health status. T1 illness perceptions were, however, a significant predictor (t = -2.798, p = 0.006) in this model, with a negative association such that a more negative view of one's illness prior to surgery was related to lower mental health status at T3. Individual item analyses showed that the only T1 illness perception that was significantly associated with lower mental health status at T3, was item 1 (consequences) (t = -2.752, p = 0.007). Similar findings were also found using T1 somatic/affective depression symptom scores in models to predict T3 physical health status, such that baseline somatic/affective depression symptom score (t = -0.505, p = 0.614) was not a significant predictor, but illness perceptions (t = -2.700, p = 0.008) were. Again, the only individual illness perception to predict lower mental health status was item 1 (consequences) (t = -2.634, p = 0.009). This result suggests that those participants who, prior to surgery, felt their illness had more negative consequences, reported lower mental health status two months after surgery. Results using cognitive/affective depression symptoms also supported this trend, such that cognitive/affective depression symptom score (t = -0.692, p = 0.490) was not a significant predictor of T3 mental health status, but illness perceptions (t = -2.974, p = 0.003) were. Individual item analyses showed that two of the illness perceptions experienced prior to surgery were predictive of lower mental health status at T3: item 1 (consequences) (t = -2.948, p = 0.004) and item 5 (concern) (t = -1.984, p = 0.049). However, since depression symptom subtypes were not significant predictors of T3 mental health status, Sobel tests of mediation were not conducted.

In summary, these results suggest that illness perceptions were a significant predictor of T3 mental health status in models controlling for all depression symptom subtypes. However, since depression symptoms subtypes were not a significant predictor of T3 mental health status, mediation did not occur, instead illness perceptions were an independent predictor.

7.7.3 Biological mechanisms – cortisol

7.7.3.1 Descriptive statistics

TABLE 7.45: T1 AND T3 NON-TRANSFORMED SALIVARY CORTISOL DATA

Cortisol (nmol/l)	*N*	*T1* *Mean ± SD*	*T3* *Mean ± SD*	*p*
Waking	135	21.11±10.80	19.37±10.50	0.102
Waking + 30 minutes	136	25.88±12.90	23.68±11.07	0.094
10:00am	143	13.32±7.52	13.08±7.12	0.735
12:00noon	141	9.64±5.58	9.58±7.14	0.926
4:00 pm	145	6.76±3.31	7.17±5.06	0.402
8:00 pm	145	4.82±4.70	4.93±5.64	0.850
Bedtime	143	3.97±3.41	3.82±3.83	0.713
Slope	73	0.02±0.01	0.02±0.01	0.876
CAR	122	5.02±13.66	3.64±11.14	0.465
AUC	146	9220.02±2986.10	9184.03±3838.90	0.925
Waking-bedtime difference	132	17.39±10.28	15.91±10.48	0.153

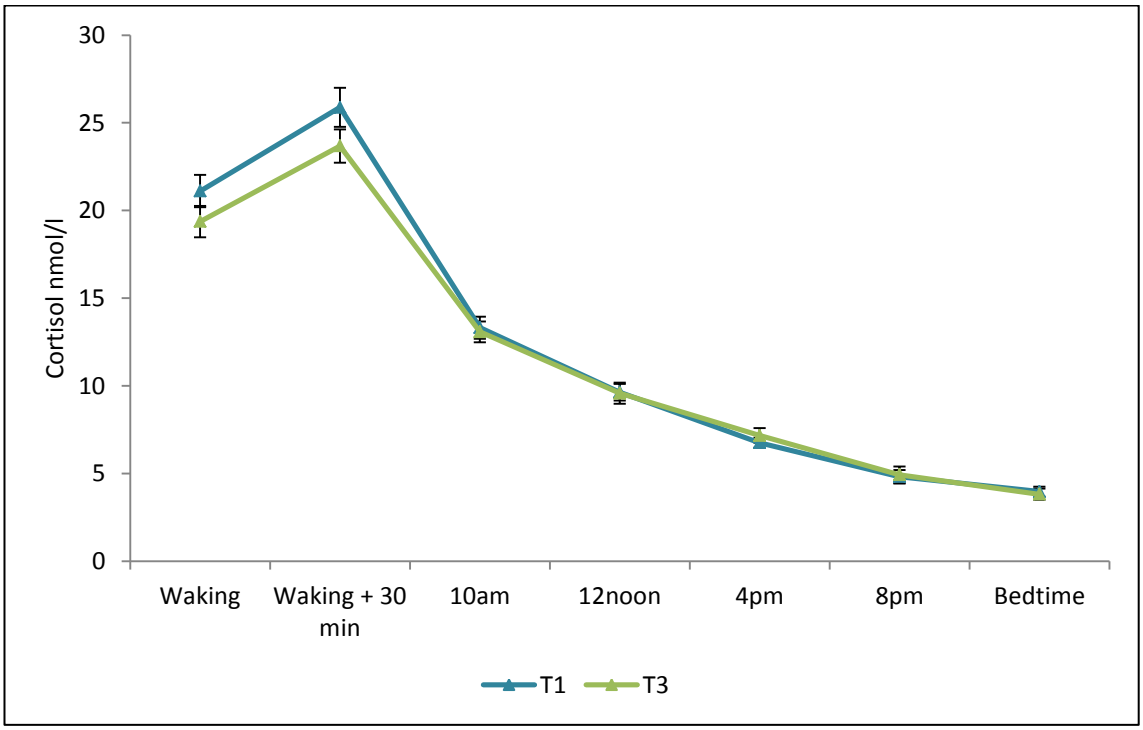

FIGURE 7.3: T1 AND T3 MEAN SALIVARY CORTISOL ACROSS THE DAY

N.B. Bars represent standard error of the means

The first biological pathway to be tested in this PhD was the role of the neuroendocrine hormone, cortisol. Descriptive statistics for cortisol at T1 and T3 are displayed in Table 7.45, with *p* representing the significance value in dependent *t*-tests. Missing cortisol data was due to some participants declining to provide samples and some outliers being removed. Data show that there were no significant differences in participants' cortisol samples at T3 compared to T1. Figure 7.3 represents the mean T1 and T3 cortisol data at the seven measurement points for participants across the course of the day, showing at T3 there was a smaller peak in cortisol at 30 minutes after waking compared to T1.

Cross-sectional associations between cardiac medication, including aspirin, beta-blockers, statins and antiplatelets, and cortisol responses, were not found using T1 or T3 data; multiple regression models supported these findings. Therefore, the regression models shown in the following sections adjust for the demographic and disease severity covariates only.

7.7.3.2 Associations with depression symptom variables

Pearson's correlation analyses were performed to assess the relationship between the different cortisol scores (CAR, AUC, slope, waking-bedtime difference) and baseline depression symptom scores. Results showed no significant correlations between cortisol and the depression symptom scores. Regression analyses were also performed to assess whether cortisol predicted any of the recovery outcomes after controlling for demographic and disease severity covariates; anxiety and health status models also controlled for baseline scores. Statistically, the correlation coefficient represents the linear dependence between variables, but it does not control for the fact that other factors may also account for the relationship, potentially producing a biased estimate. Results found that depression symptoms caseness (BDI ≥13) (t = 2.639, p = 0.009) was significantly associated with T1 cortisol AUC after controlling for covariates; see Table 7.46. This association was positive such that depressed participants had a larger total cortisol output over the course of the day than their non-depressed counterparts. This model accounted for 8.8% (R^2 = 0.088) of variance in T1 cortisol AUC. The difference in cortisol scores by depression caseness at T1 is represented in Figure 7.4, with independent *t*-tests confirming the difference between depressed and non-depressed participants in terms of AUC ($t(121)$ = -2.105, p = 0.037).

TABLE 7.46: MULTIPLE REGRESSION OF T1 CORTISOL AUC ON T1 DEPRESSION CASENESS

Model	*B*	*SE*	*ß*	*p*
Age	37.183	42.448	0.115	0.383
Sex	-1214.514	851.458	-0.136	0.156
Household income	218.143	207.512	0.097	0.295
euroSCORE	96.347	133.806	0.099	0.473
T1 Depression symptoms caseness	1791.017	678.675	0.233	0.009

R^2 = 0.088, *N* = 128

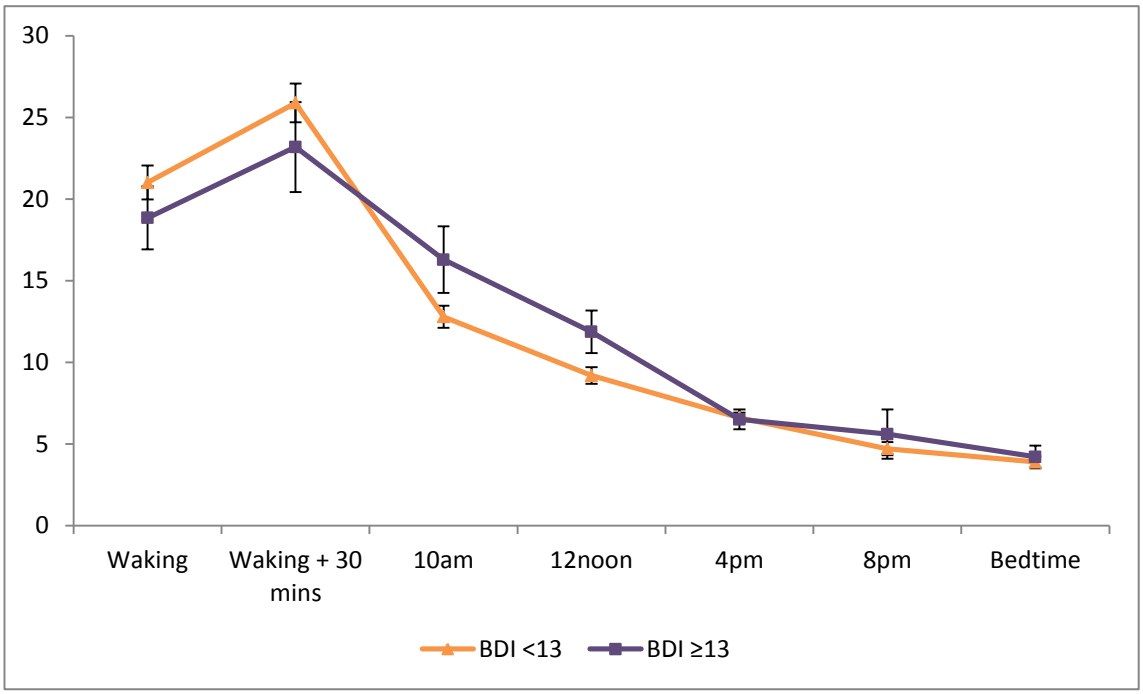

FIGURE 7.4: MEAN T1 SALIVARY CORTISOL ACROSS THE DAY BY T1 DEPRESSION SYMPTOMS CASENESS

N.B. Bars represent standard error of the means

Next, Pearson's correlation analyses were performed to assess the relationship between the different cortisol scores at baseline (CAR, AUC, slope, waking-bedtime difference) and the T3 recovery outcomes scores. Results showed no significant correlations between baseline cortisol and the outcomes measures. Multiple regression analyses were also performed using baseline cortisol to predict T3 recovery outcomes, adjusting for demographic and disease severity covariates and baseline scores on anxiety and health status outcome measures, where applicable. Results found that T1 cortisol AUC (t = 2.082, p = 0.039) was a significant predictor of mental health status at T3, after controlling for demographic and disease severity covariates (see Table 7.47). This relationship was positive, which meant that those participants with higher cortisol output across the day had higher mental health status.

This suggests that participants with a blunted cortisol output, had lower mental health status. This is contradictory to the depression symptom results which showed depression caseness was associated with greater cortisol output. The only other significant predictor in this model was baseline mental health status score (t = 4.724, p < 0.001). This model accounted for 19.6% (R^2 = 0.196) of variance in T3 mental health status scores. Cortisol was not significantly related to any other recovery outcomes in regression models controlling for covariates.

TABLE 7.47: MULTIPLE REGRESSION OF T1 CORTISOL AUC ON T3 MENTAL HEALTH STATUS

Model	*B*	*SE*	*ß*	*p*
Age	0.023	0.098	0.031	0.812
Sex	1.231	1.896	0.059	0.517
Household income	0.074	0.461	0.014	0.873
euroSCORE	-0.355	0.302	-0.156	0.242
T1 Mental health status	0.436	0.092	0.399	<0.001
T1 Cortisol AUC	0.000	0.000	0.172	0.039

R^2 = 0.196, N = 129

7.7.3.3 Mediation models of T3 health status

A regression model was built using the hierarchical method in which predictor variables were entered in steps, to assess the relative contribution of baseline cortisol AUC to the depression symptoms-T3 mental health status relationship. In order to explore the data fully, cortisol AUC was entered into regression models with each of the depression symptom scores in turn. The final model using total BDI score, confirmed the earlier presented results that T1 total BDI score (t = -1.840, p = 0.068) was not a significant predictor of T3 mental health status. T1 cortisol AUC was however a significant predictor (t = 2.363, p = 0.020) in this model. Similar findings were also found using cognitive/affective depression symptom scores as a predictor of T3 mental health status, such that T1 cognitive/affective depression symptoms (t = -1.623, p = 0.107) were not a significant predictor in the final model but T1 cortisol AUC (t = 2.269, p = 0.025) was. Since baseline total BDI depression, cognitive/affective depression symptoms were not significant predictors of T3 mental health status, Sobel tests of mediation were not conducted.

Next a hierarchical regression model was built adjusting for baseline somatic/affective depression symptoms (Table 7.48). This model shows that baseline mental health status (t = 3.686, p <0.001) was the only significant predictor of T3 mental health status in step 1 adjusted for covariates, such that higher baseline mental health status was associated with greater mental health status at T3. After adding T1 cortisol AUC into the model, T1 mental health

status (t = 3.698, p <0.001) remained a significant predictor and T1 somatic/affective depression symptoms (t = -2.028, p = 0.045) became significant. In addition, T1 cortisol AUC was also a significant predictor (t = 2.403, p = 0.018), with a positive association such that the participants with the highest cortisol responses, had the highest mental health status following surgery. The final model accounted for 22.3% (R^2 = 0.223) of variance in T3 mental health status scores. However, since somatic/affective depression symptoms were not a significant predictor in step 1 of this model, a Sobel test of mediation was not conducted.

In summary, these results suggest that cortisol AUC was a significant predictor of T3 mental health status in models controlling for total BDI, cognitive/affective and somatic/affective depression. These results demonstrated that lower cortisol output across the day was associated with lower mental health status after surgery.

TABLE 7.48: HIERARCHICAL REGRESSION OF T3 MENTAL HEALTH STATUS ON T1 CORTISOL AUC AND T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Step 1				
Age	0.011	0.100	0.015	0.909
Sex	0.770	1.899	0.037	0.686
Household income	0.149	0.465	0.028	0.750
euroSCORE	-0.259	0.306	-0.114	0.399
T1 Mental health status	0.369	0.100	0.337	<0.001
T1 BDI somatic	-0.238	0.147	-0.147	0.107
Step 2				
Age	0.000	0.098	0.000	0.999
Sex	1.387	1.881	0.066	0.462
Household income	0.070	0.458	0.013	0.879
euroSCORE	-0.305	0.301	-0.134	0.313
T1 Mental health status	0.364	0.098	0.332	<0.001
T1 BDI somatic	-0.296	0.146	-0.182	0.045
T1 Cortisol AUC	0.000	0.000	0.200	0.018

Step 1 R^2 = 0.185; Step 2 R^2 = 0.223; N = 128

7.7.3.4 T1 depression symptoms predicting T3 cortisol

Although not part of the primary hypotheses of this PhD, additional regression analyses were also performed to assess whether depression symptom subtypes at T1 were able to predict cortisol at T3, after controlling for demographic and disease severity covariates. Anxiety and health status models also controlled for baseline scores on these measures. These analyses

were performed in order to further explore the cortisol data. Results found that T1 total BDI score (t = -1.988, p = 0.049) was a significant predictor of T3 waking-bedtime difference in cortisol after controlling for covariates; see Table 7.49. This association was negative such that greater baseline depression symptoms were associated with a lower change in cortisol output from the waking to bedtime response. This smaller change is suggestive of a flatter cortisol response across the day. This model accounted for 5.4% (R^2 = 0.054) of variance in T3 waking-bedtime cortisol difference.

TABLE 7.49: MULTIPLE REGRESSION OF T3 CORTISOL WAKING-BEDTIME DIFFERENCE ON T1 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.099	0.162	-0.087	0.541
Sex	3.308	3.030	0.103	0.277
Household income	1.175	0.731	0.147	0.111
euroSCORE	0.217	0.511	0.061	0.673
T1 BDI total score	-0.313	0.157	-0.181	0.049

R^2 = 0.054, N = 131

TABLE 7.50: MULTIPLE REGRESSION OF T3 CORTISOL WAKING-BEDTIME DIFFERENCE ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.126	0.160	-0.109	0.433
Sex	2.504	2.908	0.080	0.391
Household income	1.187	0.724	0.149	0.104
euroSCORE	0.232	0.501	0.066	0.645
T1 BDI cognitive	-0.571	0.254	-0.205	0.026

R^2 = 0.059, N = 133

Results also found that T1 cognitive/affective depression symptom score (t = -2.250, p = 0.026) was a significant predictor of T3 waking-bedtime difference in cortisol after controlling for covariates; see Table 7.50. This association was negative such that greater depression symptoms were associated with a smaller change in cortisol output from their waking to bedtime response. This suggests that participants with the greatest depression symptoms experienced a flatter cortisol response across the day. This model accounted for 5.9% (R^2 = 0.059) of variance in T3 waking-bedtime cortisol difference. However, in models using somatic/affective depression symptoms to predict T3 waking-bedtime cortisol difference, T1 somatic/affective depression score was not a significant predictor (t = -1.921, p =

0.057) after adjusting for covariates. In summary, these findings demonstrate that baseline total and cognitive/affective depression symptoms were significant independent predictors of a flatter cortisol response two months after surgery.

Next, regression models were built to assess the relationship of baseline depression symptoms on cortisol AUC at T3. Results found that T1 cognitive/affective depression symptom score (t = -2.026, p = 0.045) was a significant predictor of T3 cortisol AUC after controlling for covariates; see Table 7.51. This association was negative such that participants with greater cognitive/affective depression symptoms had a smaller cortisol output across the day compared to those with fewer depression symptoms. This model accounted for 15.3% (R^2 = 0.153) of variance in T3 cortisol AUC. This contradicts the findings looking at the associations between baseline depression symptoms and T1 cortisol, whereby greater depression symptoms were associated with greater cortisol AUC. Interestingly, neither total BDI score (t = -1.519, p = 0.131) nor somatic/affective depression symptom score (t = -1.001, p = 0.319) at baseline were able to significantly predict cortisol AUC at T3. In summary, these findings demonstrate that baseline cognitive/affective depression symptoms were a significant independent predictor of a lower cortisol output across the day, two months after surgery.

TABLE 7.51: MULTIPLE REGRESSION OF T3 CORTISOL AUC ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-95.952	54.317	-0.238	0.080
Sex	-765.111	1042.716	-0.067	0.465
Household income	381.545	248.064	0.135	0.127
euroSCORE	638.200	170.036	0.518	<0.001
T1 BDI cognitive	-177.772	87.729	-0.180	0.045

R^2 = 0.153, N = 127

7.7.3.5 Cross-sectional associations between T3 cortisol and T3 recovery

The following analyses are again not related to the primary hypotheses of this PhD, which focus on prospective relationships over time, but instead are included here in order to demonstrate the cross-sectional relationship between cortisol responses and recovery at T3. These analyses were performed since there was only limited evidence of baseline cortisol affecting post-operative recovery; therefore, the cortisol data warranted exploring in greater detail.

To this effect, multiple regression analyses were performed to assess the relationship between T3 cortisol and T3 recovery, after controlling for baseline demographic and disease

severity covariates. In addition, models of anxiety and health status also controlled for baseline scores on these measures. Since these models were assessing the cross-sectional association between variables and not the temporal relationship across time, depression symptom scores at T3 were also used as a covariate in the models, including total T3 BDI score, somatic/affective and cognitive/affective depression symptom scores.

Anxiety

Results using T3 total BDI depression, found that T3 cortisol slope (t = 2.583, p = 0.011) was a significant predictor of T3 anxiety after controlling for covariates; see Table 7.52. This association was negative such that a flatter slope was associated with greater anxiety. The only other significant predictors in this model were household income (t = -2.365, p = 0.020), T1 anxiety (t = 6.547, p <0.001), and T3 total BDI score (t = 9.428, p <0.001), such that lower household income, higher baseline anxiety and higher depression symptoms at T3 were associated with greater anxiety at T3. This model accounted for 64.9% (R^2 = 0.649) of variance in T3 anxiety. Cortisol slope remained significant in models adjusting for T3 somatic/affective depression symptoms (slope: t = -2.769, p = 0.006) and cognitive/affective depression symptoms (slope: t = -2.707, p = 0.008).

TABLE 7.52: MULTIPLE REGRESSION OF T3 ANXIETY ON T3 CORTISOL SLOPE AND T3 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	-0.025	0.032	-0.065	0.438
Sex	-0.617	0.569	-0.064	0.281
Household income	-0.341	0.144	-0.130	0.020
euroSCORE	0.072	0.100	0.063	0.475
T1 Anxiety	0.307	0.047	0.378	<0.001
T3 BDI total score	0.342	0.036	0.538	<0.001
T3 Cortisol slope	-36.259	14.036	-0.139	0.011

R^2 = 0.649, N = 136

In summary, cross-sectional analyses showed that cortisol slope was significantly related to T3 anxiety after controlling for covariates in models adjusted for T3 total depression, T3 somatic/affective depression and T3 cognitive/affective depression symptoms. This relationship was such that those participants with a flatter cortisol slope across the day had greater anxiety symptoms. The direction of causality in this relationship is not clear.

Physical symptoms

The following analyses assessed the cross-sectional association between T3 CAR and T3 physical symptoms. Results using T3 total BDI depression, found that T3 CAR (t = -2.409, p = 0.018) was significantly associated with T3 physical symptoms after controlling for covariates; see Table 7.53. This association was negative such that a smaller awakening response was associated with greater physical symptoms. The only other significant variable in this model was T3 total BDI score (t = 2.760, p = 0.007), such that higher depression symptoms at T3 were associated with greater physical symptoms at T3. This model accounted for 17.0% (R^2 = 0.170) of variance in T3 physical symptoms. CAR remained significant in models adjusting for T3 somatic/affective depression symptoms (CAR: t = -2.418, p = 0.018) and cognitive/affective depression symptoms (CAR: t = -2.345, p = 0.021).

TABLE 7.53: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T3 CAR AND T3 TOTAL BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	0.026	0.128	0.033	0.840
Sex	0.008	2.119	0.000	0.997
Household income	-0.871	0.596	-0.157	0.148
euroSCORE	0.005	0.426	0.002	0.990
T3 BDI total score	0.381	0.138	0.287	0.007
T3 CAR	-0.172	0.071	-0.251	0.018

R^2 = 0.170, N = 91

In summary, these results have shown that the T3 awakening response in cortisol is significantly related to physical symptoms at T3, such that those participants who had a lower cortisol peak half an hour after waking also reported greater physical symptoms. This relationship was maintained in models adjusting for total BDI depression symptom score at T3, somatic/affective and cognitive/affective depression symptoms at T3.

7.7.4 Biological mechanisms – inflammatory markers

7.7.4.1 Descriptive statistics

The second biological pathway tested in the PhD was the role of inflammatory markers, including IL-6, hs-CRP and TNF-α. Inflammatory markers were measured both before CABG and post-CABG, during the post-surgery hospital stay. Due to the variability in collection day for the post-operative bloods, two summary scores were created. The first summary score used the

mean for the inflammatory marker values on days one, two and three post-surgery, and the second used the mean for the inflammatory marker values on days four, five, six, seven and eight post-surgery. These scores were termed 'early' and 'late' T2 bloods. Change scores were also computed by deducting baseline from follow-up values; larger change scores indicate a greater response from T1 to T2.

The change in the inflammatory markers over time was presented in Chapter 6, but for ease of reference are shown in Table 7.54 using participants who completed T1-T3 assessments. Dependent *t*-tests were used to assess change over time. Data confirm the same trend shown with the larger sample used in Chapter 6, such that for IL-6 and hs-CRP there was a significant increase from T1 to T2, for both early and late samples. In addition, there was a significant decrease from T2 early to T2 late samples for these inflammatory markers. The TNF-α data reveals that no significant changes occurred over time.

TABLE 7.54: BASELINE INFLAMMATORY MARKER NON-TRANSFORMED DATA

Inflammatory marker	*Pair*	*N*	*Mean ± SD*	*t*	*p*
IL-6 (pg/mL)	T1 T2 Early	104	5.40±1.76 218.22±56.98	-38.148	<0.001
	T1 T2 Late	99	5.17±1.69 96.12±28.51	-32.122	<0.001
	T2 Early T2 Late	74	216.03±64.74 98.13±25.43	14.995	<0.001
hs-CRP (mg/mL)	T1 T2 Early	107	7.75±6.95 76.97±58.33	-12.243	<0.001
	T1 T2 Late	100	8.95±10.04 69.53±66.56	-9.551	<0.001
	T2 Early T2 Late	74	81.67±65.27 65.02±60.05	2.213	0.030
TNF-α (pg/mL)	T1 T2 Early	107	5.65±2.72 6.04±2.68	-1.032	0.305
	T1 T2 Early	100	5.79±2.79 5.97±2.62	-0.443	0.658
	T2 Early T2 Late	74	6.07±2.75 6.36±2.75	-0.637	0.526

7.7.4.2 Associations with depression symptom variables

Pearson's correlation analyses were first performed to assess the relationship between the different inflammatory markers (IL-6, hs-CRP, TNF-α) at baseline, T2 early and T2 late, with

baseline depression symptom scores. Results showed no significant associations between any of the inflammatory markers and the depression symptom scores.

Regression analyses were next performed to assess whether depression symptoms were able to predict the inflammatory marker responses after controlling for covariates. Results found only one model was significant; this is displayed in Table 7.55 and shows that cognitive/affective depression symptoms (t = 2.031, p = 0.045) were a significant predictor of T2 early IL-6 responses, with greater depression symptoms being associated with greater IL-6 levels in the days following surgery, after controlling for demographic and disease severity covariates. This model accounted for 7.0% (R^2 = 0.070) of variance in IL-6 T2 early responses.

TABLE 7.55: MULTIPLE REGRESSION OF IL-6 T2 EARLY ON T1 COGNITIVE/AFFECTIVE BDI SCORE

Model	*B*	*SE*	*ß*	*p*
Age	1.141	1.046	0.167	0.278
Sex	33.754	19.290	0.188	0.083
Household income	-0.501	4.692	-0.011	0.915
euroSCORE	-4.362	3.198	-0.220	0.176
T1 BDI cognitive	3.535	1.740	0.205	0.045

R^2 = 0.070, N = 105

7.7.5 Associations with recovery variables

Next, Pearson's correlations were performed to assess the associations between the inflammatory markers at baseline, T2 early and T2 late, with the T3 recovery outcomes. Results found no significant correlations between the inflammatory markers and T3 recovery outcomes. However, regression models were also used to assess the relationship between inflammatory markers and the T3 recovery outcomes controlling for demographic, disease severity and depression symptom covariates. The results from these analyses are described below, but since none of the inflammatory markers associated with the recovery outcomes were also associated with depression symptoms, mediation analyses were not performed.

Anxiety

A multiple regression model was built to assess the relative contribution of inflammation to T3 anxiety. There were no significant results using hs-CRP or IL-6 responses. Instead, results showed that TNF-α T2 early response was a significant predictor. The model is displayed in Table 7.56 and shows that T1 anxiety (t = 4.992, p <0.001) and TNF-α T2 early (t = -2.727, p = 0.008) were the only significant predictors of T3 anxiety after adjusting for covariates. This

association was such that those participants, who had higher anxiety prior to surgery and a lower level of TNF-α one to three days after surgery, had greater anxiety up to two months after surgery. The model accounted for 41.3% (R^2 = 0.413) of variance in T3 anxiety scores. TNF-α T2 early was also a significant predictor of T3 anxiety in models using somatic/affective (TNF-α: t = -2.815, p = 0.006) and cognitive/affective (TNF-α: t = -2.633, p = 0.010) depression. These negative associations were an unexpected finding and it is not clear why a lower TNF-α response was predictive of greater anxiety. In summary, these results show that TNF-α in the days shortly following surgery was an important independent predictor of greater anxiety two months after surgery.

TABLE 7.56: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T2 TNF-α EARLY

Model	*B*	*SE*	*ß*	*p*
Age	-0.027	0.050	-0.067	0.595
Sex	-1.779	0.927	-0.173	0.058
Household income	-0.389	0.221	-0.148	0.081
euroSCORE	0.127	0.159	0.105	0.428
T1 Anxiety	0.409	0.082	0.502	<0.001
T1 BDI total score	0.071	0.062	0.113	0.257
T2 TNF-α early	-0.292	0.107	-0.217	0.008

R^2 = 0.413, N = 103

Physical symptoms

The following analyses were performed to assess the relative contribution of inflammation to T3 physical symptoms. There were no significant results using hs-CRP or TNF-α responses. Instead, results showed that IL-6 T2 late response and change in IL-6 from baseline to T2 late, were both significant predictors. The model using IL-6 T2 late response is displayed in Table 7.57 and shows that T2 late IL-6 (t = 2.746, p = 0.007) was the only significant predictor of T3 physical symptoms after adjusting for covariates and baseline total BDI score. This association was positive such that those participants who had a higher level of IL-6 four to eight days after surgery, had greater physical symptoms up to two months after surgery. The model accounted for 12.6% (R^2 = 0.126) of variance in T3 physical symptom scores. T2 late IL-6 response was also a significant predictor of T3 physical symptoms in models using T1 somatic/affective (t = 2.837, p = 0.006) and cognitive/affective (t = 2.738, p = 0.007) depression symptom scores. Only T1 somatic/affective depression symptoms (t = 2.023, p = 0.046) also remained a significant predictor of T3 physical symptoms in models using T2 IL-6 late.

TABLE 7.57: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T2 IL-6 LATE

Model	*B*	*SE*	*ß*	*p*
Age	0.047	0.154	0.053	0.761
Sex	2.217	2.711	0.084	0.416
Household income	-0.945	0.613	-0.156	0.126
euroSCORE	-0.112	0.475	-0.041	0.814
T1 BDI total score	0.168	0.142	0.125	0.241
T2 IL-6 late	0.077	0.028	0.278	0.007

R^2 = 0.126, N = 96

TABLE 7.58: MULTIPLE REGRESSION OF T3 PHYSICAL SYMPTOMS ON T1 TO T2 LATE IL-6 CHANGE

Model	*B*	*SE*	*ß*	*p*
Age	0.004	0.165	0.004	0.983
Sex	2.202	2.768	0.085	0.429
Household income	-0.957	0.653	-0.154	0.146
euroSCORE	0.045	0.517	0.016	0.930
T1 BDI total score	0.167	0.149	0.122	0.265
IL-6 change T1-T2 late	0.075	0.030	0.264	0.014

R^2 = 0.124, N = 91

The model using IL-6 change from T1 to T2 late is displayed in Table 7.58 and shows that IL-6 change (t = 2.520, p = 0.014) was the only significant predictor of T3 physical symptoms after adjusting for covariates and baseline total BDI score. This association was positive such that those participants who had a higher change in IL-6 from before CABG to four to eight days after surgery, had greater physical symptoms up to two months after surgery. The model accounted for 12.4% (R^2 = 0.124) of variance in T3 physical symptom scores. T2 late IL-6 was also a significant predictor of T3 physical symptoms in models using T1 somatic/affective (t = 2.583, p = 0.012) and cognitive/affective (t = 2.500, p = 0.014) depression symptom scores. Somatic/affective depression symptoms (t = 1.981, p = 0.051) was borderline significant in the model, but cognitive/affective depression symptoms were not significant.

In summary, these results show that the IL-6 response four to eight days following surgery was an important independent predictor of physical symptoms experienced up to two months after surgery. In particular, those participants with the greatest increase in IL-6 from baseline to four to eight days after surgery had the greatest physical symptoms at T3.

Health status

TABLE 7.59: MULTIPLE REGRESSION OF T3 MENTAL HEALTH STATUS ON T2 TNF-α EARLY

Model	*B*	*SE*	*ß*	*p*
Age	-0.176	0.113	-0.220	0.125
Sex	1.506	2.092	0.071	0.473
Household income	-0.170	0.505	-0.032	0.736
euroSCORE	0.172	0.346	0.074	0.621
T1 Mental health status	0.355	0.105	0.334	0.001
T1 BDI total score	-0.265	0.127	-0.207	0.040
T2 TNF-α early	0.706	0.244	0.259	0.005

R^2 = 0.245, *N* = 105

TABLE 7.60: MULTIPLE REGRESSION OF T3 MENTAL HEALTH STATUS ON T1 TO T2 EARLY TNF-α CHANGE

Model	*B*	*SE*	*ß*	*p*
Age	-0.180	0.119	-0.226	0.135
Sex	2.284	2.193	0.107	0.300
Household income	-0.187	0.519	-0.035	0.719
euroSCORE	0.114	0.370	0.049	0.758
T1 Mental health status	0.367	0.107	0.345	0.001
T1 BDI total score	-0.301	0.130	-0.232	0.023
Change TNF-α T1-T2 early	0.459	0.174	0.241	0.010

R^2 = 0.256, *N* = 99

A multiple regression model was next built to assess the relative contribution of inflammation to T3 health status. There were no significant results using IL-6 or hs-CRP responses. Results did however show that TNF-α T2 early response and change in TNF-α from T1 to T2 early were significant predictors. The model using TNF-α T2 early is displayed in Table 7.59 and shows that T1 mental health status (t = 3.384, p = 0.001), total BDI score (t = -2.085, p = 0.040), and TNF-α T2 early (t = 2.890, p = 0.005) were all significant predictors of T3 mental health status in this model. This association was such that those participants who had higher baseline mental health status, fewer baseline depression symptoms, and a higher level of TNF-α one to three days after surgery, had better mental health status up to two months after surgery. The model accounted for 24.5% (R^2 = 0.245) of variance in T3 mental health status scores. TNF-α T2 early was also a significant predictor of T3 mental health status in models using somatic/affective (TNF-α: t = 2.917, p = 0.004) and cognitive/affective (TNF-α: t = 2.764, p = 0.007) depression. In

summary, these results show that TNF-α in the days shortly following surgery was an important predictor in models using depression symptom subtypes. Interestingly, it was those participants who had a lower TNF-α response who had poorer mental health status; the reason for this is not clear, but is in line with the findings described earlier showing lower TNF-α was predictive of greater anxiety at T3.

The model using change in TNF-α from T1 to T2 early is displayed in Table 7.60 and shows that T1 mental health status (t = 3.422, p = 0.001), total BDI score (t = -2.310, p = 0.023), and TNF-α T2 early (t = 2.636, p = 0.010) were all significant predictors of T3 mental health status in this model. This association was such that those participants, who had higher mental health status and low depression symptoms prior to surgery, and a higher level of change in TNF-α, had better mental health status up to two months after surgery. The model accounted for 25.6% (R^2 = 0.256) of variance in T3 mental health status scores. Change in TNF-α T2 early was also a significant predictor of T3 mental health status in models using somatic/affective (TNF-α: t = 2.610, p = 0.011) and cognitive/affective (TNF-α: t = 2.497, p = 0.014) depression symptom scores. In summary, these results show that change in TNF-α from baseline to the days shortly following CABG surgery was an independent predictor of mental health status as T3. However, it is not clear why a smaller change in the inflammatory response was predictive of poorer mental health status.

7.7.6 Post-operative inflammation and greater T3 depression symptoms

The final model to be tested in this PhD was the association between inflammation occurring in the days after surgery and depression symptoms at T3. This relationship was assessed using both the total BDI continuous score at T3 and the post-CABG depression categorical variable (yes/no). No significant results were found using any of the IL-6 or hs-CRP responses. However, significant findings were found using TNF-α responses in the days after surgery. The model using TNF-α T2 early response is shown in Table 7.61, whereby after controlling for demographic and disease severity covariates and baseline total BDI score, TNF-α T2 early (t = -2.661, p = 0.009) was a significant predictor of greater depression symptoms at T3. This association was negative, such that greater inflammation was predictive of lower depression symptoms. The only other significant predictor in this model was baseline depression symptoms (t = 4.859, p <0.001). The model accounted for 27.0% (R^2 = 0.140) of variance in T3 BDI scores. This result was also replicated in models to predict T3 somatic/affective (t = -2.369, p = 0.020) and cognitive/affective (t = -2.447, p = 0.016) depression symptoms. This negative association between TNF-α and depression symptoms is in line with findings reported earlier showing greater TNF-α at T2 early was associated with better mental health status at T3.

TABLE 7.61: MULTIPLE REGRESSION OF T3 BDI SCORE ON T2 EARLY TNF-α

Model	*B*	*SE*	*ß*	*p*
Age	-0.031	0.095	-0.046	0.741
Sex	-0.489	1.753	-0.027	0.781
Household income	-0.621	0.426	-0.135	0.148
euroSCORE	-0.020	0.291	-0.010	0.945
T1 BDI total	0.484	0.100	0.440	<0.001
T2 early TNF-α	-0.548	0.206	-0.234	0.009

R^2 = 0.270, *N* = 104

Significant findings were also found using TNF-α responses in the days following surgery to predict post-CABG onset depression. Results showed that the TNF-α T2 late response was a significant predictor. The model is displayed in Table 7.62 and shows that TNF-α T2 late (*t* = -2.210, *p* = 0.030) was the only significant predictor of post-CABG onset depression after adjusting for covariates. In line with the results to predict greater total BDI scores at T3, this association was negative such that those participants who had a lower level of TNF-α four to eight days after surgery were significantly more likely to have post-CABG depression up to two months after surgery. The model accounted for 14.0% (R^2 = 0.140) of variance in post-CABG onset depression. In summary, these results show that TNF-α in the days following surgery was an important predictor of depression symptoms two months following surgery.

TABLE 7.62: MULTIPLE REGRESSION OF POST-CABG ONSET DEPRESSION ON T2 LATE TNF-α

Model	*B*	*SE*	*ß*	*p*
Age	-0.015	0.006	-0.416	0.020
Sex	0.042	0.118	0.042	0.721
Household income	-0.004	0.027	-0.015	0.894
euroSCORE	0.025	0.019	0.237	0.194
T2 late TNF-α	-0.030	0.013	-0.247	0.030

R^2 = 0.140, *N* = 75

7.8 Discussion

7.8.1 Summary of results

The table (Table 7.63) displays a summary of the main findings presented in this chapter. Somatic/affective and post-CABG onset depression symptoms were related to all the recovery

outcomes after controlling for covariates. Persistent depression symptoms were related to all the recovery outcomes except physical health status. Total, cognitive/affective and resolved depression symptoms were not significantly related to any of the T3 recovery outcomes after adjustment for covariates. However, due to the small number of depression cases for resolved, persistent and post-CABG onset depression, the role of mechanistic variables was only examined for the prospective relationship between baseline depression symptom subtypes and recovery outcomes at T3.

Health behaviours including physical activity, sleep and BMI were predictive of recovery outcomes. Physical activity was an important predictor of T3 emotional distress and affective pain, such that participants who walked for a greater number of hours per week prior to CABG were most anxious and experienced more affective pain two months after surgery. Notably, baseline depression symptoms were not related to baseline physical activity and so physical activity was shown to exert an independent effect on T3 anxiety and affective pain. The positive association was an unexpected result, but perhaps shows that the most physically able participants prior to surgery were most affected by the limitations imposed by undergoing a major procedure. Baseline BMI was another health behaviour that was able to predict recovery, with the most overweight participants prior to surgery reporting greater sensory pain after surgery. The reason for this is not clear, but perhaps suggests that overweight participants recovered more slowly from the physical symptoms of surgery than those participants who had a lower BMI. Depression symptoms were unrelated to BMI, and therefore this effect was independent of baseline depression symptom status. Lastly, poorer sleep prior to surgery, and in particular difficulty maintaining sleep, was a significant predictor of greater physical symptoms after surgery and poorer physical health status. This suggests that good sleep was an important factor for predicting better functional recovery after surgery. Sleep was not considered to be a mediator of the depression symptoms-recovery relationship, since poor sleep is in itself a symptom of depression.

Baseline illness perceptions were broadly predictive of the T3 recovery outcomes. Indeed, greater negative illness perceptions prior to surgery mediated the relationship between somatic/affective depression symptoms and greater affective pain and greater physical symptoms. In particular, in models using somatic/affective depression, the specific illness perception of concern was most relevant in predicting greater physical symptoms at T3, but none of the individual illness perceptions were independent predictors of affective pain. The perception of concern captures a distress element of illness perceptions, suggesting those participants who were most emotionally affected by their illness, were particularly vulnerable to poor physical and emotional adaptation following surgery. Perhaps more notable is the fact that illness perceptions did not mediate all the relationships between depression and recovery,

with somatic/affective depression symptoms exerting an independent effect on some of the recovery outcomes, including anxiety, sensory pain and physical and mental health status.

TABLE 7.63: SUMMARY OF SHORT-TERM OUTCOME RESULTS

Main findings	*Supported using depression symptom models?*
1. Pre-operative total BDI scores were not able to predict any of the recovery outcomes at T3.	• Pre-operative cognitive/affective depression scores were not able to predict any of the recovery outcomes at T3. • Pre-operative somatic/affective depression score was a significant predictor of greater sensory and affective pain, greater physical symptoms and lower physical health status at T3. It was a borderline significant predictor of T3 anxiety.
2. Resolved depression was not significantly related to any of the recovery outcomes at T3. Post-CABG onset depression was associated with greater anxiety, greater sensory and affective pain, greater physical symptoms and lower physical and mental health status at T3; persistent depression was associated with all the outcomes except physical health status.	-
3. Greater pre-operative physical activity was significantly associated with greater anxiety and greater affective pain at T3, in models using total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
4. Greater pre-operative BMI was significantly associated with greater sensory pain at T3, in models using total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.
5. Greater pre-operative sleep problems were significantly associated with greater physical symptoms and lower mental health status at T3, in models using total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
6. Baseline illness perceptions were associated with greater affective pain, greater physical symptoms and lower mental health status at T3 in models using total BDI score.	• Baseline illness perceptions mediated the relationship between T1 somatic/affective depression score and greater affective pain and physical symptoms at T3. T1 illness perceptions were a significant predictor of lower mental health status at T3 after including somatic/affective depression score in the model. • Greater pre-operative illness perceptions were associated with greater anxiety, greater physical symptoms and lower physical and mental health status in models using cognitive/affective depression scores.
7. T1 lower cortisol AUC was significantly associated with lower mental health status at T3, in models using total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.

8.	Pre-operative total BDI scores were able to predict a lower change in cortisol output from waking to bedtime at T3.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms. • Pre-operative cognitive/affective depression scores also predicted a lower cortisol AUC at T3.
9.	T3 cortisol slope was significantly associated with greater anxiety at T3, and T3 CAR was significantly associated with greater physical symptoms at T3, in models using total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
10.	Greater T2 late IL-6 response and greater change in IL-6 from baseline to T2 late was significantly associated with greater physical symptoms at T3, in models using total BDI score.	• The same finding was found adjusting for both somatic/affective and cognitive/affective depression symptoms.
11.	Lower T2 early TNF-α response was significantly associated with greater anxiety and lower mental health status at T3, and a smaller change in TNF-α from baseline to T2 early was associated with lower mental health status at T3, in models using total BDI score.	• The same findings were found adjusting for both somatic/affective and cognitive/affective depression symptoms.
12.	Lower T2 early TNF-α and lower T2 late TNF-α were associated with greater total BDI scores at T3 and post-CABG onset depression respectively.	• Lower T2 early TNF-α was associated with greater somatic/affective and cognitive/affective depression symptoms at T3.

Biological factors were also assessed as mediators of the depression-recovery relationship. The baseline AUC of cortisol was significantly related to the recovery outcome, mental health status. This effect was independent of all the depression symptom subtypes; however it was not in the predicted direction. Depression symptoms were associated with an increase in cortisol output across the day, but lower mental health status was associated with lower AUC. This suggests that cortisol AUC was not a mediator of the relationship between depression symptoms and mental health status.

The inflammatory markers also produced interesting results, with IL-6 and TNF-α responses both predicting recovery outcomes. It was hypothesised that heightened inflammatory responses would lead to poorer recovery. IL-6 results were in line with this hypothesis. For example, the participants who had the highest IL-6 response four to eight days after surgery and the greatest change from baseline to four to eight days post-surgery had the greatest physical symptoms. This is in contrast to results found in Chapter 6, whereby lower IL-6 responses in the days after surgery were predictive of longer hospital stays. TNF-α results also add to the inconsistent picture, such that lower TNF-α in the days shortly after surgery were predictive of greater anxiety and poorer mental health status. It is not clear why a greater inflammatory response for IL-6, but a lower TNF-α response, was predictive of better recovery outcomes at T3. More work is needed to delineate the independent effects the different inflammatory markers exert on recovery outcomes in this patient group. These results do however suggest that the extent of the inflammatory response is an important

independent predictor of emotional adaptation and adjustment after CABG surgery, even after taking depression symptoms into account. Nonetheless, it is important to note that the inflammatory responses were not shown to mediate the depression symptoms-recovery relationship, since while depression caseness was found to be associated with inflammatory responses, these did not correspond to the inflammatory markers predictive of recovery outcomes.

The inflammatory responses after surgery (T2 early and T2 late) were also tested to see if they were able to predict greater depression symptoms at T3, including the onset of post-CABG depression. Results showed that a lower TNF-α response in the days following surgery were predictive of greater depression symptoms and post-CABG onset depression. In particular, it was found that a lower TNF-α response one to three days following surgery was an independent predictor of greater depression symptoms at T3, even after controlling for baseline depression symptoms. What is more, lower TNF-α responses four to eight days after surgery were also found to predict post-CABG onset depression symptoms independently from demographic and disease severity covariates.

7.8.2 Analysis of results

7.8.2.1 Hypothesis 1: Depression symptoms and recovery

This hypothesis stated that depression symptoms would be associated with impaired adaptation following CABG surgery. In particular it stated that somatic/affective depression, persistent depression symptoms and post-CABG onset depression symptoms would carry greater risk than no depression, cognitive/affective depression symptoms and resolved depression symptoms for poor adaptation up to two months following surgery. This hypothesis was upheld since the only depression symptom subtypes significantly related to the recovery outcomes at T3 were somatic/affective, persistent and post-CABG onset depression symptoms. Indeed, total BDI depression score, cognitive/affective depression symptoms and resolved depression were not significantly related to any of the T3 recovery outcomes. However, since persistent and post-CABG onset depression capture T3 depression symptoms, it is probable that the associations with recovery outcomes for these depression subtypes were driven by the cross-sectional associations between greater T3 depression symptoms and poorer T3 recovery. All recovery endpoints were associated with these depression subtypes, including poorer emotional recovery in terms of anxiety, longer surgical recovery including greater sensory and affective pain and greater physical symptom reporting, and poorer physical and mental adaptation as measured by health status on the SF-12.

These results partially support recent evidence which has shown the greater cardiac risk associated with post-ACS depression symptoms may be in large part attributable to an

increase in depression symptoms following MI, rather than the prolongation of recurrent depressive symptoms from before the MI (Zuidersma, Ormel, Conradi, & de Jonge, 2012). In particular these authors reported that each new depression symptom experienced post-MI carried an increased risk of new cardiac events of 15%, remaining significant even after adjusting for baseline disease severity and demographic confounders. However, this PhD found that persistent depression symptoms, as well as post-CABG depression symptoms, were important predictors of recovery outcomes in CABG patients up to two months after surgery, but it is not clear to what extent this effect would continue in the longer term. Moreover, the effect of persistent and post-CABG onset depression was not assessed in relation to cardiac morbidity.

Previous studies using CABG patients have also examined the risk of mortality associated with the onset of depression in relation to the surgical procedure. For example, Connerney and colleagues (Connerney, Sloan, Shapiro, Bagiella, & Seckman, 2010) found post-CABG depression symptoms were significantly associated with elevated cardiac mortality. Moreover, in models adjusted for sex, age, ejection fraction and diabetes, those patients with new onset depression symptoms (n = 39) (HR 2.12, 95% CI 1.09-4.15, p = 0.03) had twice the risk of cardiac mortality compared with those patients who had never been depressed (n = 198). The recurrent depression group (n = 24) was not significantly different to the never depressed group (HR 1.72, 95% CI 0.78-3.80, p = 0.18). This PhD was not able to assess mortality and further work is needed to understand the cardiac risk associated with the timing and recurrence of a depressive episode.

In addition, this PhD has shown somatic/affective depression symptoms to be particularly damaging, which is in line with previous literature using MI patients. Analyses performed on two large datasets comprising more than 2000 patients compared three dimensions of depression symptoms derived from the BDI in relation to cardiovascular risk markers, mortality and readmissions over an average of 2.5 years after ACS (De Jonge, Ormel, et al., 2006). Cox regression analyses found somatic/affective symptoms (e.g. fatigue, pessimism) to predict cardiovascular events and mortality, even after controlling for cardiac risk factors (LVEF, Killip class, and previous myocardial infarction), while cognitive/affective (e.g. social withdrawal, work difficulty) and appetitive symptoms (e.g. loss of appetite, weight loss) did not. Other studies have reported similar findings (Doyle, Conroy, McGee, & Delaney, 2010; Hoen et al., 2010; Linke et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; McGowan et al., 2004). Somatic depression symptoms have also shown to be positively correlated to intima-media thickness of the carotid artery, a marker of atherosclerotic disease progression (Bus et al., 2011). However, this trend of results has not been supported using CABG patients. For example, Connerney and colleagues (Connerney,

Sloan, Shapiro, Bagiella, & Seckman, 2010) found cognitive-affective but not somatic symptoms to be predictive of cardiac mortality in models adjusted for confounders. These results have been supported by another recent study of morbidity and mortality in CABG patients, which also found cognitive depressive symptoms to be particularly damaging (Tully et al., 2011). However, this PhD was only able to study the effect of depression symptom subtypes on impaired adaptation, and not mortality, which may partly explain the discrepant findings.

7.8.2.2 Hypothesis 2: Social-behavioural mechanisms

This hypothesis stated that social-behavioural factors would affect the depression symptoms-poor adaptation relationship and that those patients who showed more negative health behaviours and lower social support before surgery would be more likely to have poorer emotional adaptation and recovery up to two months following surgery. In fact, the results only partially supported this hypothesis. Physical activity, sleep and BMI were all related to recovery endpoints, but no significant findings were found for alcohol intake, smoking status or social support.

Physical activity was associated with anxiety, but as previously discussed this was not in the anticipated direction, such that lower physical activity predicted greater anxiety. This was found to be the case even after adjusting for depression symptoms. Physical activity has been shown to be an important component of cardiac rehabilitation, being associated with reduced total and cardiovascular mortality and hospital readmission (Heran et al., 2011). A recent study showed that the relationship between depressive symptoms and future cardiac events in patients with CHD was largely accounted for by poor health behaviours, particularly physical inactivity (Whooley et al., 2008). Few studies have investigated these effects in CABG patients although physical activity is thought to have important protective effects in these patients (Nery & Barbisan, 2010). Therefore, the finding that the most active participants had the greatest anxiety at T3 is surprising. This can possibly be interpreted as the most active participants prior to surgery finding it the hardest to adapt to the limitations imposed on their lifestyle due to the CABG procedure.

BMI was found to be significantly related to greater sensory pain following surgery and this was independent from the depression symptom subtypes. Obesity is a cardiac risk factor that has been associated with depression symptoms (Luppino et al., 2010), and although many studies using CABG patients do not report body mass index (BMI) statistics, the few that have do not show BMI or obesity to be associated with depression symptoms (Blumenthal et al., 2003; Burg, Benedetto, Rosenberg, et al., 2003; Dunkel et al., 2009). The results from this PhD confirm that depression symptoms were not associated with BMI; however, these findings do

suggest that BMI is an important factor for predicting the amount of pain participants experience up to two months after CABG surgery, with the most overweight participants having a slower recovery process.

Sleep was a significant predictor of greater physical symptoms and poorer physical health status up to two months following surgery. This was confirmed in all models including the depression symptom subtypes. This is in line with results presented using the pilot data in Chapter 3. Sleep duration and quality have been associated with both cardiovascular disease and events (Leineweber et al., 2003; Sabanayagam & Shankar, 2010; Schwartz et al., 1998). Poor sleep is also thought to have negative consequences for emotional wellbeing and research has shown an association between poor sleep quality and depression symptoms (Almeida et al., 2011; Benca et al., 1992). While depression symptoms were associated with poor sleep, mediation analyses were not performed since sleep is a symptom of depression. Instead, this PhD assessed the relationship between sleep and recovery outcomes, independent from covariates and depression symptom subtypes. Although sleep is recognised to be an important issue in post-CABG recovery (Jenkins et al., 1996; Redeker & Hedges, 2002), very few studies have investigated the impact of poor sleep on physical and emotional adaptation and recovery following cardiac surgery. Hunt and colleagues (Hunt et al., 2000) assessed 108 CABG patients 12-months after surgery and used cross-sectional analyses to test for associations between poor self-reported sleep quality and poor health status. These authors found patients reporting poor sleep were 4.8 times more likely to also report poor health status. Redeker and colleagues (Redeker et al., 2004) studied 72 cardiac surgery patients in a study which implemented both self-report and objective measures of sleep on quality of life after surgery. They reported cross-sectional associations between poor sleep and worsened physical and emotional quality of life at four and eight weeks after surgery. The results from this PhD furthered these findings with results showing that poor sleep prior to surgery was not only predictive of worse physical health status after surgery, but also greater physical symptoms after surgery. In particular, this PhD found that problems maintaining sleep, as opposed to difficulty initiating sleep, were most important for recovery.

7.8.2.3 Hypothesis 3: Cognitive mechanisms

This hypothesis stated that cognitive factors would affect the depression symptoms-poor adaptation relationship, such that patients who had lower cognitive function and who showed more negative illness perceptions before surgery would be more likely to have poorer emotional adaptation and recovery up to two months following surgery. In line with findings presented in Chapter 6, baseline cognitive function was again not related to either T1 depression symptoms or recovery outcomes at T3. Previous literature has not assessed

cognition in relation to adaptation following surgery, but instead has demonstrated low levels of cognitive function to be associated with greater all-cause (Bosworth & Siegler, 2002) and cardiac mortality (Batterham et al., 2012). This latter study followed-up 592 community-dwelling participants for up to 17 years, and showed that while initial cognitive function was the better predictor, deterioration in cognition function over time was also predictive of future mortality, after adjustment for demographic, physical functioning and depression symptoms and anxiety scores. This association was not tested in this PhD. Moreover, the ARCS study did not assess cognitive function over time, and therefore could not test whether deterioration in neurocognition was associated with poorer recovery.

Illness perceptions were found to be implicated in linking depression symptoms to poorer physical and emotional adaptation following CABG surgery. The illness perception perspective emphasises the importance of patients' beliefs about their treatment and the course of their illness. The majority of the work in this area has used MI patients, and negative illness perceptions have been associated with an array of poorer outcomes for this population. In addition, more negative illness perceptions have also been related to poorer emotional responses to ACS, such as greater depression symptoms (Grace, Krepostman, et al., 2005; Stafford et al., 2009). In a study which assessed illness perceptions in the days following hospital admission for MI, more negative beliefs were associated with the development of new onset depression symptoms in particular (Dickens et al., 2008b). This finding was not tested in this PhD. However, previous research has also suggested a mediation model (Dickens, Cherrington, & McGowan, 2011) whereby the negative illness perceptions of consequences, identity, illness concern and emotional representation have been shown to partly mediate the prospective, negative, relationship between baseline depression symptoms and follow-up health related health status. Results from the ARCS study are in line with this hypothesis, since illness perceptions were shown to mediate the relationship between greater somatic/affective depression symptoms and greater affective pain and physical symptoms two months after surgery. However, illness perceptions did not mediate the relationship between greater somatic/affective depression symptoms and anxiety, sensory pain, physical and mental health status. Therefore it seems while illness perceptions are important for some recovery outcomes two months following CABG surgery, the effects are not consistent.

7.8.2.4 Hypothesis 4: Biological mechanisms

Hypothesis 4 stated that biological factors would affect the depression symptoms-poor adaptation relationship. This hypothesis was split into three sub-hypotheses. First, patients who showed a flatter cortisol response before surgery would be more likely to show poorer emotional and physical recovery up to two months following surgery. Second, patients who

showed greater inflammatory responses in the days after surgery would be more likely to show poorer emotional and physical recovery up to two months following surgery. Lastly, patients who showed greater inflammatory responses in the days after surgery would be more likely to experience greater depression symptoms and develop post-CABG onset depression up to two months following surgery.

The first of these sub-hypotheses only received limited support. Depressed participants were found to have greater cortisol output across the day (AUC) compared to non-depressed participants, but there was no difference between groups in terms of cortisol slope. Moreover, baseline cortisol slope was not related to any of the recovery outcomes after controlling for covariates. The only baseline marker of cortisol response to be related to recovery was in fact the AUC. Cortisol AUC prior to surgery was related to mental health status two months after surgery, but this association was not in the predicted direction, such that lower cortisol output predicted lower mental health status. It is not clear why those participants with higher cortisol had better mental health status, since this is incongruent with the association with depression symptoms. It may suggest that the BDI and SF-12 are capturing different dimensions of affect. Further exploratory analyses were performed in order to assess the relationship between baseline depression symptoms and cortisol responses at T3. Results from these analyses showed that greater pre-operative depression symptoms were associated with a flatter cortisol response, from waking to bedtime, up to two months after surgery. Moreover, cognitive/affective depression symptoms prior to surgery were associated with a lower cortisol output across the day at T3, but these findings were not replicated in models using total BDI score or somatic/affective depression symptom score; therefore it is not clear to what extent this may be a spurious finding. Cross-sectional associations were also found, with T3 cortisol slope being associated with T3 anxiety and T3 CAR being associated with T3 physical symptoms. Therefore, there is some indication that cortisol dysregulation is important for recovery. There have been very limited studies investigating cortisol in CABG surgery patients, although there is some evidence that there is heightened cortisol output in the post-operative period (Roth-Isigkeit & Schmucker, 1997; Tønnesen et al., 1987) and one study found this pattern to be associated with post-operative complications, in particular delirium (Mu et al., 2010). Cortisol responses were not, however, found to mediate the relationship between depression symptoms and the recovery outcomes in the ARCS study.

The second of these sub-hypotheses was also only partially upheld, with TNF-α and IL-6 responses, but not hs-CRP, being associated with recovery outcomes. Greater inflammation was shown to be linked to poorer recovery using IL-6 data. Specifically, greater IL-6 responses four to eight days after surgery were associated with greater physical symptoms two months after surgery. However, lower TNF-α one to three days after surgery was found to be

associated with greater anxiety and lower mental health status at T3. It is not clear why there were inconsistencies in the direction of the inflammatory effect on recovery, since this is not in line with previous research. For example, an observational study of 29 cardiopulmonary bypass patients by Holmes and colleagues (Holmes et al., 2002) used a median split to compare outcomes between those patients who showed a heightened inflammatory response at four hours post-CABG, to those who did not. Findings showed that hyper-responders in IL-8, IL-6 and CR3 (an anaphylatoxin) had greater risk of adverse clinical outcomes. Therefore, it was expected that a higher inflammatory response would be associated with poorer recovery in ARCS. A key finding from the early-term outcome results presented in Chapter 6 was that lower IL-6 responses were associated with longer hospital stays. The direction of the IL-6 response was not in line with this finding using the T3 data. Instead, greater IL-6 responses were associated with greater physical symptoms. The reason for this discrepancy is not clear, but suggests that the relationship between IL-6 and recovery may change over time. These findings need careful interpretation and corroboration using the full ARCS dataset once recruitment has finished.

Finally, the last of these sub-hypotheses was not upheld, since lower, rather than greater, TNF-α was predictive of greater depression symptoms at T3 and post-CABG onset depression. These findings are in line with the aforementioned findings in which lower TNF-α was also associated with greater anxiety and lower mental health status. This rationale for a positive association was based on the literature which has suggested depression symptoms in cardiac patients may be induced by a faulty sickness behaviour response to surgery. Sickness behaviour is thought to be adaptive in organising bodily responses that fight infection, promoting cellular immunity which targets intracellular organisms through activation of macrophages, cytotoxic T lymphocytes and natural killer cells (Dantzer, Castanon, Lestage, Moreau, & Capuron, 2006). A sickness behaviour model of depression symptoms posits that, in the case of ACS and CABG, the extent of tissue trauma invokes a large inflammatory response, capable of triggering a series of sickness behaviours. In these vulnerable individuals, where the immune response is exacerbated in duration and intensity, decompensation (i.e., functional deterioration) occurs, causing a shift in balance between pro-inflammatory and anti-inflammatory markers towards one of inflammation. However, this PhD found results incongruent with this hypothesis, such that lower TNF-α was predictive of greater depression symptoms. Only one other study to date has assessed the association between depression symptoms and inflammation in CABG patients (Yang et al., 2012). These authors studied 232 patients undergoing CABG surgery and found that higher pre-operative hs-CRP was predictive of depression symptoms up to six months following surgery, after controlling for covariates. There was no evidence of hs-CRP being associated with T3 recovery outcomes, but the sickness

behaviour model of depression does warrant further investigation using the full data once recruitment has finished.

7.9 Chapter summary

This chapter has assessed the relationship between pre-operative depression symptoms and recovery up to two months following surgery. Depression symptoms were classified as symptom subtypes including somatic/affective and cognitive/affective symptom subtypes, and onset subtypes including resolved, persistent and post-CABG onset. The recovery outcomes included emotional distress, physical symptoms and health status. In addition, mechanisms accounting for this relationship between baseline depression symptom subtypes and recovery were explored, finding little evidence of social-behavioural or biological mediation. Illness perceptions were found to mediate the relationship between somatic/affective depression symptoms and affective pain and physical symptoms. It appears that depression symptoms exert a unique influence on short-term recovery not entirely explained by the mechanisms explored in this PhD. Further research is needed to clarify why depression symptom and onset subtypes differentially affect recovery.

Chapter 8. Discussion

8.1 Introduction

Individual discussion sections for the results of this PhD were presented in the respective chapters. My PhD had two aims, firstly to develop the ARCS research study and secondly, to use this study to test my hypotheses. The pilot study was developed to meet the first aim of this thesis and will only be briefly discussed here. Instead, the primary discussion will relate to the second part of my PhD, which involved the testing of the hypotheses. As such, this discussion chapter will offer a broad view of the literature in which this PhD is nested and will highlight the strengths and limitations of the ARCS study, before suggesting the clinical implications of this work and areas for further research.

8.2 Discussion of findings

8.2.1 Developing ARCS

The P-ARCS study was performed to enable the development of the main study; in particular the aim of P-ARCS was to assess the feasibility of the study design and the suitability of the chosen measures. The results from the pilot work informed the design of the ARCS study and established the clinical collaboration for data collection at St. George's Hospital, London. As a result of the pilot, several amendments were made to the study protocol and questionnaire packs. These included the addition of a 12-month follow-up assessment point for the study of long-term outcomes in CABG surgery patients, collection of biological data to include cortisol sampling and blood for the analysis of inflammatory cytokines, and a partner study to assess the influence of the dyadic relationship between patient and partner on recovery outcomes. Adjustments were also made to the questionnaire packs, in particular the CPQ (Stansfeld & Marmot, 1992) was included in the main ARCS study instead of the marital functioning questionnaire. The only measure removed from the questionnaire pack as a result of P-ARCS was the BDI from T2. It was concluded that the length of the BDI and the nature of the questions, which often overlap with the physical symptoms experienced as a result of the surgery and the hospital environment, made it an inappropriate choice.

Preliminary analyses were also performed on the data to explore the associations between variables. In particular, models identified pre-surgical sleep and illness perceptions to be important independent predictors of recovery outcomes. These findings were used to guide the analyses using data from the main ARCS dataset. The development and undertaking of P-ARCS was a crucial element in preparing for recruitment of participants into the ARCS study.

However, the analyses to test the central hypotheses of this thesis were performed using data from the main ARCS study.

8.2.2 Depression symptoms prevalence

CABG surgery is a surgical intervention aimed to improve life expectancy and quality of life in patients with CHD. Therefore, it is surprising that CABG is now understood to have negative emotional effects, and both severe depression in the clinical range and subclinical milder depression are both commonly experienced by patients (Pignay-Demaria et al., 2003). Depression has been found to be common in patients prior to scheduled surgery (Blumenthal et al., 2003; Borowicz et al., 2002; Burg, Benedetto, Rosenberg, & Soufer, 2003; Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Krannich et al., 2007; Tully, Baker, & Knight, 2008) as well as afterwards (Blumenthal et al., 2003; Borowicz et al., 2002; Connerney et al., 2001; Krannich et al., 2007).

Previous literature has shown that the prevalence of depression symptoms varies widely both before and after CABG surgery; a full review was provided in Chapter 1 of this thesis. This review found that before CABG the prevalence of depression symptoms was between 14.3% and 43.1%, while after surgery estimates were between 12.8% and 50%. These data were used to calculate weighted means: on average 28.22% of patients were depressed pre-surgery and post-surgery 28.17% of patients were depressed. Therefore, overall estimates suggest very similar prevalence rates both pre- and post-operatively.

In the ARCS study, depression was measured using the BDI, which assesses the extent to which symptoms have been experienced in the previous two-week period, rather than as a clinical categorisation. Using this questionnaire, participants were grouped according to two severity cut-offs, >10 in accordance with the BDI handbook and ≥13 in accordance with previous work using cardiac patients (Gutierrez & Davis, 1999). Using a cut-off of >10, 29.2% (27.2% using T1-T3 sample) of participants were classified as depressed in the ARCS study at baseline; this compares to 24.2% of participants in P-ARCS. However, when the more conservative cut-off was implemented at ≥13, only 18.4% of participants were classified as depressed in the main ARCS study; this compares to 21.4% of participants in P-ARCS. Therefore, the prevalence rates using the respective cut-offs were similar in both P-ARCS and ARCS. Overall, these results suggest that depression symptoms are commonly experienced prior to surgery in CABG patients.

Depression symptoms were also assessed two months after surgery using the BDI. Again, prevalence was captured using the two cut-offs. After surgery at T3, 20.4% of participants scored >10 on the BDI in P-ARCS, which was identical to the main study where 20.4% of participants also scored >10. Using the higher cut-off, P-ARCS showed only 9.2% of

participants scored ≥13 after surgery at T3, while 15.0% of participants in the main ARCS study were depressed at T3. These findings suggest that fewer participants were depressed at T3 than before surgery, although depression symptoms were still frequently reported. In terms of the prevalence rates using the ≥13 cut-off, compared to the weighted means from previous studies, the ARCS study had lower levels of depression symptoms both pre and post-operatively. Details of participants' psychiatric history were also obtained in the main ARCS study, showing that 15.8% of participants had a history of depression symptoms and a further 12.9% had a history of anxiety.

The BDI prevalence findings reflect the importance of using an appropriate cut-off for depression. The cut-off implemented by researchers to determine caseness varies greatly between studies, even among those using the same instrument. In particular, the study by Timberlake and colleagues (Timberlake et al., 1997) used a cut-off of ≥9 on the BDI, which in large part may account for their finding of 50% depression cases in the days following surgery. Therefore, this study likely over-estimated the effect. This example highlights the difficulty in comparing prevalence rates across studies. In fact, the analyses described in this PhD are the only study to date which has implemented the BDI cut-off of ≥13 in a sample of CABG patients. However, this step was taken in order to increase the specificity of the measure and to increase the salience of the findings. Indeed the results using this conservative cut-off are in line with prevalence rates from Mitchell and colleagues (Mitchell et al., 2005) who used both questionnaires and diagnostic clinical interviews to measure depression. For example, in terms of pre-CABG surgery estimates, they showed using the MINI (Mini International Neuropsychiatric Interview) that 28.2% of participants were depressed compared to 39.0% classified as depressed using the BDI cut-off ≥10. In addition, these same authors also estimated depression symptoms prevalence after CABG, finding the MINI diagnosed 16.4% of participants with depression symptoms compared to 30.0% on the BDI (≥10). Despite the variation in use of cut-offs, this PhD largely side-stepped this issue by assessing depression symptoms along a continuum rather than demarking participants as depressed or not depressed.

Besides the use of cut-offs, other reasons for the difference in prevalence rates for depression found between ARCS and the previous literature are likely to involve dissimilarities in the patient demographic and the pre-operative environment. For example, some of the studies included urgent (Baker, Andrew, Schrader, & Knight, 2001; Burg et al., 2003; Connerney et al., 2001) and re-do (Borowicz et al., 2002; Burg et al., 2003; Connerney et al., 2001; McKhann, Borowicz, Goldsborough, Enger, & Selnes, 1997) cases in their sample, while ARCS was restricted to first-time elective patients. Moreover, since the 1980s, the use of medications for the prevention and treatment of CHD has risen in an exponential fashion, and

even since the late 1990s the UK has seen a fifteen-fold increase in the prescription of lipid-lowering medications (Scarborough et al., 2011). These differences in pre-surgical medication use may therefore partly account for the differences in depression prevalence, particularly since there is some evidence for the depression-protective effects of statins (Otte et al., 2012; Stafford & Berk, 2011). Furthermore, the use of antidepressant medication has been inconsistently taken into account across studies, with only the studies by Blumenthal and colleagues excluding those who were taking antidepressants on study entry (Blumenthal et al., 2003; Phillips-Bute et al., 2008); this may have lead some studies to underestimate the prevalence of depressive symptoms, although this was not supported in the ARCS data. Variation in depression prevalence may also be due to differences in the surgical procedure such as the use of cardiopulmonary bypass, the duration of surgery and the number of grafts performed, alongside differences in post-operative care such as between hospital variations in analgesic protocols and the length of in-hospital minimum stay. These factors are not routinely disclosed in published findings, making it difficult to draw comparisons between studies. Moreover, cross-cultural differences may also play a role, since the majority of work has been performed in the USA and Australia, with Timberlake and colleagues (Timberlake et al., 1997) providing the only UK data of depression prevalence in CABG patients.

8.2.3 Depression symptoms and recovery

8.2.3.1 Impaired adaptation

This PhD tested the hypothesis that greater depressive symptoms prior to surgery would lead to impaired adaptation and slower recovery after surgery. The majority of previous literature has focussed on the role of post-operative depression in predicting poorer outcomes after CABG (Wellenius et al., 2008) (Tully, Baker, Turnbull, et al., 2008) (Doering et al., 2005) (Doering et al., 2008, 2005; Kendel et al., 2010), and few studies have studied the prospective relationship using pre-operative measures of depression symptoms. The results presented in this thesis showed that pre-operative depression symptoms were associated with greater emotional distress, greater physical symptoms, longer hospital stays, and poorer quality of life, both in the days and months following surgery. This is in line with work by Burg and colleagues (Burg, Benedetto, Rosenberg, & Soufer, 2003) who showed that patients who were depressed pre-surgery had higher levels of medical complications during the six months following surgery, and were more likely to report poor quality of life and worse recovery.

In addition, my results have demonstrated that more information can be gleaned by examining depression according to its different symptom and onset subtypes, since these were predictive of different recovery endpoints. In addition, these associations varied according to the point at which recovery was measured after surgery (T2 or T3). These findings suggest care

needs to be taken when making comparisons across studies. The depression subtypes will be discussed in turn in the following sections.

8.2.3.2 Depression symptom subtypes

Depression is an illness without discrete boundaries, encompassing an array of symptoms and having a heterogeneous diagnosis. Indeed there is little consensus amongst clinicians and researchers about how best to categorise depressive disorders (Wakefield, 2011). The ICD-10 and DSM-IV classifications of depression symptoms both require a series of symptoms to be present most days for at least two weeks and at least one of these symptoms must include low mood or loss of interest and pleasure; the ICD-10 also includes loss of energy as one of the key diagnostic symptoms. Further symptoms also need to be reported such as feelings of guilt/worthlessness, appetitive changes, sleep disruption, suicidal ideation, loss of concentration and psychomotor agitation or retardation. Following the work of de Jonge and colleagues (De Jonge, Ormel, et al., 2006) this PhD has demonstrated that different depression symptoms can predict different recovery outcomes. In particular, two different symptom clusters were analysed: somatic/affective and cognitive/affective. The only BDI item not to be included in either of these clusters is item 19 pertaining to weight loss, all other symptoms of depression were captured.

As discussed in the literature review, the symptom profile of patients with post-ACS depression symptoms seems to affect the risk of future cardiac events. Some types of symptoms are thought to be more cardiotoxic than others, with somatic symptoms found to be particularly damaging in ACS patients (de Jonge, Ormel, et al., 2006; Doyle, Conroy, McGee, & Delaney, 2010; Hoen et al., 2010; Linke et al., 2009; Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010; McGowan et al., 2004). The CABG literature has little studied depression symptom subtypes in relation to recovery and the results have generally not tallied with the ACS studies. For example, Connerney and colleagues (Connerney, Sloan, Shapiro, Bagiella, & Seckman, 2010) found cognitive/affective but not somatic symptoms to be predictive of cardiac mortality in models adjusted for confounders. These results have been supported by another recent study of morbidity and mortality in CABG patients, which also found cognitive depressive symptoms to be particularly damaging (Tully et al., 2011). It is not clear why ACS and CABG surgery should have these differences in the cardiotoxicity of the depression symptom subtypes, but issues surrounding the different methods of grouping the items of BDI into different clusters and differences in the patient demographic, may partly contribute to the discrepancy. The difference may also be related to the phenomenology of the experience. CABG is planned, somewhat predictable, and optional (the patient can choose whether to have surgery), while on the other hand an ACS is unplanned, unexpected, unpredictable and

uncontrollable. Cardiac function over the recovery period may also be different in the two situations, so somatic correlates could differ.

Since the weight of evidence in cardiac patients supports the cardiotoxicity of somatic/affective depression, this PhD hypothesised that somatic/affective symptoms would lead to more adverse outcomes than cognitive/affective symptoms. In fact, I found mixed evidence to support this hypothesis, showing that the recovery timeframe was a critical determinant of the relationship between depression symptoms and the recovery outcome. For example, somatic/affective, but not cognitive/affective depression symptoms, were a significant predictor of greater anxiety and affective pain in the days following surgery, but neither symptom subtypes were predictive of sensory pain and both were predictive of greater physical symptoms in hospital and longer post-operative hospital stays. In comparison, by two months post-surgery, only somatic/affective depression symptoms were a significant predictor of recovery outcomes after adjusting for covariates. Cognitive/affective depression symptoms prior to surgery were not significantly related to any of the two-month post-surgery endpoints, including emotional distress, sensory and affective pain, physical symptom reporting and quality of life. Therefore, both symptom dimensions of the BDI were important predictors of early-term physical recovery, but there were differences between subtypes in predicting early-term emotional recovery and physical and emotional short-term recovery. Therefore, it appears the relationship between depression symptoms and recovery is not static, but rather dynamic, changing and shifting over time.

The reason why greater pre-operative somatic/affective depression symptoms, but not cognitive/affective symptoms, predicted poorer recovery two months after surgery is not clear. Since euroSCORE was a covariate in all analyses, it does not seem that the difference was due to differences in underlying disease severity. Nevertheless, somatic depression symptoms have been shown to be positively correlated to intima-media thickness of the carotid artery, a marker of atherosclerotic disease progression (Bus et al., 2011). Therefore, it is possible that the different depression symptoms subtypes have different underlying physiological correlates. However, disease severity has been investigated in another recent study by Meurs and colleagues (Meurs, Zuidersma, Dickens, & de Jonge, in press) who used data from 494 MI patients and studied associations of somatic/affective and cognitive/affective depression symptoms with recurrent cardiac events, before and after controlling for GRACE scores. Findings showed that controlling for GRACE score did not affect the relationship of total depression symptom score nor cognitive/affective depression symptoms on prognosis and only partly attenuated the risk of somatic/affective depression symptoms on prognosis. Therefore, it appears somatic/affective depression symptoms exert an effect on cardiac morbidity largely independent of disease severity.

Another related concept to somatic/affective depression symptoms is vital exhaustion, which is commonly defined as symptoms of excessive tiredness, increased irritability and a sense of demoralisation (Appels et al., 1987). Vital exhaustion has been shown to be predictive of cardiac prognosis in MI and heart failure patients (Smith et al., 2010). Although depression symptoms and vital exhaustion are often considered to be separate constructs (Kopp et al., 1998), in a recent study this was only observed in men and not women (Lindeberg et al., 2012). Another study used principal component analyses on questionnaire responses of 528 MI patients on the BDI and Maastricht Questionnaire (a measure of vital exhaustion) (Vroege et al., 2012). These authors showed strong conceptual overlap between the two scales, with all but two items from the Maastricht Questionnaire loading on the somatic/affective dimension of the BDI. Moreover, this somatic/affective dimension was able to predict recurrent events, but not the cognitive/affective dimension. Therefore, the reason why somatic/affective symptoms appeared to lead to poorer outcomes at T3 in this PhD may reflect the effect of greater levels of vital exhaustion, as opposed to greater depression. Interestingly, these authors also reported individual item analyses of the BDI and Maastricht Questionnaire in relation to recurrent cardiac events, showing no specific cardiotoxic items; instead, greater risk was attributed to nearly all the items. More work is needed in order to study the effect of the different somatic symptoms in detail, to demark the two syndromes.

It was hypothesised that the different depression symptom subtypes may actually reflect a manifestation of underlying biological processes, in particular differences in inflammation. I analysed the role of the inflammatory response to surgery in predicting T3 depression symptoms and post-CABG onset depression in order to assess the evidence for a sickness behaviour model of depression in CABG surgery patients (Dantzer et al., 2008; Poole, Dickens, & Steptoe, 2011). This model posits that, in the case of ACS and CABG, the extent of tissue trauma invokes a large inflammatory response, capable of triggering a series of sickness behaviours. In these vulnerable individuals, where the immune response is exacerbated in duration and intensity, decompensation (i.e., functional deterioration) occurs, causing a shift in balance between pro-inflammatory and anti-inflammatory cytokines towards one of inflammation. Only one previous study to date has assessed the association between depression and inflammation in CABG patients, finding that higher pre-operative hs-CRP was predictive of depression symptoms up to six months following surgery, after controlling for covariates (Yang et al., 2012). However, this PhD tested the inflammatory response to surgery and its impact on later depression symptoms; results showed that a lower TNF-α response was associated with greater depression symptoms two months after surgery and post-CABG onset depression. Therefore, while inflammation was shown to play a role, it was not in the anticipated direction, limiting the interpretation of this finding. While the sickness behaviour

model offers a strong conceptual basis for interpreting the new onset depression literature in cardiac patients, further work is needed in order to substantiate this hypothesis.

8.2.3.3 Onset subtypes

There is now a large body of evidence suggesting that different subtypes of depression exist according to the timing, duration and recurrence of the depression symptoms in relation to the cardiac event. These definitions relate to the chronicity of the depressive episode as well as pointing towards different underlying aetiology. This has been well studied in ACS patients, but has been little explored in CABG surgery patients.

Recent evidence indicates there is a stronger association with mortality and recurrent cardiac events in patients with new onset depression symptoms (post-ACS depressed with no prior history of depression) (Carney et al., 2009; de Jonge, van den Brink, et al., 2006; Dickens et al., 2007, 2008a; Grace, Abbey, et al., 2005; Lespérance et al., 1996; Parker et al., 2008). However, as with the study of symptom subtypes, little work has explored the importance of depression onset subtypes in relation to CABG surgery recovery. One of the few studies to date which has begun to address these issues was published recently (Connerney, Sloan, Shapiro, Bagiella, & Seckman, 2010). These authors found post-CABG depression was significantly associated with elevated cardiac mortality. Moreover, in models adjusted for sex, age, ejection fraction and diabetes, those patients with new onset depression symptoms had twice the risk of cardiac mortality compared with those patients who had never been depressed. Recurrent depression was not significantly different to the never depressed group.

Due to a lack of new onset cases, this PhD was restricted to studying post-CABG onset depression symptoms (i.e. pre-CABG BDI <13, but post-CABG depression symptoms ≥13) in comparison to resolved depression symptoms (i.e. pre-CABG BDI ≥13, but post-CABG BDI <13) and persistent depression symptoms (i.e. pre- and post-CABG BDI ≥13). By stratifying depression caseness according to these onset subtypes, results demonstrated that patients who had resolved depression symptoms had no poorer recovery outcomes at two months post-CABG than those who were never depressed. In contrast, both persistent and post-CABG depressed participants experienced poorer recovery compared to their never depressed counterparts. These results need to be interpreted with caution due to the small number of positive cases in each of these groups, but it appears there is some preliminary evidence to suggest the chronicity of the depressive episode and the timing of depression symptoms in relation to the surgical procedure affects recovery. However, it is likely that these differences between the onset subtypes in this PhD were driven by cross-sectional associations between depression and recovery outcomes at T3. Further work will be needed to assess these effects on recovery at 12 months post-CABG.

Previous research has shown the greater cardiac risk associated with post-ACS depression may be in large part attributable to an increase in depressive symptoms following MI, rather than the prolongation of recurrent depressive symptoms from before the MI (Zuidersma, Ormel, Conradi, & de Jonge, 2012). In particular these authors reported that each new depression symptom experienced post-MI carried a 15% increased risk of new cardiac events, remaining significant even after adjusting for baseline disease severity and demographic confounders. While this PhD supports the evidence for the negative effects of post-CABG depression, it also suggests that persistent depression is also damaging. However, as already described, it will be necessary to explore whether these effects remain at the 12-month follow-up, when the full ARCS dataset becomes available for analysis.

8.2.4 Early- and short-term outcomes

8.2.4.1 T1 depression symptoms and post-operative recovery

Pre-operative depression symptoms were assessed in relation to recovery in the days following surgery (T2) and up to two months later (T3). This allowed for longitudinal examination of the relationship between depression symptoms and CABG recovery over time. With regards to the early-term outcomes, pre-operative somatic/affective depression symptoms and cognitive/affective depression symptoms were not related to the same recovery outcomes at T2. Somatic/affective and cognitive/affective depression symptom subtypes were both relevant for predicting physical recovery at T2, whereas somatic/affective depression symptoms were the better predictor of distress at T2. In terms of the short-term outcomes, somatic/affective depression, but not total or cognitive/affective depression symptoms were predictive of recovery outcomes. In addition, persistent and post-CABG, but not resolved depression, were predictive of the T3 recovery outcomes.

Previous literature has also shown the importance of the timing of assessments in understanding the relationship between depression symptoms and poorer adaptation following CABG. For example, Burg and colleagues found that pre-operative depression was able to predict greater risk of cardiac hospitalisations, continued surgical pain and failure to return to previous functioning up to six months after surgery (Burg, Benedetto, Rosenberg, et al., 2003). However, the course of this prospective relationship over time has received little attention in previous research, and my results are the first to show the negative sequelae of pre-operative depression symptoms for recovery in both the early- and short-term stages of the post-CABG period. In order to understand why and how depression symptoms affect recovery, the role of possible covariates and mediating variables were explored. Each of these will be discussed in turn below.

8.2.4.2 Covariates

Covariates were identified based on *a priori* assumptions, but were then selected for inclusion in regression models based on results from correlation analyses. This approach was taken in order to limit the number of variables in models and so to maximise power, especially in the case of the biological data where there were a reduced number of cases. Age, sex, household income and euroSCORE were used as covariates in all statistical models. In addition, baseline measures of anxiety and quality of life were included in models, where appropriate, to take into account pre-existing scores on these variables. Notably, while co-morbidities and other clinical factors such as use of medication were not included in regression models, these factors were not found to be related to either depression or the recovery outcomes. Moreover, euroSCORE is a composite risk marker and takes into account multiple clinical risk indices such as diabetes, LVEF and recent MI among others.

Several significant findings were found for the covariates across the statistical models. Male sex was associated with greater anxiety at T2 and female sex was significantly associated with greater sensory pain at T3 and lower physical health status at T3. Significant findings were also found for household income, with the participants from the lowest income households being more likely to have an extended post-operative hospital stay, greater anxiety, sensory pain and physical symptoms at T3 and lower physical health status also at T3. Age and euroSCORE were found to be less important, with older age only being associated with greater physical symptoms at T2 and euroSCORE only predicting greater sensory pain at T3.

Gender and age were included as covariates in analyses since these demographic factors are established risk factors for both depression (Dunkel et al., 2009; McKenzie et al., 2010) and mortality (Lehmkuhl et al., 2012; Sen et al., 2012) in CABG patients. In fact, in ARCS, few associations were found between gender and age and post-operative recovery. Male sex was associated with greater anxiety in the early term post-CABG period and female sex was significantly associated with greater sensory pain and lower physical health status two months after surgery. Older age was only associated with greater physical symptoms in the days following surgery, but not with any of the other recovery outcomes.

Interestingly, household income was associated with a range of recovery outcomes, including length of post-operative hospital stay, anxiety, sensory pain and physical symptoms and lower physical health status; these associations were such that the participants from the lowest income households had the poorest recovery outcomes. These findings are in line with previous research which has shown the importance of socioeconomic position for cardiac health and longevity (Ferrie, Martikainen, Shipley, & Marmot, 2005; Sacker et al., 2008;

Stringhini et al., 2010) and prognosis following CABG (Gibson et al., 2009). For example, Britton and colleagues (Britton, Shipley, Marmot, & Hemingway, 2004) reported an inverse social gradient for CHD within the Whitehall II cohort of UK civil servants, such that the lowest employment grades experienced higher rates of cardiac morbidity and mortality than those participants from the higher employment bands. The importance of the socioeconomic environment in which one resides has also been shown to be an important risk factor for recurrent cardiac events in a longitudinal analysis of over 1000 MI survivors (Koren, Steinberg, Drory, & Gerber, 2012), with those from the poorest neighbourhoods having the greatest risk of adverse outcomes. In addition, previous research has also studied the extent to which socioeconomic status is related to depression in CABG patients. For example, some have shown that low education is associated with greater risk of pre-operative depression (Dunkel et al., 2009; Pirraglia et al., 1999), but not others (Burg, Benedetto, Rosenberg, et al., 2003). In terms of post-operative depression, Connerney and colleagues (Connerney et al., 2001) reported no difference in education levels between depressed and non-depressed CABG patients and this has been found by others (Pirraglia et al., 1999). The mixed results may be a result of education being a weak marker of socioeconomic position in this patient group, since most will have completed formal education several decades prior to the onset of cardiac disease (Steptoe et al., 2011). The results of this PhD did not examine whether socioeconomic position moderates or mediates the relationship between depression and recovery, so this will be an important line of enquiry in future analyses, with the added advantage that several measures of socioeconomic position can be explored.

8.2.4.3 Causal pathways – Social-behavioural factors

Several mechanisms were explored in order to try and explain why participants experiencing greater depression symptoms had poorer recovery over and above the covariates. The relationship between greater depression symptoms and poor recovery was first attempted to be attributed to a higher preponderance of unhealthy behaviours among those participants reporting greater depressive symptomatology. Social-behavioural factors included BMI, physical activity, smoking status, alcohol intake, sleep and social support. In fact, this hypothesis was not supported, since while health behaviours were found to exert independent effects on recovery, these were not associated with depression symptoms. These findings do however suggest that behaviour modification is an important part of cardiac rehabilitation, but the reach of such programmes is not entirely clear in ARCS, since less than half the sample actually participated in a cardiac rehabilitation programme. Despite this, alcohol intake did decrease following surgery and several participants quit smoking, though the extent to which cardiac rehabilitation contributed to these lifestyle changes is uncertain.

While the results of this PhD were compelling for the negative effect of smoking on length of hospital stay, the protective effect of physical activity was less clear. Specifically, greater physical activity was associated with reduced anxiety in the days following surgery, but greater anxiety in the months following surgery. This is surprising since there has been recent interest in the use of physical exercise as a treatment for mental illness (Blumenthal, 2011; Phillips et al., 2003) and our own work has supported the mood-enhancing benefits of physical activity, both in terms of reducing negative mood symptoms (Poole, Hamer, et al., 2011) and promoting positive wellbeing (Poole, Steptoe, et al., 2011). Therefore, more work is needed to delineate these effects in greater detail and to determine the mechanisms through which exercise affects recovery, including greater understanding of the timeline over which the beneficial effects of exercise are able to impact wellbeing in these patients. It is possible that the physical activity measure used in ARCS was not able to capture the frequency and intensity of exercise bouts most applicable for wellbeing as it was restricted to time spent walking only. Participants may have been engaging in physical activities not screened, including both recreational sports, such as swimming, and activities of daily living, such as housework and gardening. A recent randomised controlled trial to assess the effectiveness of exercise therapy for depression in cardiac patients showed that aerobic exercise performed at 70-85% of a participant's maximal heart rate conferred a mood benefit (Blumenthal et al., 2012); the effect of less vigorous activity in this patient group is not well understood.

Obesity is another cardiac risk factor that has also been associated with depression (Luppino et al., 2010), but the effects in CABG patients have not been fully investigated, with only a handful of studies reporting BMI statistics in papers of depression in CABG patients (Blumenthal et al., 2003; Burg, Benedetto, Rosenberg, et al., 2003; Dunkel et al., 2009). This PhD was able to show no differences in BMI in relation to depression symptom reporting, but those participants who were more overweight were shown to experience greater sensory pain two months after surgery. The association between pain and obesity has been established previously using a large-scale birth cohort study (Lake, Power, & Cole, 2000), though it has not been previously established in CABG patients and it is not clear to what extent this relationship is causal.

Sleep was also assessed as a behavioural factor predicting poor recovery since a recent meta-analysis of prospective studies found that both short and long sleep duration was associated with increased risk of developing or dying from CHD and stroke (Francesco P Cappuccio et al., 2011). The research in this area has previously been discussed in relation to results from P-ARCS (Chapter 4) so will only be briefly outlined again here. Sleep is recognised to be an important issue in post-CABG recovery (Jenkins et al., 1996; Redeker & Hedges, 2002), but very few studies have investigated the impact of poor sleep on physical and emotional

adaptation and recovery following cardiac surgery. To date, two studies have reported cross-sectional associations between poor sleep and reduced quality of life after CABG surgery (Hunt et al., 2000; Redeker et al., 2004). One other study showed that the pre-surgery sleep symptom of feeling unrefreshed on awakening explained 44.5% of variance in quality of life scores six months after surgery (Edéll-Gustafsson & Hetta, 1999). This PhD also found that specific pre-operative sleep symptoms were differentially predictive of recovery outcomes and in particular that problems with sleep maintenance, as opposed to sleep initiation, were most important for predicting greater physical symptoms and lower mental health status up to two months after surgery. Interestingly, these effects were only observed at T3 and not at T2, suggesting that different processes are in operation at these time points. Understanding the impact of different sleep problems on adaptation and recovery is an important line of enquiry for guiding future intervention studies.

The role of social processes has been little studied in the CABG population and the results of this PhD found that while depression symptoms were associated with social support, social support was not related to recovery outcomes. Therefore, the mediation hypothesis was not upheld. This hypothesis was based on research which has shown positive effects of social support in CABG patients. For example, Okkonen and colleagues found that lower perceived family support prior to surgery was associated with greater depression symptoms, feelings of hopelessness and anxiety (Okkonen & Vanhanen, 2006). Another study found that instrumental social support was associated with positive improvements in mental health but not physical functioning at six months following CABG (Barry et al., 2006). As in P-ARCS, the ESSI questionnaire showed a skewed response profile, with the majority of participants reporting high levels of social support. Therefore, measurement issues may partly account for the lack of observed findings. In addition, it is possible that perceived support is less important for predicting recovery compared to other forms of support, such as instrumental support. Instrumental support captures the practical aspect of social support, with help engaging in healthy lifestyle behaviours (Kouvonen et al., 2012) and adherence to medication regimes (Molloy, Perkins-Porras, Bhattacharyya, et al., 2008) being potentially relevant to CABG patients. Further work is also needed to evaluate the effects of other social support measures used in ARCS on the recovery outcomes, such as social networks, attachment style and marital functioning.

In summary, evidence from the ARCS study does suggest that having an unhealthy lifestyle prior to surgery has a negative impact on physical recovery after CABG. However, in the case of physical activity, this benefit was restricted to the early term and actually caused greater distress in the months following surgery in the ARCS sample. It is not clear to what extent this effect would persist up to a year following surgery. Moreover, health behaviours

exerted their effect on recovery independent from depression, demographic and disease severity covariates, and so while not mediators of the depression-recovery relationship, they were important independent predictors.

8.2.4.4 Causal pathways – cognitive factors

Cognitive factors were described in the literature review as a potential mechanism linking pre-operative depression to impaired adaptation following CABG. The first cognitive mechanism to be explored in this PhD was the role of neurocognitive function. Lower cognitive function was hypothesised to be associated with greater depression symptoms and poorer recovery. In fact, no evidence was found in support of this hypothesis. There has been marked interest and debate in the role of neurocognitive processes following CABG, such as memory loss and difficulties with concentration and problem-solving and both short- and long-term deficits in neurocognition have been observed in CABG patients (van Dijk et al., 2000). Unfortunately, the ARCS study was unable to observe any deterioration in CABG over time since the MoCA was only administered prior to surgery. However, low levels of cognitive function have previously been associated with greater all-cause (Bosworth & Siegler, 2002) and cardiac mortality (Batterham et al., 2012). This latter study showed the importance of initial cognitive function, not just deterioration in cognitive function over time, on cardiac mortality. Cognitive difficulties are also well-established in depression, among the geriatric depressed (Butters et al., 2004; Rapp et al., 2005) and also younger adults (Castaneda et al., 2008; Herrmann et al., 2007; Thomas et al., 2009), but have been inconsistently reported in CABG samples (Andrew et al., 2000; McKhann et al., 1997; Tsushima et al., 2005; Tully et al., 2009). Therefore, more work is needed in order to explore the effects of neurocognition on depression and recovery following CABG surgery.

The second cognitive factor to be explored in my thesis was the role of illness perceptions. Illness perceptions were found to mediate some of the relationships depression symptoms had with recovery outcomes in the early- and short-term follow-ups. This is consistent with previous literature which has shown negative illness perceptions to be associated with an array of poorer outcomes in ACS patients, including greater illness related disability at home and at work (Petrie et al., 1996), reduced quality of life (French et al., 2005; Stafford et al., 2009) and greater risk of in-hospital complications (Cherrington et al., 2004), among others. In addition, more negative illness perceptions have also been related to poorer emotional responses in CABG surgery patients (Hermele et al., 2007; Juergens et al., 2010).

Results from this PhD were able to show that depression and illness perceptions were associated, and while causality was not ascertained, these results are consistent with the cognitive vulnerability theory of depression. This theory suggests that negative cognitive

appraisals, or negative schemas, are triggered during stressful situations and consequently are then capable of leading to depression onset, maintenance and relapse/recurrence (Scher et al., 2005). Not only was this PhD able to show a cross-sectional relationship between greater depression symptoms and greater negative illness perceptions, but also that there was evidence in favour of a mediation model, whereby baseline illness perceptions fully mediated the relationship between greater baseline depression symptoms and greater anxiety and greater physical symptoms in the days following surgery. Interestingly, only partial mediation was shown for the relationship between baseline somatic/affective depression symptoms and T2 anxiety. Mediation also extended to the two month recovery outcomes, such that greater negative illness perceptions fully mediated the relationship between somatic/affective depression symptoms at baseline and greater affective pain and physical symptoms two months after surgery. These findings are in keeping with results from a recent study by Dickens and colleagues (Dickens, Cherrington, & McGowan, 2011) of stable CHD outpatients who completed baseline and six-month follow-up assessments. They showed the negative illness perceptions of consequences, identity, illness concern and emotional representation partly mediated the prospective, negative, relationship between baseline depression and follow-up health related quality of life.

Understanding why illness perceptions are predictive of recovery involves identification of the specific perceptions that were significant in the models. For example, in the ARCS study, the emotional distress illness perceptions were most predictive of the T2 recovery outcomes, suggesting that illness specific distress prior to surgery accounted for the relationship between greater pre-operative depression and greater anxiety and physical symptom reporting. Negative perceptions more generally, rather than any of the individual items, were related to greater affective pain at T3, while concern was the only significant predictor of greater physical symptoms at T3. These results seem to suggest that those participants who were more depressed prior to surgery, were also likely to perceive their illness to be more threatening and more worrisome, and this illness specific distress was particularly important for some of the self-reported outcomes. Interestingly, depression symptoms, but not illness perceptions, were an important independent predictor of length of hospital stay, suggesting while these concepts may be similar, they are not one and the same. An important future line of enquiry for work in this area is in understanding the extent to which the emotional distress aspects of illness perceptions are a separate construct to depression and anxiety. It is plausible that the worry and concern invoked by the surgical procedure actually reflects a manifestation of an underlying mood disorder.

8.2.4.5 Causal pathways – biological factors

Two different biological pathways were tested in this PhD: cortisol and the inflammatory markers IL-6, hs-CRP and TNF-α. Baseline levels of cortisol were not significantly related to the recovery outcomes at T2. Depressed participants did, however, have a higher cortisol output over the course of the day, but this did not mediate the relationship depression symptoms had with the T2 recovery outcomes. At T3, baseline AUC of cortisol was significantly related to the recovery outcome, mental health status. This effect was independent of all the depression symptom subtypes; however it was not in the predicted direction. Depression symptoms were associated with an increase in cortisol output across the day, but lower mental health status was associated with lower AUC. This suggests that cortisol AUC was not a mediator of the relationship between depression symptoms and mental health status. Cross-sectional associations were found to be more consistent with the hypothesised effect, such that a flatter cortisol slope at T3 was associated with greater anxiety at T3 and a smaller T3 CAR was associated with greater physical symptoms at T3.

Elevated cortisol has been linked to cardiac risk factors such as hypercholesterolemia, abdominal obesity and hypertension, by some (Brown, Varghese, & McEwen, 2004), but not all (Otte et al., 2004), authors. In addition, flatter cortisol rhythms across the day have been linked with the progression of coronary calcification (Matthews, Schwartz, Cohen, & Seeman, 2006). In line with the hypothesis that the pattern of the diurnal response, as opposed to the total output, would be important for recovery, this PhD found cross-sectional associations between flatter cortisol slope and greater anxiety and a smaller morning awakening response and greater physical symptoms two months following surgery.

Cortisol has also been implicated in the pathophysiology of depression (Zunszain et al., 2011). HPA axis abnormalities have been observed in patients with major depression, including increased secretion and reactivity of cortisol (Cowen, 2010). Moreover, Steptoe's group recently showed that alterations in the diurnal profile of cortisol were associated with depressed mood in patients with CHD. This PhD found no significant differences between depressed and non-depressed participants in terms of the diurnal profile of cortisol; however results did show a significant difference in cortisol AUC, such that depressed participants had a higher cortisol output across the day than non-depressed participants. The long-term effects of this higher cortisol level on recovery was not observed, therefore future work is needed to understand the consequences of these changes to the neuroendocrine system in greater detail. More work is needed to understand the effects of the chronicity of the depressive episode on the neuroendocrine system. For example, a recent study found that disturbances in CAR were only observed among post-ACS patients whose depression was diagnosed through a

clinical interview as opposed to a questionnaire measure (Messerli-Bürgy et al., 2012). Therefore, problems with the measurement of depression may partly account for my findings. In addition, the cortisol sampling method used in ARCS may also play a role, with problems surrounding the non-completion of samples, non-adherence to the pre-sampling procedure such as not eating or taking any medication, and the short assessment period, all potentially compromising the results.

An extensive review of inflammatory processes was provided in Chapter 2, so only a brief summary will be provided again here. Two recent meta-analyses have concluded that depression is associated with an increased inflammatory response, including CRP, IL-1, IL-6 and TNF-α (Dowlati et al., 2010; Howren et al., 2009). Epidemiological evidence for the directionality of the depression-inflammation relationship is mixed, with some studies suggesting that depression precedes inflammation (Stewart et al., 2009), while others show that inflammation precedes depression (Gimeno et al., 2008). Results from this PhD were able to show that participants who had greater depression symptoms pre-operatively had a higher post-operative IL-6 response in the days shortly following surgery. While CABG surgery is known to be associated with an acute inflammatory response (Biglioli et al., 2003), which indeed was supported in the ARCS data, the extent of the inflammatory response is thought largely to reflect the amount of trauma derived from the surgical procedure itself. However, this PhD showed that the relationship between pre-operative depression and post-operative IL-6 was independent from euroSCORE, which is partly comprised of perioperative risk factors.

The inflammatory response was not consistently related to recovery outcomes in ARCS. For example, lower IL-6, but higher CRP, was associated with poorer recovery at T2, but higher IL-6 and lower TNF-α, were associated with poorer recovery at T3. Previous research has shown a positive relationship between the extent of the inflammatory response to surgery and clinical outcomes (Holmes et al., 2002; Kaireviciute et al., 2010). The baseline CRP findings shown in ARCS were congruent with previous research (De Lorenzo et al., 2012; Perry et al., 2010), such that those participants with higher CRP prior to surgery had greater anxiety, greater pain and greater physical symptoms during the in-hospital period. Some authors (Hemingway et al., 2010; Kushner, Broder, & Karp, 1978) have argued that the literature relating elevated CRP with poor prognosis in CHD patients is seriously flawed, with poor control for confounders, poor methodology and publication bias. Our results would certainly suggest that the picture is not as clear-cut as previous research would suggest, and greater work is needed to explore the inflammatory response to CABG surgery in greater detail. This may include analysis of a greater array of inflammatory markers and greater consideration of other contributing factors, such as the use of in-hospital medications, which were not measured in ARCS and therefore not controlled for in these analyses.

8.2.5 Defining depression

The results of my PhD have implications for our understanding of depression, how to characterise depressive episodes and the relevance of depression symptoms for predicting outcomes in cardiac patients. In fact, one of the key findings of this PhD has been that depression is not a homogenous disorder in cardiac patients, and lacks discrete boundaries. Moreover, my work has highlighted the conceptual problems with the nosology of depression. For example, depression symptoms can present different symptom clusters in different individuals and symptoms of major depression overlap with other disorders such as anxiety. Moreover, patients also differ according to the severity of the depressive disorder, which is based both on the number and intensity of an individual's symptoms and the level of distress and impairment in normal functioning. This causes difficulty in studying depression symptoms and comparing across individuals, since different patients present differently.

Some studies have compared whether the way depression is measured affects its association with recovery. This has been investigated in ACS patients, but not in CABG populations. A recent study has examined this question in detail (Zuidersma et al., 2012) using data from 2704 post-MI patients who were administered the BDI and the Composite International Diagnostic Interview at three months after their cardiac event, and who were followed for up to 10 years post-MI for all cause and cardiac mortality and cardiac readmissions. Results found that those scoring ≥19 on the BDI had more than two times greater risk of all-cause mortality (HR: 2.47, 95% CI: 1.64-3.70, p <0.001) and almost three times greater risk of cardiac mortality (HR: 2.70, 95% CI: 1.38-5.27, p <0.01) than those participants who scored <5, after controlling for age, sex, LVEF, previous MI, diabetes and smoking. These analyses were also performed using recurrent cardiac events and a lower BDI cut-off of 10-18, with the significant effect also being confirmed. In comparison, participants with a clinical diagnosis of depression had a lower risk of all-cause (HR: 1.48, 95% CI: 1.12-1.96, p <0.01) but not cardiac mortality, in fully adjusted models. However, after adjusting for scores on the BDI, this effect actually became non-significant. Therefore, these authors concluded that after MI, self-reported BDI symptoms were a better predictor of cardiac outcomes than clinically diagnosed depression. Other studies have supported this finding (Frasure-Smith, Lespérance, & Talajic, 1995; Whooley et al., 2008), but two other studies have shown that depression as measured using a diagnostic interview was associated with greater risk of adverse cardiac outcomes than depression symptoms measured by questionnaire (Frasure-Smith & Lespérance, 2008; Penninx et al., 2001). Therefore, further work is needed to explore the effect of measurement on morbidity and mortality risk in cardiac patients. In particular, it

will be important to determine why and how these measurement methods generate different risk profiles.

In addition, measurement problems are not restricted to the instrument used to capture depression, but also relate to difficulties teasing apart the relative contribution of depression symptoms from other diagnoses such as anxiety and vital exhaustion. The vital exhaustion literature has already been described in Section 8.2.3.2 above, so the following section will focus on anxiety.

8.2.5.1 Anxiety

Common to all anxiety disorders are intense and excessive feelings of fear and worry that impact on an individual's ability to function as usual in everyday life. According to the DSM-IV, GAD refers to chronic feelings of anxiety and worry that are not specific to a single object or situation, that are difficult to control, and that persist on more days than not for at least six months. At least three accompanying symptoms must also be present, to include: feelings of restlessness or being 'on edge', fatigue, difficulty in concentrating, irritability, muscle tension and sleep disturbance. Therefore, anxiety and depression symptoms share some common symptoms, and it is not clear to what extent these symptoms operate under two higher order constructs or whether they represent features of a more generalised disorder of distress.

There is growing evidence surrounding the role of anxiety in predicting poorer prognosis in those patients with CHD (Player & Peterson, 2011). For example, in patients with stable heart disease, anxiety was able to predict increased risk of cardiac events in two large-scale prospective studies (Martens, de Jonge, et al., 2010; Moser et al., 2011). Moreover in ACS patients, a recent meta-analysis concluded that anxiety following MI is associated with a 36% increased risk of adverse cardiac outcomes (Roest, Martens, Denollet, & de Jonge, 2010). These observations in MI patients were recently confirmed in a 10-year follow-up study of MI patients showing that three months after MI, those patients with GAD were almost twice as likely to experience adverse events (mortality or cardiac-related hospital readmissions) than those without GAD, even after controlling for baseline disease severity, demographic and depression symptom variables (Roest, Zuidersma, & de Jonge, 2012). Similar observations have also been reported in CABG patients. Tully and colleagues (Tully, Baker, & Knight, 2008) found that those patients with higher levels of pre-operative anxiety were at greater risk of mortality (HR 1.88, 95% CI 1.12–3.17, p = 0.02). Another study has also confirmed the effect of anxiety on mortality in patients who had previously undergone CABG surgery (Rosenbloom et al., 2009). Oxlad and colleagues showed anxiety in the immediate post-operative period was associated with greater hospital readmissions six months after CABG (Oxlad et al., 2006).

My PhD did not directly test the role of pre-operative anxiety in predicting poorer recovery. Instead analyses were performed to assess anxiety as an outcome measure of emotional stress after surgery. Indeed, the results were able to show that pre-operative depression symptoms were a significant predictor of greater anxiety symptoms in the days shortly following CABG and up to two months later. Theories have been proposed in which anxiety and depressive disorders should be viewed collectively as part of a higher-order diagnosis of negative affectivity, characterised by heightened levels of distress, negative emotionality and neuroticism (Andrews et al., 2009; Brown & Barlow, 2009; Prenoveau et al., 2010; Watson, 2009). In this PhD only somatic/affective depression symptoms were predictive of anxiety both in the days and months following surgery, and not cognitive/affective symptoms. Therefore, it is possible that the somatic/affective depression symptoms partly reflect the somatic manifestations of anxiety, particularly problems sleeping, restlessness and appetitive changes. However, these effects were shown even after controlling for baseline anxiety, and so it seems that while similar, the two are not quite the same. As such, more work is needed to explore the differential effects of anxiety and depression symptoms in greater detail, as it is unclear whether negative affectivity is more important than either depression symptoms or anxiety alone.

8.2.6 Cardiac populations

The majority of research investigating depression symptoms in cardiac patients has been restricted to the ACS population. One difficulty in interpreting findings from ACS patients is that mental health before the cardiac event is assessed retrospectively. The ARCS study was able to address this issue, since measures of mood were taken both before and after surgery. Another problem with ACS studies is that the temporal relationship of depression symptoms and CHD is not clear. However, by using a CABG population, the prospective relationship between depression symptoms and recovery was demonstrated, showing that pre-operative depression symptoms were able to partially account for variation in recovery outcomes after surgery. However, there are several distinctions that were highlighted in the literature review, which need to be borne in mind when making comparisons between the ACS and CABG literature.

First, even though we can measure depression symptoms pre-operatively, this does not mean patients are being tested in a disease-free state. For example, in ARCS approximately one-third of patients had experienced at least one previous MI. Therefore, it is possible for pre-CABG depressed patients to also be classified as post-ACS depressed. It was not possible to disentangle the relative risk associated with post-CABG depression symptoms over and above

post-ACS depression symptoms in the ARCS study, although it is interesting that persistent and post-CABG onset depression symptoms was both associated with poorer recovery.

Second, although the post-ACS depression literature provides a useful model on which we could base the research rationale and hypotheses, this does not amount to post-ACS and post-CABG depression symptoms being one in the same, even in new onset cases. Only a minority of participants with either resolved, persistent or post-CABG onset depression were found to have a positive history of depression, and due to the limited cases it was not possible to classify participants as having new onset or recurrent depression, nor pinpoint the initial onset of recurrent cases. While, some participants in the ARCS study did develop post-CABG onset depression, the underlying aetiology is not clear; while there were some preliminary results which pointed towards the possible contribution of the inflammatory response to surgery, the small number of cases limits the inferences that can be drawn. Further work is needed to delineate the differences between post-ACS and post-CABG depressed patients and the underlying mechanistic pathways related to new onset depression episodes.

The final caveat is that it is not yet clear whether CABG surgery patients tell us anything over and above patients undergoing other major surgery. Nor is it clear to what extent CABG surgery differs from other types of cardiac surgery. While the majority of work has focussed on depression symptoms in CABG surgery patients, recent evidence suggests similar effects of depression symptoms on mortality in percutaneous coronary intervention patients too (Damen et al., in press). Unfortunately, ARCS was not able to address this issue, but my findings remain relevant since cardiac disease and revascularisation treatment are so common. These findings are able to contribute to the cardiac literature as well as the dialogue on the commonality of disease processes (Field, 2001; Southerland et al., 2006), suggesting mind and body are inextricably linked.

8.3 Methodological shortcomings

The ARCS study is able to make a significant contribution to the current literature based on several key methodological features. Firstly, its longitudinal design allows for multiple assessment points for the analysis of temporal relationships between variables. Importantly, this also allowed for the collection of baseline and follow-up measures of depression symptoms using the BDI. Secondly, the multidisciplinary approach allowed recruitment to be supported by the pre-assessment clinic nurses, for blood to be collected by the ward phlebotomists and for clinical data to be obtained from the clinical research analyst at St. George's hospital. Thirdly, we were able to collect a wide range of repeated measures, including biological samples and questionnaire data; the latter included measures of behavioural, psychological, social and cognitive factors potentially relevant to recovery after

CABG surgery. However, there are a number of limitations that also need consideration; these will be described in turn below.

8.3.1 Uptake and attrition

Refusal to participate and attrition warrant consideration as a limitation of the ARCS study. Four hundred and six participants were invited to participate, with only 243 participants returning their T1 assessment. In total, 104 patients refused to take part in the ARCS study and while some participants were unable to take part due to inadequate English or because they were too unwell, 59 participants stated they were not interested. This raises several issues.

Firstly, since non-English speaking participants were not included in the study, the sample is not entirely representative of the community from which participants were drawn. St. George's Hospital is situated in an ethnically diverse area of South West London, with approximately 22% of the borough stating their ethnicity as non-White in the UK 2001 census, and 27% of respondents stating a non-UK country of birth (Wandsworth Council, 2001). In total, 12.3% of the entire ARCS sample stated their ethnicity to be non-White. Previous research has shown that south Asians are less likely to confer the same long-term improvements after revascularisation procedures compared to white Europeans (Zaman et al., 2009). However, the analyses performed in this thesis did not take into account variation in ethnicity and culture not captured by household income, therefore future analyses should explore the impact of religious and ethnic status on the recovery outcomes.

Secondly, refusal to participate because participants were not interested or too stressed or anxious potentially means that those patients who were most relevant to the hypotheses of my PhD may not have been recruited. Therefore, it is possible that my results have underestimated the effect of emotional distress on recovery outcomes. Moreover, in terms of attrition, it is possible that the participants who withdrew from the study were those who were most affected by the procedure, either physically or mentally, and therefore again there is a chance the effect size has been underestimated in this data. However, in order to maintain full ethical compliance and to ensure the wellbeing of participants, right to withdraw at any time was one of the safeguards put in place to protect participants. Given the length of the questionnaire booklets, it is feasible that some participants felt undergoing a stressful life experience such as CABG surgery, was not conducive to the additional burden of participating in a research study. The resulting drop-out has implications in terms of power. The ARCS study was designed to recruit 200 participants. Due to the timescale of this PhD, 216 participants were included in analyses of early-term outcomes, but only 154 participants provided data for the short-term analyses. Due to missing biological samples, the analyses using the cortisol and inflammatory cytokine data were performed on a reduced number of participants, again

affecting the power of this study to detect an effect and increasing the risk of committing type I and II errors. When recruitment and data collection has completed, this issue can be addressed in future analyses using the full dataset.

8.3.2 Inclusion criteria

With regards to the inclusion criteria there are several potential problems. Participants were included in the ARCS study if they were elective, first-time CABG patients. Therefore we excluded any participants who were having a repeat procedure or were admitted via Accident and Emergency for an emergency procedure. Therefore, the ARCS sample does not capture the full breadth of clinical presentations for patients undergoing a CABG procedure, particularly the most unwell. In addition, participants with co-morbidities were permitted to take part in ARCS, and in line with the average age of the sample, many different conditions were self-reported including diabetes, osteoarthritis and cancer. These participants were maintained in the sample in order to strengthen the ecological validity of the sample. However, these co-morbidities were all considered during data analysis with no associations with the predictor or recovery variables found. Similarly, participants who were undergoing current treatment for psychiatric disorders were also allowed to participate, but again during data analysis associations were not found between antidepressant or anxiolytic treatment and scores on the BDI; therefore, these participants were retained in analyses.

8.3.3 Gender

There was a preponderance of male participants in the ARCS study and this was reflected in both P-ARCS and the main ARCS study, with 24.3% and 13.6% of the sample being female respectively. This male majority is characteristic of the CABG surgical population more generally, with men more likely to receive a revascularisation procedure than women in the UK. For example, in the ARCS study 406 patients were invited to participate, out of these only 55 patients (13.5%) were female. Therefore, the total number or women recruited to the sample is representative of the targeted clinical population. Moreover, sex was included in all analyses as a covariate, in order to assess whether any of the recovery outcomes were particularly relevant for men or women, since some studies have shown greater mortality risk for women after CABG (Lehmkuhl et al., 2012). However, due to the lack of female participants it is difficult to draw any firm conclusions about a gender effect in these data.

8.3.4 Time intervals between assessments

Another possible limitation is with regards to the difference between participants in terms of the time intervals between assessments. This is arguably a problem with all research that

occurs in a naturalistic setting where control over extraneous variables is reduced. Participants were recruited at the pre-assessment clinic, which the hospital aims to schedule approximately two weeks prior to surgery. In fact, on average participants completed their T1 questionnaire 29 days prior to surgery. Similarly, after surgery, the researchers aimed to conduct the T2 interview between three and five days after surgery, at a time convenient to the participant. On average, the T2 assessment did indeed take place approximately 4.5 days after surgery. Finally, with regards to the T3 assessment all participants were contacted and posted their T3 questionnaire pack six weeks after surgery, with the mean completion date being 60 days after surgery. The problem is that variation in these time points may have affected participants' responses, in particular with regards to the recovery outcomes and depression scores. Regression analyses were performed to assess the relationship between the time lag and BDI and recovery variables, with no significant findings found; however this needs greater consideration in future analyses.

8.3.5 Length of follow-up

Since analyses were restricted to the two-month follow-up of participants, clinical endpoints such as recurrent cardiac events, post-operative complications and mortality could not be investigated. Instead, my PhD was limited to investigate self-reported outcomes including emotional distress, pain and physical symptoms and quality of life. The only objective measure of recovery used was length of post-operative stay. It is possible that the associations between depression symptoms and the self-report outcomes were due to a reporting bias, such that participants with low mood were more likely to over-report negative symptoms. Nevertheless, it is interesting that the effect of depression on recovery was corroborated using the length of post-operative hospital stay outcome. Further analyses using the one-year follow-up data will be useful to verify the findings of this thesis with analyses of the associations between depression symptoms and other clinical endpoints.

8.3.6 Questionnaire measures

The next limitation of the ARCS study is the reliance on questionnaire measures of emotional distress, including depression symptoms and anxiety. The main issue is that clinical diagnosis of these conditions can only be given through administration of a clinical interview. As such, questionnaire measures are said to capture depression symptoms and not depression *per se*. Therefore, care must be taken when making inferences using results from the BDI and this thesis implemented a conservative cut-off of ≥13 in order to maximise the sensitivity and specificity of the measure. In addition, continuous variables were predominantly used in

analyses to make comparisons according to the degree of depression symptoms rather than depression caseness.

In terms of anxiety, the validity of the HADS has recently been questioned, with concerns regarding its latent structure and its ability to differentiate between cases of depression symptoms and anxiety (Cosco et al., 2012; Coyne & van Sonderen, 2012). These latter authors also point out issues surrounding use of colloquialisms in the HADS such as "butterflies in the stomach" and the subtlety of the reverse phrasing of some items such as "I can sit at ease and feel relaxed", which they argue may cause response errors. Issues of interpretation are inherent with all questionnaire measures where the researcher relies on the participant to comprehend the written instructions. In the ARCS study it is likely to have been the cause of missing data on some of the questionnaires, but it is not clear to what extent questions were misinterpreted. Inferences can be drawn using the internal consistency values in the form of the Cronbach's alpha coefficient, which for the BDI and anxiety were good across all three time points (>0.75). However, the criticism charged at the HADS regarding its latent structure requires consideration, and has been addressed in this work by terming anxiety an 'emotional distress' outcome. Moreover, the HADS score was used as a continuous measure in all regression models, again sidestepping the issue of caseness.

Ceiling effects on questionnaire measures were assessed during P-ARCS with the ESSI showing a high positive skew, such that the majority of participants reported high levels of social support. This was also the case in the ARCS study and creates issues surrounding the estimation of central tendency. This is possibly why no difference was observed between depressed and non-depressed participants in terms of social support. Future analyses will benefit from making use of the other social measures included in ARCS, such as social networks and marital functioning.

8.3.7 Confounders and covariates

Adequate control for confounders is crucial for interpreting of any relationship between a predictor and an outcome variable. One of the major concerns with the research in this field relates to the issue of reverse causality, which questions whether rather than depression causing poor cardiac prognosis, poor cardiac prognosis actually causes depression. In considering how to unpick this relationship, proper control for confounders becomes of crucial importance since both depression and poor cardiac prognosis could in fact be the product of a separate underlying disease process, like, for example, inflammation. A randomised trial would be able to test this hypothesis by assessing the extent to which treatment of the possible confounder, in this example inflammation, was able to reduce both depression and improve cardiac prognosis. Careful examination of all possible confounders will enable future research

to illuminate the direction of the causal relationship between depression and cardiac prognosis.

In ARCS, all analyses were adjusted for age, sex, socioeconomic status (household income), euroSCORE and where applicable, baseline measures of questionnaire outcomes. However, it is important to note that not all possible confounders of the depression-recovery relationship have been captured in ARCS, such as use of illicit drugs and aspects of people home environment such as the ambient temperature. In addition, problems surrounding the measurement of confounders also warrant consideration as a limitation of the ARCS study. For example, smoking was included in models as a binary variable, demarking participants according to their current smoking status. This does not take into account the nuances in smoking such as the duration of the smoking habit and the number of cigarettes typically smoked. Nor does it capture the influence of indirect tobacco effects through passive smoking. In addition, while some covariates were measured, the literature is yet to elucidate how they influence risk; an example being ethnicity (see Section 8.3.1). A final point here is that while disease severity was captured by euroSCORE, this only takes into account coronary disease, and no measure of global cardiovascular disease (including cerebrovascular and peripheral arterial disease) was included in analyses; this needs to be addressed in future work using the ARCS sample. Comprehensive assessment of disease severity is an important step in understanding the causal relationship between depression and cardiac disease, particularly in understanding whether depression precedes atherosclerosis or incident ACS, or whether depression arises as a consequence of these underlying disease processes. Inclusion of multiple disease severity covariates will be important when studying post-CABG onset depression using the full ARCS dataset.

8.3.8 Biological measures

Another limitation of the ARCS study is with regards to the collection of the biological data. Cortisol was assessed using saliva samples, which was used as it has the advantage of being a non-invasive and convenient method of assessing diurnal variation of cortisol in a naturalistic setting (Kirschbaum & Hellhammer, 1989, 1994). However, this approach relies on participants taking the samples themselves and accurately reporting the time of assessment. This reflects a trade-off, since the control over the measurement is surrendered in order to gain ecological validity. Participants were instructed to choose one day prior to surgery in which to give seven samples at set time points: on awakening, 30 minutes after awakening, 10am, midday, 4pm, 8pm and bedtime. Participants were told not to eat, drink caffeinated beverages, smoke cigarettes, take any medications, or brush their teeth, for the 30 minutes prior to giving the sample. However, non-adherence to this protocol meant that some samples were not given,

some were given at the incorrect time and outliers had to be removed, leaving a reduced number of cases on these analyses.

To assess inflammatory activity, a 20ml blood sample was drawn into plain serum tubes by venepuncture from the forearm at T1 and T2. However, although blood was planned to be drawn at days one and four after surgery, this was not always achieved due to inconsistencies in nursing staff. The reasons for the variability in collection day meant some participants had blood drawn on any combination of two days post-surgery. This led to a range of collection days between day one and day eight post-surgery. Although not foreseen during the planning stages of the ARCS study, this meant cytokine responses had to be averaged across two time periods: days one to three and days four to eight, to produce an early and late mean.

8.3.9 Medication

Problems interpreting the role of prescribed and non-prescribed medications on the depression-recovery relationship are another limitation of my analyses. Depression has been shown to be associated with cardiac medications such as statins and beta-blockers. Statins have actually been shown to have a protective effect for depression, with several longitudinal studies finding use of statins to confer a risk reduction for depression onset in CHD patients (Otte et al., 2012; Stafford & Berk, 2011). In contrast, the literature on beta-blockers and depression is less clear, with some early evidence suggesting they may be capable of inducing mood disturbance (Greenblatt & Koch-Weser, 1974). More recently, evidence from systematic reviews has not substantiated this link, although the popular misconception persists in prescription practice (Ko et al., 2002). In my results, analyses were performed to assess the relationship between medication use and the recovery outcomes and the biomarkers, with no significant findings found. Moreover, the cardiac medication usage of this patient group is largely standardised, following the prescription guidelines of NICE. While information was gathered from participants regarding their medications prior to surgery and at the T3 assessment, no information was collected regarding the administration of drugs during the in-hospital stay. It is possible that differences in the administration of medications at this time, particularly analgesics, affected responses given at the T2 assessment. More work is needed to understand how these medications may interact to affect the relationship between depression and later recovery in CABG patients.

8.3.10 Cognitive function

The next limitation is that cognitive function was only assessed pre-operatively, to assess baseline levels of neurocognition. Therefore, it was not possible to assess the effect of

cognitive deterioration from before to after the surgical procedure, and the effect of any change on the depression symptoms-recovery relationship. Previous research in this area is mixed, and while there is some evidence that cognitive decline is an important predictor of cardiac mortality (Batterham et al., 2012), it is not yet clear how this interacts with depression to effect prognosis in CABG patients. For example, McKhann and colleagues (McKhann et al., 1997) found no association between depression and cognitive decline in a one-year follow-up study of 124 CABG patients and a more recent study has shown cross-sectional associations between depression and cognitive function at six months and five years following CABG surgery, though the effects were only small and explained no more than 7.2% of variance in any of the cognitive domains (Tully et al., 2009). In addition, since levels of cognitive function were already below normative values in the ARCS sample at baseline, it is unclear to what extent a further deterioration over time would have contributed to the depression symptoms-recovery relationship.

8.3.11 Causality

The final limitation of the ARCS study is with regards to the issue of causality. Mediation analyses were performed on the data to assess the extent to which the candidate mechanisms accounted for the relationship between depression symptoms and the recovery outcomes. However, given the timeline of the study it is difficult to assess the direction of the causal relationship between depression symptoms and the candidate mechanisms. For example, it is not clear to what extent depression symptoms caused physical inactivity or vice versa. Nevertheless, the prospective relationship between depression symptoms and the recovery outcomes was established in this study, showing the effect of pre-operative depression symptoms on post-operative recovery.

8.4 Clinical implications and suggestions for further research

The findings of this study have important clinical implications, primarily surrounding the identification of different depression symptom subtypes and mechanisms of the depression-recovery relationship. My work has shown depression symptoms to be heterogeneous with different subtypes being predictive of different recovery outcomes. Depression symptoms were grouped into subtypes including total depression, cognitive/affective and somatic/affective depression, as well as depression onset subtypes including resolved, persistent and post-CABG onset depression. These findings are relevant at two stages of the clinical process: screening and treatment.

8.4.1 Screening

One of the main problems with treating depression is the failure to identify cases of depression in primary care. The current UK Quality Outcome Framework incentivises the screening of depression in primary care, and advocates the use of the Patient Health Questionnaire-2 and -9 questionnaire measures of depression for this purpose. However, difficulty arises when one considers the fact that individuals often fail to consult with their GP about mood symptoms (Meltzer et al., 2003). Moreover, GPs are not currently required to routinely screen for depression in persons with known CHD; routine screening would eliminate the need for GPs to react to cues provided by the patient as to whether screening is required.

The identification of different depression subtypes in my results has consequences for the identification and screening of depression. For example, traditional cut-off scores on depression screening instruments do not distinguish between different symptom clusterings of depression symptoms. Theoretically, a total depression symptom score above the threshold for caseness may not actually be clinically relevant for those patients who score lowly on both cognitive/affective and somatic/affective subscales. What seems to be more important than total score, in terms of short-term recovery, is the preponderance of somatic/affective but not cognitive/affective symptoms. Designing screening tools for depression symptom subtypes with appropriate cut-offs is an area for further research. However, having said this, greater work is still needed to explore the consequences of cognitive/affective depression. It could be that cognitive/affective depression symptoms have synergistic effects with somatic/affective symptoms that cannot be captured in a simple questionnaire. Care must be taken not to negate the importance of cognitive/affective depression symptoms in a screening instrument, as in my results of the early-term recovery outcomes they were similarly predictive as somatic/affective symptoms.

Of course, screening for depression is not necessarily as straightforward as having a good and valid measurement. While the American Heart Association now recommends routine screening for depression in all heart disease patients (Bigger & Glassman, 2010; Lichtman et al., 2008), such guidelines have yet to be introduced in the UK. Moreover, screening for depression has yet to be shown to actually impact patient outcomes (Thombs et al., 2008). Therefore, it is not clear to what extent screening would actually have any added benefit for these patients. This issue is further complicated since even mild levels of depression symptoms, not just depression caseness, have been shown to confer cardiac risk (Zuidersma et al., 2012). Regardless, a standardised approach to depression screening in cardiac patients appears to be the most efficient way to ensure patients receive the support they require, and offers an effective way of identifying those patients who may be at greatest risk of adverse

events and poorer recovery after CABG. The lack of an effective treatment strategy does however limit the benefits of screening; this will be discussed below.

8.4.2 Treatment

The NICE guidelines for depression (National Collaborating Centre for Mental Health, 2010a) recognise that some cases of depression will remit spontaneously without treatment, while other cases will recur and take a more chronic course. The results of this PhD suggest that different depression subtypes of depression may exist and therefore strategies aimed to improve and treat depression as a homogenous disorder, and according to currently diagnostic criteria, may not necessarily confer clinical benefits. Indeed, intervention studies designed to improve emotional wellbeing after CABG have shown mixed results. Positive results were found by Freedland and colleagues (Freedland et al., 2009) who conducted a 12-week randomised controlled trial to assess the efficacy of two different types of non-pharmacological treatment for depression symptoms after CABG, in comparison to usual care controls. Results showed significantly higher rates of remission in depressed patients who received cognitive behavioural therapy or supportive stress-management compared to usual care controls, at three- and nine-month follow-up. A more recent intervention study, the Bypassing the Blues randomised controlled trial, investigated the impact of a telephone delivered collaborative care intervention in post-CABG depressed patients, compared to usual care depressed controls and non-depressed controls. The intervention group received a tailored nurse-led telephone delivered programme for up to eight months following CABG. Results showed significant improvements in health-related quality of life and mood in the intervention group compared to usual care controls, however the effect was stronger for men than women (Rollman & Herbeck Belnap, 2011; Rollman et al., 2009). Despite these studies demonstrating a positive impact on emotional wellbeing, three other randomised controlled trials have been less conclusive (Furze et al., 2009; Lie et al., 2007; Sebregts et al., 2005). Notably, these studies sought to improve emotional wellbeing, and the clinical consequences of such improvements were not assessed. Turning to the MI literature suggests the effect would not necessarily have extended to clinical endpoints such as mortality (Berkman et al., 2003).

Interestingly, another randomised controlled trial using cognitive behavioural therapy for post-ACS patients, not specifically targeting depression symptoms, but instead stress management, did show clinical benefits. These authors were able to show that participants in the intervention arm had a 41% lower rate of fatal and non-fatal first-time recurrent cardiac events compared to standard care controls (Gulliksson et al., 2011). The reason why a stress management intervention programme should confer such large prognostic benefits over and

above a depression-centred intervention is likely multifaceted. For example, issues surrounding the timing of recruitment into the study, differences in the inclusion criteria, problems with spontaneous remission of some depression patients but onset or relapse of control patients, and use of out-of-study medications and therapies, are all likely to play a role. Understanding these differences is essential for directing future intervention studies. If such benefits could be replicated in further work and could be translated into objective clinical results, such as shorter hospital stays, lower cardiac recurrence rates and lower use of GP and outpatient services, there would be a sustained health economics argument for investment in such work.

The lack of clear findings are reflected in the European Society of Cardiology guidelines (Perk et al., 2012).These guidelines recognise and promote the management of psychosocial factors, including depression, but only as a means to promote healthy lifestyle choices. In reviewing the evidence for interventions aimed at reducing depression, these guidelines recognise the fact that studies which have shown a reduction in negative mood symptoms have not also seen improvements in cardiac outcomes. This highlights the need for further work to develop the field. The recognition of the different predictive power of the different depression subtypes was crucial to understanding the relationship between depression symptoms and recovery in my results. In fact, in terms of predicting short-term outcomes, somatic/affective depression symptoms were the only significant depression subtype predictive of impaired adaptation, after controlling for demographic and disease severity covariates. This also has consequences for the design of tailored interventions. More work is needed to investigate whether different treatment strategies are particularly effective for the different symptom subtypes.

Based on the findings of this PhD I would propose a large, multi-centre randomised controlled trial to investigate the impact of a pre-CABG depression treatment programme on clinical, physical and psychological post-CABG recovery. Participants would be screened for trial inclusion on first notification of the need for elective CABG and, on meeting a depression diagnosis, would be randomised to either usual care or an intervention group. The content of the intervention itself would be determined by patient preference (Davidson et al., 2010), and would involve a mixed-treatment approach to depression including components of exercise, cognitive behavioural therapy and traditional pharmacotherapy. The length of the intervention prior to surgery would vary according to the amount of time each individual spent on the waiting list, but the intervention would continue post-CABG to ensure maximum benefit. In particular, careful attention would be paid to measuring depression symptoms and studying the effect of treatment on individual symptom remission. While the importance of recurrent cardiac events and mortality are obviously of critical importance when assessing the efficacy of

psychosocial interventions, other evaluative markers would also be included. For example, some authors argue that prognostic studies should not be limited to the assessment of cardiac endpoints, but should also include subjective markers of wellbeing and quality of life (Hemingway et al., 2009). This appraisal could also be extended to intervention trials. Results from the ARCS study suggest that an array of subjective parameters may be useful for assessing an intervention's success, including pain, physical symptom reporting, physical and mental health status and other symptoms of emotional adjustment such as anxiety. Therefore, I would propose a trial powered to evaluate not only mortality, but also subjective outcomes such as quality of life. Such a distinction is also important for informing the next round of guidelines, and it could be suggested that organisations such as the European Society of Cardiology should recognise a more diverse range of endpoints, reducing the emphasis on 'hard' clinical outcomes.

While there is a need for more methodologically robust intervention work, greater attention also needs to be paid to how we make use of existing data. An alternative method for adding credence to the depression-cardiac prognosis literature could involve the pooling of data from existing depression treatment trials. This approach would allow a large sample of participants' data to be analysed to assess whether depression treatment in a psychiatric population was associated with a reduction in cardiac events and/or mortality. In addition, it would also be possible to assess the type and level of depression treatment required to show an effect. Such a design could be strengthened by individual-level analysis, making use of resources such as the NHS's hospital episode statistics data. While the pooling of data from depression treatment trials has yet to be carried out, an example of a large scale observation study is provided by Osborn and colleagues (Osborne et al., 2007) who conducted analyses using the General Practice Research Database of over 46 thousand individuals with severe mental illness. This retrospective cohort study was able to show that the hazard of CHD mortality among those with severe mental illness compared to controls was 2.88 (95% CI 1.77-4.70) for 18 to 49 year olds, even after controlling for multiple risk factors. A significant effect was also found for older individuals aged 50 to 75 years (HR 1.76, 95% CI 1.54-2.01), but not among the very old (≥75 years) (HR 1.04, 95% CI 0.91-1.18). This study demonstrates the utility of large scale observations, although this evidence has yet to be replicated among those with major depression specifically. Such work presents a clear pathway for progression of the field, and while such large scale research lacks the detailed information about each individual that benefits the smaller trials, it offers a clear advantage in terms of the sample size increasing the power of the observations.

8.4.3 Other avenues for intervention

My PhD has also produced results suggestive of other areas of further research. For example, behavioural factors such as smoking and physical activity were shown to have important effects on recovery. Working out the most effective way to disseminate knowledge regarding the health benefits of lifestyle improvements warrants further research. A recent longitudinal examination of smoking status in over 4.5 thousand post-ACS patients (Boggon et al., in press) found that smoking cessation advice, while advocated by NICE, was only provided by GPs to 24% of patients after ACS. Moreover, less than half of the ARCS study actually partook in a cardiac rehabilitation scheme routinely offered to all patients under the NHS. Understanding adherence to lifestyle and medical advice is one way in which further research could help to advance our knowledge of this area.

Illness perceptions were also shown to be an important independent predictor of recovery in this PhD. This work has added relevance since research has shown that illness perceptions are amenable to change in several intervention studies, with results of one trial showing improvements in functional recovery, i.e. faster return to work, as a result of a brief in-hospital intervention to challenge and replace negative illness perceptions in MI patients (Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009). It is not clear to what extent such interventions could work to moderate the negative effect of depression symptoms on recovery, and further work is needed to investigate whether such interventions could affect clinical prognosis.

The results using the biological data in this thesis are also indicative of the need for further research. Biological and inflammatory marker research would benefit from being more widely investigated during intervention studies so that the underlying physiological pathways linking the psychological or cognitive behavioural intervention to later improvements could be delineated. Current trials are evaluating techniques for limiting acute inflammatory responses, for example, the MRC-ILA-HEART study (Crossman et al., 2008). If these trials are successful, they would provide the opportunity to test links between inflammation and the development of depression in ACS patients.

8.5 Conclusion

I studied the effect of pre-operative depression symptoms on impaired adaptation and physical recovery following CABG surgery and explored the underlying mechanistic pathways. Outcomes were studied in the early- and short-term stages of recovery, namely the days and months following surgery, showing that greater depression symptoms were predictive of greater emotional distress, greater physical symptoms and pain, longer in-hospital stays and impaired physical and mental health status, independent of demographic and disease severity

factors. Specifically, somatic/affective depression symptoms were predictive of the two-month post-operative outcomes, but not total or cognitive/affective depression symptoms. Social-behavioural mediation of this relationship was not shown, but instead physical activity, BMI and smoking status all had independent effects on recovery outcomes. Cognitive mediation was found, showing that greater negative illness perceptions prior to surgery mediated the relationship between pre-operative depression symptoms and anxiety and physical symptoms in the early term and affective pain and physical symptoms in the short term. Biological mediation was not shown, and although depression symptoms were related to neuroendocrine and inflammatory patterns suggestive of poorer physical functioning, these patterns did not consistently relate to any of the post-surgery recovery outcomes. Finally, there was little evidence in support of a sickness behavioural model of depression in this data. Further work is needed to translate these findings into new ways to approach the measurement, diagnosis and treatment of depressed cardiac surgery patients.

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Appendices

Please note, Appendices 1, 2, 3 & 9 have been removed from this version since they contain copyrighted material.

APPENDIX 4: EUROSCORE SCORING

From: http://www.euroscore.org/euroscore_scoring.htm

	Description	Score
Patient related factors		
Age	(Per 5 years or part thereof over 60 years)	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction disease	Severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium.	3
Serum creatinine	>200m micromol/L preoperatively	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	3
Cardiac related factors		
Unstable angina	Rest angina requiring IV nitrates until arrival in the anaesthetic room	2
LV dysfunction	Moderate or LVEF 30-50% Poor or LVEF <30	1 3
Recent myocardial infarct	(<90 days)	2
Pulmonary hypertension	Systolic PA pressure>60 mmHg	2
Operation related factors		
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	3
Post-infarct septal rupture		4

APPENDIX 5: PARTICIPANT INFORMATION SHEET

ADJUSTMENT AND RECOVERY AFTER CARDIAC SURGERY – THE ARCS STUDY

PATIENT INFORMATION SHEET

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
Recovery after coronary artery bypass graft (CABG) surgery is influenced by lots of different things including your mood, your daily life activities and your beliefs about your health. We are trying to understand more about all these different factors and the way in which they affect recovery and adaptation after CABG surgery. We are particularly interested in linking psychological factors with the underlying biology of heart disease, to see whether there are differences in the various chemicals in the blood that are involved in some heart conditions. The results of this study will help to advance our knowledge of the links between the mind and body, and may help to develop new methods of improving patient care after surgery.

Who is organising and funding the research?
The study is being carried out by Professor Marjan Jahangiri from the Department of Cardiac Surgery at St George's Hospital in collaboration with Professor Andrew Steptoe from the Department of Epidemiology and Public Health at University College London. The research team who will carry out the work are Dr Tara Kidd, Ms Lydia Poole and Ms Lizzy Leigh.

Why have I been chosen?
Up to 250 patients admitted to this hospital for CABG surgery will be invited to participate over the next twelve months. If you have a spouse or partner they will also be invited to participate in a similar study looking at their experiences of your surgery.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to participate you will be given this information sheet and asked to sign a consent form. You are still free to withdraw from the study at any time and without giving a reason. A decision not to take part or withdraw will not affect your medical treatment in any way.

What will happen to me if I take part?
The study consists of 4 parts:
Part 1: We will ask your permission to take part in our study when you come to your pre-surgical outpatient's appointment at St. George's Hospital. If you agree, with your consent we will inform your GP that you have agreed to take part in the study and that we can consult your hospital medical notes.

You will not need to have any extra blood tests, but we will ask your permission to use some of the blood from samples you give during your pre-assessment clinic appointment and after your operation in order to analyse certain substances that will help us understand more about the processes underlying heart disease.

We will interview you briefly to ask about your memory and concentration. This will take about twenty minutes and will take place in a private room in the Outpatients Department at St George's Hospital. We will do this on the same day and time you come for your pre-surgical assessment appointment; you will not be required to make an extra visit to the hospital.

We know that there are several hormones that affect the way the body works which vary over the course of the day, and fortunately these can be measured in saliva. We will therefore ask you to provide some saliva samples at home. This involves putting a cotton dental swab in your mouth for a couple of minutes several times over the course of one day and then returning it to a special storage tube which we will provide. The samples you collect at home can be posted back to us using a freepost envelope which we will provide. We will also give you a short questionnaire to complete at home and we will ask you to return this to us using a freepost envelope which we will provide.

Part 2: Depending on your recovery, about 4-5 days after your CABG surgery, we will interview you again to ask you how you are feeling after your surgery. This interview will last approximately ten minutes and will be conducted discreetly on the ward and at a time convenient to you.

Part 3: About 8 weeks after your surgery we will contact you by telephone and send you a questionnaire by post. We will ask you to return this to us using a freepost envelope which we will provide. We will also ask you to provide some more saliva samples as described above.

Part 4: About 12 months after your CABG surgery, we will contact you by telephone and send you a questionnaire by post. We will ask you to return this to us using a freepost envelope which we will provide. We will also ask you to provide some more saliva samples as described above.

What else do I have to do?
There are no other requirements and you should carry on as normal.

What are the possible disadvantages of taking part?
We do not anticipate any disadvantages in participating in this study. If you find any of the questions sensitive in nature you are free to ask for a break or terminate the session altogether if you feel unwell or upset. If any problems become apparent that may require ongoing medical management we will advise you to contact your GP so that you can seek medical treatment as early as possible. A doctor in our research team will also be obliged to inform your GP, on your behalf.

What are the possible benefits of taking part?
The information we get from this study may help to improve treatment and recovery for future patients after having CABG surgery like yours. Your participation to help further this research would be very much appreciated.

Will my taking part in this study be kept confidential?
We want to emphasise that all results obtained will be strictly confidential and will only be used for medical research purposes. All personal information will be coded and kept separately to your name and address so that you cannot be recognised from it. All paper questionnaires will be kept in locked filing cabinets, in locked offices, accessible only to members of the research team. In compliance with UCL regulations all data will be stored in this way for up to 20 years before being destroyed.

What if something goes wrong?
We do not expect you to suffer any adverse effects from this study and every care will be taken to ensure your wellbeing and safety is not compromised during the course of the study. However, UCL has special insurance arrangements in place (called 'no-fault compensation') in the [unlikely] event that something unforeseen happens and on the balance of probabilities, harm is attributed to your participation in this study. The normal National Health Service complaints mechanisms will be available to you. If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should speak to the research team in the first instance, who will do their best to answer your questions (telephone 020 8725 1804). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

What will happen to the results of the research study?
The study will recruit up to 250 participants over a twelve month period. The results will be statistically analysed and findings subsequently published in scientific journals. You will not be identified in any publication.

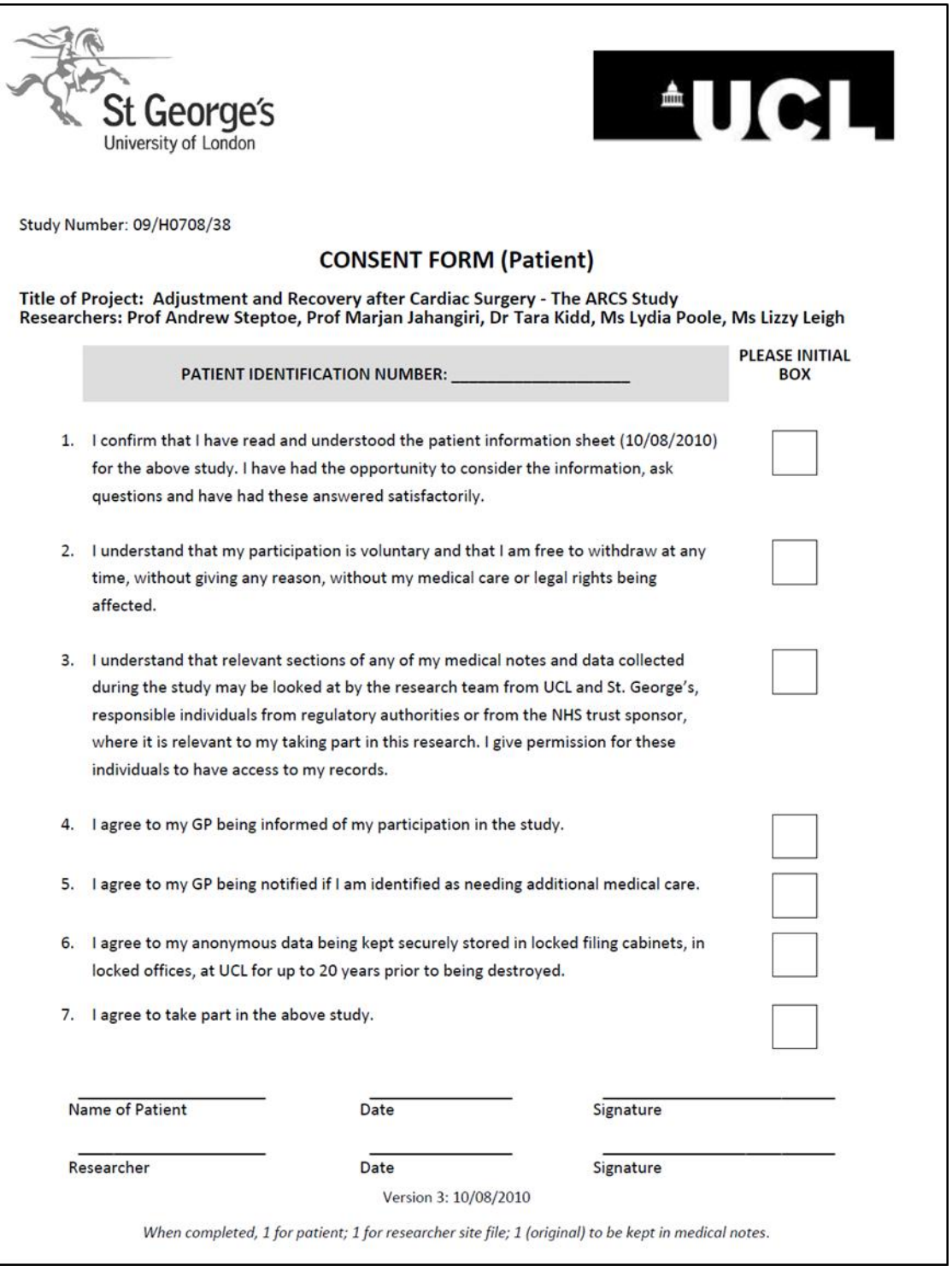
Who has reviewed the study?
This study has been reviewed and given a favourable opinion by Brompton, Harefield and NHLI Research Ethics Committee.

Many thanks for reading this information sheet.
We hope you will feel able to take part in our study, which will help us understand more about recovery after CABG surgery.

Contact for further information
If you have any questions or concerns please contact the research team (Lydia Poole, Tara Kidd or Lizzy Leigh) at the Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT. Telephone: 020 7679 1804.

Version 4: 10/08/2010

APPENDIX 6: PARTICIPANT CONSENT FORM



St George's University of London

UCL

Study Number: 09/H0708/38

CONSENT FORM (Patient)

Title of Project: Adjustment and Recovery after Cardiac Surgery - The ARCS Study
Researchers: Prof Andrew Steptoe, Prof Marjan Jahangiri, Dr Tara Kidd, Ms Lydia Poole, Ms Lizzy Leigh

PATIENT IDENTIFICATION NUMBER: _____	PLEASE INITIAL BOX

1. I confirm that I have read and understood the patient information sheet (10/08/2010) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by the research team from UCL and St. George's, responsible individuals from regulatory authorities or from the NHS trust sponsor, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to my GP being notified if I am identified as needing additional medical care. ☐
6. I agree to my anonymous data being kept securely stored in locked filing cabinets, in locked offices, at UCL for up to 20 years prior to being destroyed. ☐
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Version 3: 10/08/2010

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes.

APPENDIX 7: EXAMPLE PAGE FROM CORTISOL SAMPLING DIARY

TUBE 1 : AS SOON AS YOU WAKE UP

1. ***What is the time now?*** _____a.m. / p.m.

2. ***What was the exact time you collected the sample?*** _____a.m. / p.m

2a. Was there a delay between waking up and collecting your first sample? **Yes** **No**

2b. ↳If yes, how long? ____ hrs & ____ mins

In the last 30 minutes how much did you feel.....

		Not at all				***Very much***
3.	In control	1	2	3	4	5
4.	Tired	1	2	3	4	5
5.	Happy	1	2	3	4	5
6.	Frustrated or angry	1	2	3	4	5
7.	Sad	1	2	3	4	5
8.	Stressed	1	2	3	4	5
9.	Pain	1	2	3	4	5
10.	If you talked with others, how pleasant was the interaction?					
	Not applicable ☐	1	2	3	4	5

In the last 30 minutes, but before you collected your sample did you....

Brush your teeth	No	Yes
Drink any tea, coffee or other caffeinated drinks	No	Yes
Take any medicines	No	Yes
Eat a meal	No	Yes
Drink any alcohol	No	Yes
Do any exercise?	No	Yes
Smoke any cigarettes?	No	Yes

APPENDIX 8: LOGISTIC EUROSCORE

From: http://www.euroscore.org/logisticEuroSCORE.htm

	Description	Beta weight
Patient related factors		
Age	(Per 5 years or part thereof over 60 years)	0.0666354
Sex	Female	0.3304052
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	0.4931341
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	0.6558917
Neurological dysfunction disease	Severely affecting ambulation or day-to-day functioning	0.841626
Previous cardiac surgery	Requiring opening of the pericardium.	1.002625
Serum creatinine	>200m micromol/L preoperatively	0.6521653
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	1.101265
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	0.9058132
Unstable angina	Rest angina requiring IV nitrates until arrival in the anaesthetic room	0.5677075
LV dysfunction	Moderate or LVEF 30-50% Poor or LVEF <30	0.4191643 1.094443
Recent myocardial infarct	(<90 days)	0.5460218
Pulmonary hypertension	Systolic PA pressure>60 mmHg	0.7676924
Emergency	Carried out on referral before the beginning of the next working day	0.7127953
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	0.5420364
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	1.159787
Post-infarct septal rupture		1.462009