The role of perseverative negative thinking in predicting depression, anxiety and quality of life in people with coronary heart disease.

Submitted by Leanne Victoria Trick,
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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

(Signature) ……

Abstract

Depression is common in people with coronary heart disease (CHD) and is associated with worse physical outcomes. The nature of the causal association between CHD and depression, and the mechanism underpinning the association of depression with worse physical outcomes, remains unclear. Perseverative negative thinking may contribute to the development of depression in people with CHD.

The aim of this thesis was to investigate the prospective association of perseverative negative thinking with depression, anxiety and worse physical outcomes in people with CHD, and to explore factors that may mediate this association.

First, a systematic review identified 30 studies, of which the majority found an association between measures of perseverative negative thinking and subsequent depression, anxiety or emotional distress in people with long term conditions. Studies that controlled for covariates showed more mixed results, though the majority (15 / 25) still supported a significant association, with effects being small in magnitude. Findings were limited mainly to the association of rumination and/or catastrophizing with subsequent depression, and study quality was limited.

Next, in an observational prospective cohort study 169 inpatients and outpatients with recent acute coronary syndrome (ACS) completed self-report assessments of rumination (Ruminative Responses Scale brooding subscale), worry (Penn State Worry Questionnaire), depression (Patient Health Questionnaire-8), anxiety (Beck Anxiety Inventory), and health-related quality of life (EuroQol-5D health-related quality of life, Seattle Angina Questionnaire) after hospitalisation, and at 2 month and 6 month follow-up. Additionally, assessments of potential mechanistic factors (social support, problem solving, instrumental behaviours and negative cognitive biases) were made.

Baseline brooding was a significant independent predictor of depression at 6 months after controlling for the effects of important confounding variables, accounting for 2% of the variance. Findings suggested that the association of brooding with depression may be explained by deficits in problem solving ability.

Rumination and problem solving may provide useful targets for the development of evidence-based interventions to improve depression among people with CHD, although the findings presented here fall short of proving a causal relationship. Future trials could be used to investigate the causal nature of the association of rumination and problem solving with depression in people with ACS.

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List of abbreviations

ACS	Acute coronary syndrome
BA	Behavioural activation
BAI	Beck Anxiety Inventory
CBT	Cognitive behavioural therapy
CERQ	Cognitive Emotion Regulation Questionnaire
CHD	Coronary heart disease
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CRP	C-reactive protein
CI	Confidence interval
DSM-V	Diagnostic and statistical manual of mental disorders fifth edition
EMBASE	Excerpta Medica Database
ESSI	*ENRICHD* study Social Support Inventory
EQ5D	EuroQol-5D measure of general health-related quality of life
HADS	Hospital Anxiety and Depression Scale
HRV	Heart rate variability
IMD	Index of Multiple Deprivation
IQR	Interquartile range
LTCs	Long term conditions
MCBT	Mindfulness-based cognitive behavioural therapy
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST segment elevation myocardial infarction
NYHA	New York Heart Association
PHQ-8	Patient Health Questionnaire-8 item version
PSWQ	Penn State Worry Questionnaire
PsycINFO	Psychological Information Database
RFCBT	Rumination-focused cognitive behavioural therapy
RRS	Ruminative Responses Scale
RSQ	Response Styles Questionnaire
SAQ	Seattle Angina Questionnaire
SD	Standard deviation
SE	Standard error
SPSI	Social Problem Solving Inventory
STEMI	ST-segment elevation myocardial infarction
STROBE	Strengthening the reporting of observational studies in epidemiology

VAS	Visual analogue scale
VIF	Variance inflation factor
WCC	White cell count
WHO	World Health Organisation

Study/trial acronyms

CREATE	Canadian Cardiac Randomized Evaluation Of Antidepressant And Psychotherapy Efficacy
ENRICHD	Enhancing Recovery in Heart Disease study
INTERHEART	A Study Of Risk Factors For First Myocardial Infarction In 52 Countries And Over 27,000 Subjects
MIND-IT	Myocardial Infarction and Depression-Intervention Trial
SADHART	Sertraline Treatment Of Major Depression In Patients With Acute MI Or Unstable Angina

Authors statement of contribution

Chapter 2: Systematic review

The systematic review presented in Chapter 2 is published in the Journal of Psychosomatic Research: Trick L, Watkins E, Windeatt S, Dickens C (2016) The association of perseverative negative thinking with depression, anxiety and psychological distress in people with long term conditions: A systematic review. *Journal of Psychosomatic Research*, 91: 89-101.

With supervisory support I developed the research question and search strategies. I conducted database and literature searches. I was the primary reviewer for title/abstract/full text screening, quality assessment and data extraction. My co-authors acted as second reviewers at screening, quality assessment and data extraction stages. I prepared a first draft of the manuscript for publication (including preliminary synthesis of data) and my co-authors reviewed and edited the manuscript.

Chapters 3, 4, 5: Observational prospective cohort study

My supervisors were responsible for the initial conception of the research. With supervisory support I further developed the research questions and hypotheses, designed the study, obtained ethical approval, collected and analysed the data, and wrote the relevant methods and results chapters presented in this thesis. The cardiac rehabilitation team at the Royal Devon & Exeter Hospital facilitated recruitment by identifying and making initial approach to eligible patients. With my direction Jessica Bollen (Associate Research Fellow) assisted with collection of follow-up data.

Chapter 1 Introduction

1.1 Chapter outline

This thesis concerns repetitive thought such as rumination and worry (i.e. perseverative negative thinking) as a cognitive process that may contribute to the development of, or maintain, depression in the context of chronic physical illness, in particular coronary heart disease (CHD). The research presented here seeks to (a) clarify the association of perseverative negative thinking with depression, anxiety and health-related quality of life in people with CHD, and (b) explore factors that may mediate the association of perseverative negative thinking with subsequent depression, anxiety and health-related quality of life.

This introductory chapter summarises key literature related to:

i. The prevalence and impact of chronic physical illness and depression; and the association of depression and CHD.
ii. How cognitions about health and illness may impact on mental and physical wellbeing.
iii. Definition and theoretical models of perseverative negative thinking; and empirical research and theories related to the association of perseverative negative thinking with psychopathology and physical health.

Following this, gaps in the literature are identified, the aims of this thesis are outlined, and the structure of the thesis is described.

1.2 Background

1.2.1 Definitons, prevalence and impact of long term conditions and depression

1.2.1.1 Long term conditions

Chronic physical illnesses (i.e. long term conditions – LTCs) are conditions that cannot currently be cured but can be controlled with medication and/or other therapies, and includes a broad spectrum of conditions such as CHD, asthma, diabetes, chronic kidney disease, hypothyroidism, chronic obstructive pulmonary disease, arthritis and hypertension among others. It is estimated that 15 million people in

England (approximately 30% of the population) have at least one LTC and this is set to rise to 18 million by 2025. LTCs can restrict physical and mental wellbeing, and can limit everyday activities including employment. In addition, the treatment of LTCs imposes a significant economic burden, accounting for 70% of all health and social care spending in England[1, 2].

1.2.1.2 Coronary heart disease

CHD is a term used to describe a group of diseases caused by the gradual build-up of fatty deposits (atheroma) in the walls of the blood vessels supplying the heart muscle that can restrict or block blood flow. Common symptoms of CHD include chest pain (angina), shortness of breath and heart attack (myocardial infarction). Risk of CHD rises with age and is higher in males than females[3]. Other risk factors include hypertension, raised cholesterol, smoking and diabetes mellitus[4]. Prevalence of CHD is estimated at 2.3 million people in the UK[5], and although prognosis among people with CHD has improved dramatically in the last two decades (e.g. [6, 7]) it remains the leading cause of mortality in the UK, accounting for approximately 80,000 deaths in 2010. There were 405,000 inpatient admissions for CHD in England in the same year, and direct healthcare costs in the UK are estimated at £1.8billion annually[3]. CHD is also associated with poor health-related quality of life[8] and impaired functional status[9, 10].

1.2.1.3 Depression

Major depressive disorder is a heterogeneous disorder characterized by core symptoms of severe sadness, despondency, and/or a loss of interest or pleasure in activities that would previously have been considered enjoyable. DSM-V[11] defines a major depressive episode as depressed mood or loss of pleasure over a 2 week period, combined with at least 4 more of the following symptoms: weight loss or gain, changes in sleep, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, inability to concentrate, and recurrent thoughts of death or suicidal ideation. The symptoms must be present nearly every day, must cause clinically significant distress or impairment in social, occupational or other areas of functioning, and must not be due to the physiological effects of a substance or other medical condition.

The World Health Organisation (WHO) estimates that 350 million people worldwide are affected by depression[12]. Prevalence estimates vary although epidemiological surveys suggest a 12 month prevalence rate for major depressive disorder of approximately 5% in Europe[13, 14]. The total cost of depression in England, including health and social care spending and loss of earnings, was estimated at £7.5 billion in 2007[15].

Globally depression is ranked the fourth largest cause of disease burden[16]. This is unsurprising considering that depressive episodes can be prolonged (estimates of duration vary although untreated episodes can last an average of 6 to 8 months[17], and likelihood of recovery worsens with increasing duration of the episode[18]), many episodes progress to a chronic course (approximately 20% of episodes last 2 years or more e.g.[19, 20]) and relapse and recurrence are common [21-23]. In addition depression is frequently comorbid with other mental health conditions[24-27] particularly anxiety disorders (58% of people with a lifetime diagnosis of major depressive disorder will also receive a diagnosis of anxiety) and is linked with suicide risk[28, 29].

1.2.2 Comorbidity of depression and LTCs

The prevalence of depression is elevated (approximately 20%) in people with LTCs including CHD [30-34], and comorbidity is problematic because it is associated with social problems, delayed return to work[35], increased healthcare utilisation and healthcare costs[36-38], and also with worse physical health outcomes including reduced quality of life and increased morbidity and mortality[10, 39-50].

Several correlates of depression in LTCs and CHD have been identified. Egede et al. (2007)[30], for example, found that similar sociodemographic characteristics were associated with depression in adults with and without LTCs (younger age, female sex, lower income, higher BMI, unemployment, worsening health status and smoking). Koivula et al. (2009)[51] found that gender, perceived health, cardiac symptoms at rest and poor social support were associated with elevated depressive symptoms in long term CHD patients.

1.2.2.1 Evidence and direction of causal link

The association of depression and CHD appears to be bi-directional[52, 53] although proof of the causal link has not been established. There are several strands of research that suggest (a) depression may have a causal role in the onset and progression of cardiac disease, (b) depression may be a consequence of CHD, or that (c) depression and CHD may both be caused by a common underlying mechanism. The sections below outline some possibilities regarding each of these interpretations.

1.2.2.1.1 Depression as a risk factor for CHD

Evidence that depression may be causally associated with CHD comes from three main sources: etiological studies, prognostic studies, and studies demonstrating a dose-response relationship.

1.2.2.1.1.1 Etiological studies

First, many studies show that depression precedes CHD. A large multicentre case-controlled study (INTERHEART) based on retrospective reports showed that patients with first myocardial infarction (MI) experienced more psychosocial stress in the preceding 12 months compared to controls, and that cases were more likely than controls to have experienced depressive symptoms for at least 2 weeks in the preceding 12 months (odds ratio 1.55)[54].

Several systematic reviews and meta-analyses, based upon partially overlapping etiological prospective cohort studies of samples without CHD at baseline, showed that clinical depression and depressive symptoms increased the relative risk of coronary disease onset, MI or cardiac mortality by approximately 60% to 80%[43, 55-57].

1.2.2.1.1.2 Prognostic studies

Second, once CHD is established depression appears to worsen prognosis[39, 58]. For example, in a sample of 222 patients recruited immediately post-MI both 6 month[59]and 18 month mortality[60] was predicted by depression, after controlling for severity of cardiac disease, and risk stratification based on standard risk factors (such as severity of cardiac disease and previous history of MI) was improved by additionally considering depression status. A large meta-analysis of 34 individual prognostic studies that involved a total of 17,842 participants, showed depression was

associated with an 80% increased risk of poor CHD prognosis over an average follow-up period of 3.2 years, although the effect size was considerably smaller after controlling for confounding variables such as severity of cardiac disease[43].

Studies have also shown that depression is associated with lack of functional benefits after coronary artery bypass surgery or revascularisation, even after controlling for severity of cardiac disease[48, 61].

1.2.2.1.1.3 Dose response relationship

Finally, a dose response relationship has been observed between depression and cardiac morbidity, such that more severe depression is associated with worse cardiac outcomes. For example, meta-analyses have shown that the association of depressive symptoms with onset of CHD and worse CHD prognosis is weaker than the association of clinical depression with CHD onset and worse CHD prognosis[43, 57].

A graded relationship was also reported in the Whitehall II cohort study of cardiovascular disease using a 'cumulative caseness' approach[62]. Depression was measured on six occasions over 20 years and fatal and non-fatal CHD events were recorded. The results showed a 50% increase in risk of incident CHD events for those who had satisfied criteria for depression on two or three occasions, compared to those who had been classified as depressed on one occasion only.

The sections above are intended to illustrate that there is a large volume of work suggestive of a causal link between depression and CHD. Effect sizes are comparable to those of other conventional risk factors for CHD. However, it remains unclear whether depression is an independent predictor of CHD. Alternative explanations for the observed association between depression and poor physical health outcomes, for example due to the confounding effects of other risk factors including severity of cardiac disease, remain possible (e.g.[35, 43, 63]). This is important since increasing levels of left ventricular dysfunction (an index of severity of cardiac disease) have been associated with increasing severity of depressive disorder at hospitalisation and with increased rates of depressive order over 12 months follow-up[64].

Further, it is unclear whether the time at which depressive symptoms present, relative to onset of CHD, is important for prognosis (e.g.[65]) or whether the duration of depression is associated with CHD[58].

1.2.2.1.2 Depression as a consequence of CHD

On the other hand, depression might arise as a reaction to the illness or as the result of adjustment to the burden of chronic disease[66]. Although this would suggest that greater disease burden rather than depression itself causes worse CHD outcomes, which is not consistent with the results of studies that find depression is associated with poorer outcomes even after controlling for disease burden e.g.[61].

The high prevalence of 'incident' depression following MI may also suggest that depression is triggered by CHD. It has been estimated that approximately half of post-MI cases of depression are new[67], and several researchers have suggested that the nature of incident depression is different from pre-existing or recurrent depression[65, 67-71]. Whereas the factors associated with depression that precedes CHD appear to be similar to those observed in typical psychiatric populations (e.g. being female, younger age, social isolation, low educational level, previous psychiatric history, neuroticism), incident depression is characterised by more severe cardiac disease (including worse left ventricular ejection fraction, higher probability of coronary revascularisation during hospitalisation, and more arrhythmic events), greater functional disability and reduced response to antidepressant therapy. This raises the possibility that post-MI depression could be a particularly 'cardiotoxic' subtype of depression[70].

1.2.2.1.3 Possibility of a common underlying mechanism

An alternative explanation is that there is a common underlying cause of both CHD and depression[72-74]. Davidson (2012) argues, for example, that since depressive symptoms can be the result of cerebrovascular disease, it is possible that (vascular) depression could be the result of the same risk factors responsible for CHD[72], and Mosovich et al. (2008) propose a model in which chronic stress initiates a cascade of effects via changes in immune function that lead to disrupted production of serotonin and increased platelet aggregation contributing to both depression and heart disease[73].

1.2.2.2 Mechanisms linking depression with CHD

A variety of plausible behavioural and physiological mechanisms have been proposed to explain the link between depression and worse physical health outcomes in CHD, though none has been proven to explain the association[58, 72, 75-78].

Suggested physiological mechanisms include: (1) increased platelet 'stickiness' and thrombus formation, (2) changes in heart rhythms and cardiac autonomic tone, particularly decreased heart rate variability, (3) elevated inflammatory response, (4) hypothalamic-pituitary-adrenal axis dysregulation, (5) alterations in vascular endothelial function, and (6) the 'vascular depression' hypothesis.

The main behavioural mechanism that has received attention is lack of adherence to treatment. For example, CHD patients with elevated depressive symptoms during hospitalisation for MI were less likely than those without depressive symptoms to adhere to daily aspirin therapy[79] or to comply with advice to reduce cardiac risk in the months following discharge (e.g. implementing changes to diet and exercise, and smoking cessation)[80, 81]. Lack of motivation and memory problems associated with depression may explain reduced adherence to medication and rehabilitation advice[45].

Other suggested behavioural mechanisms include: (1) unhealthy lifestyle choices, or poor adherence to recommendations to alter lifestyle factors as described above, (2) lack of social support/failure to recognise or utilise available social support resources, and (3) failure to adapt to adverse symptoms of physical illness.

1.2.2.3 Recognition and treatment of depression in CHD

1.2.2.3.1 Recognition of depression

Depression is underdiagnosed and undertreated in patients with CHD, despite its high prevalence and association with poor physical outcomes. For example, Zieglestein et al. (2005) reported that among CHD inpatients 75% of cases with elevated depressive symptomatology were not recognised by cardiac nurses or medical students[82]. Similarly, Huffman et al. (2006) found that <15% of cardiac inpatients with major depressive disorder or with elevated depressive symptomatology were identified by medical care providers and only 11% of patients with depression were receiving antidepressant therapy[83].

Detection of depression in people with CHD could be confounded by the presence of physical symptoms related to CHD (e.g. fatigue, weight loss, sleep disturbance). However, since depression in CHD could contribute to non-compliance with medical treatment and poorer CHD prognosis, its detection and treatment should be a priority. Early screening for depression and case-finding in CHD patients is recommended[84-86].

1.2.2.3.2 Treatment strategies

The National Institute for Health and Care Excellence (NICE) recommends a variety of treatment options for depression in people with LTCs using a stepped-care model: low intensity psychological therapies (such as group-based physical activity or peer support programs, guided self-help and computerised cognitive behavioural therapy) for subthreshold or mild depression, high intensity group or individual cognitive behavioural therapy, couples therapy, antidepressant drugs or, where other high intensity therapies have not succeeded, collaborative care[87]. Functional limitations related to the physical illness should be considered when selecting a treatment approach, and adaptations to delivery mode made where necessary. It is recommended that side effect profiles and interactions with other drug treatments are considered when prescribing antidepressant drug treatments.

1.2.2.3.3 Effects on depression and cardiac outcomes

Due to the association of depression with poor CHD outcomes, some researchers have suggested that treating depression among people with CHD may not only improve psychological well-being, but could also improve physical health outcomes[59, 66, 88].

1.2.2.3.3.1 Antidepressants

Randomised, double blind, placebo controlled trials have shown limited or small effects of antidepressant drug treatments on depression. For example, Glassman et al. (2002) found 24 weeks of sertraline treatment in acute coronary syndrome (ACS) patients provided no improvement in depression compared to placebo [89], and in the SADHART study[90] 12 weeks of sertraline treatment was only effective in a subgroup of ACS patients with non-incident depression. In a Cochrane review Baumeister et al. (2011) identified 8 trials (including the SADHART[90], CREATE[91] and MIND-IT[92, 93]

studies) that compared pharmacological treatment with placebo and concluded that there was a small beneficial effect of SSRIs in improving depression[94].

However, both observational studies and trials have failed to demonstrate convincingly that treatment with antidepressants improves cardiac health outcomes[90, 95-97]. It is unclear whether the effects of pharmacological treatment on depression were too small to impact upon cardiac outcomes, or whether this indicates that there is no causal association between depression and CHD[95].

1.2.2.3.3.2 Psychological treatments

Baumeister et al. (2011) identified 6 trials that compared the effectiveness of psychological treatments for depression in CHD patients with usual care[94]. Psychological interventions included cognitive behavioural therapy, interpersonal therapy, resource-orientated psychotherapy, telephone counselling and an intervention based on health education. Overall there was a small beneficial effect of psychological interventions on outcomes related to depression. This is consistent with reviews by Whalley et al. (2011)[98] that reported small to moderate improvements in depression and anxiety following psychological interventions, and Dickens et al. (2013)[99] that found small beneficial effects of cognitive behavioural therapy (CBT) and problem solving.

However, evidence that psychological interventions improve cardiac outcomes is sparse. In both a randomised controlled trial[100] and a non-randomised study[101] a cognitive behavioural therapy-based disease management approach to challenge misconceptions about angina appeared to reduce angina frequency, use of medication for the symptomatic treatment of angina and hospital admissions. On the other hand, in a randomised controlled trial (the ENRICHD study[88]) cognitive behavioural therapy aimed at reducing depression and improving perceptions of social support after myocardial infarction was compared to treatment as usual. Despite some improvements in depression and social support there was no improvement in cardiovascular outcomes including mortality and event-free survival in the treatment arm. Reviews of observational studies[97] and of randomised trials[94, 98] support this finding, concluding that there is no effect of psychological interventions on cardiac outcomes such as mortality, risk of revascularisation, or other non-fatal CHD events.

Interestingly, some studies have shown that depression in CHD patients is characterised by fewer cognitive/affective symptoms (e.g. depressed mood, feelings of guilt) than that seen in typical psychiatric populations[102], and that somatic/affective symptoms of depression (e.g. fatigue, psychomotor agitation) are particularly associated with greater severity of cardiac disease (left ventricular dysfunction, previous history of myocardial infarction and more comorbidities). In addition only the somatic symptoms predicted mortality and cardiac events[103, 104]. As a result it is suggested that treatments for depression which selectively focus on somatic/affective symptoms might be more beneficial in cardiac patients[103].

1.2.3 Cognitions about health and illness

Cognitive processes could be implicated in the association between depression and CHD. Leventhal's self-regulatory 'common sense model' of illness representations[105-107] proposes that when faced with a chronic physical illness patients generate cognitive and emotional representations of their illness related to several key dimensions of the illness: (1) consequences, (2) duration, (3) controllability/curability, (4) cause (5) identity/symptoms, and (6) emotional perceptions. The representations of illness are thought to influence coping efforts, which in turn impacts on outcomes. Thus, the way people think about their illness acts as a mediator between the disease process and physical/psychological wellbeing[108].

Studies in CHD patients show that negative illness perceptions are associated with adverse outcomes. For example, negative perceptions of illness related to longer course, greater severity and limited controllability were correlated with greater depressive symptoms in ACS patients[109]. Similarly, a prospective study showed that negative beliefs about the anticipated duration and perceived likely outcome of coronary disease soon after MI predicted the development of depression in the 12 months afterwards[110]. In addition, a systematic review of illness perceptions after CHD showed that negative beliefs about illness predicted quality of life as well as depression[111].

Persistently dwelling on negative illness perceptions could, then, initiate and maintain depression and worse quality of life following CHD. Such repetitive thinking has been linked with depression in healthy and psychiatric populations, and could therefore be helpful in better understanding depression in people with CHD.

1.2.4 Perseverative negative thinking

Repetitive thought involves frequent, prolonged and recurrent thoughts about oneself and one's concerns[112], and is central to a number of constructive and unconstructive cognitive processes such as, but not limited to, rumination, worry, perseverative cognition, mind wandering, counterfactual thinking, post-event processing and reflection[113]. This thesis will focus specifically on *unconstructive*, *negative* forms of repetitive thought i.e. perseverative negative thinking.

The literature on perseverative negative thinking has been dominated by the concepts of rumination and worry. These constructs have emerged from distinct theoretical backgrounds, although they share in common, with other forms of perseverative negative thinking, three defining characteristics: they are (a) repetitive, (b) passive / relatively uncontrollable and (c) focused on negative content[114].

1.2.4.1 Rumination

1.2.4.1.1 Definition

Rumination has been defined as repetitive thought that revolves around a personal theme in the absence of any external cues to provoke such thoughts[115] or, in the case of 'depressive rumination', as a response to negative mood which involves "passively and repetitively focusing on one's symptoms of distress and the circumstances surrounding those symptoms"[116]. In each of these views, rumination is considered to be past-orientated with a focus on understanding the meaning of events and gaining insight. Rumination is considered a maladaptive coping strategy involving elaboration of negative content, and has been closely associated with depression.

1.2.4.1.2 Theoretical models of rumination

Several theoretical accounts of rumination have been proposed (for a review see[117]), the most prominent being (1) 'control theory' approaches[115] and (2) Nolen-Hoeksema's 'response styles theory'[118].

The control theory approach conceptualises rumination as recurrent instrumental thinking about an unresolved goal. This is based on a self-regulation model in which all behaviour (including cognitive activity) is controlled by feedback processes[119]. It is proposed that individuals compare perceptions of their current state with reference values such as desired goals, and that discrepancies between the current state and the reference value lead to changes in behaviour in an attempt to move closer to the reference value. Control theory approaches to rumination suggest that rumination is triggered by unresolved goals or inadequate progress towards goals, and that rumination will continue until the discrepancy between current state and reference value is resolved either by attainment or abandonment of the desired goal[115]. Therefore, in the context of chronic physical illness such as CHD, control theory would predict that rumination would be the result of actual or perceived limitations related to physical function and lifestyle that might make desired goals seem less attainable.

Response styles theory[118, 120] focuses on the process of 'depressive rumination' which is conceptualised as a stable dispositional style of responding to negative mood that is linked with the onset, duration and severity of depression[121, 122]. Rumination is thought to exacerbate and prolong distress by passively focusing attention on the possible causes and consequences of negative mood, without initiating active problem solving to change the circumstances surrounding the symptoms of distress, resulting in a vicious circle of negative self-focus and negative mood. A conceptual extension of the response styles theory is the 'stress-reactive rumination' model of Robinson & Alloy (2003)[123]. This suggests that negative cognitive styles associated with hopelessness (negative inferential styles and dysfunctional attitudes) encourage negative thought content in response to stressful life events, and that this negative content is activated and rehearsed through the process of rumination. Together the stress-reactive model of rumination and response

styles theory would suggest that the experience of chronic physical illness triggers negative thoughts and appraisals of illness, and that rumination, in turn, would be triggered by that negative thought content leading to a ruminative-depressive cycle.

1.2.4.2 Worry

1.2.4.2.1 Definition

Worry is defined as "a chain of thoughts and images, which are negatively affect laden and relatively uncontrollable" [124]. It is conceptualised as a future-focused avoidant process closely related to fear that involves repetitive thought about anticipated future threats in an attempt to plan and problem solve. Worry is a central cognitive feature of generalised anxiety disorder[11].

1.2.4.2.2 Theoretical models of worry

The dominant theoretical models of worry can be broadly grouped into models concerned with the avoidant function of worry (e.g.[124-127]) and those that deal with beliefs about worry itself[128, 129].

Borkovec and colleagues propose a cognitive avoidance model of worry that suggests worry is motivated by avoidance of threatening stimuli (both internal and external experiences) and that it is maintained by a process of negative reinforcement[124, 125]. Suppression of somatic anxiety, discovery of ways to avoid threatening events, and distraction from deeper fears are suggested mechanisms through which worry may function. In addition, since worry concerns feared catastrophic events that often do not come to pass, the process of worry is reinforced and maintained.

The intolerance of uncertainty model also proposes that worry serves an avoidant function. Intolerance of uncertainty is a trait disposition characterised by negative beliefs about, and the tendency to respond negatively to, uncertain situations and events[126]. High intolerance of uncertainty, even of improbable events, is thought to trigger worry as a means of attempting to increase control and eliminate the threat of uncertainty[127].

On the other hand, the metacognitive model of worry suggests that worry arises as a result of positive and negative appraisals about the nature and consequences of worry[128, 129]. This model distinguishes between worries that

occur in response to everyday events and experiences (as a form of coping strategy) and 'meta-worry'. Worrying as a coping strategy ('Type 1 worry') is thought to be associated with positive beliefs about worry (e.g. that worrying is useful). Meta-worry on the other hand tends to be associated with negative beliefs (e.g. that worry is uncontrollable or dangerous). Type 1 worries once initiated trigger meta-worry and a cycle of intensifying worry and anxiety is initiated.

Each of these models are relevant in the context of chronic physical illness. Disease and treatment may present threats to physical function, wellbeing and lifestyle that the individual would prefer to avoid for example, and aspects of both illness and treatment may be uncertain (e.g. likely duration of illness, treatment outcome). Furthermore, lay understandings of illness (e.g. 'stress is bad for your heart') may contribute to meta-worry.

1.2.4.3 Overlap of rumination and worry

There is some debate over the extent to which rumination and worry represent distinct or overlapping processes[114, 130].

The two concepts have emerged from separate theoretical backgrounds, and as a result the suggested functions, content, processes and measurement of the constructs differ. For example, it is proposed rumination is a maladaptive coping style that involves elaboration of negative material[131] whereas worry is motivated by cognitive avoidance[125]. Rumination tends to be focused on symptoms of distress and failure to achieve personal goals[115, 118, 120], whereas the content of worry centres around future threats[125]. It has also been suggested that rumination and worry may vary along process and metacognitive dimensions such as past vs. future focus, use of verbal thought vs. imagery, effort and confidence in problem solving, and compulsion to act[132]. A raft of self-report instruments have been developed to measure the frequency, severity and content of worry (e.g.[133-139]), and the tendency to ruminate (e.g.[140-145]). The wide range of individual measures illustrates that the assessment of rumination and worry have previously been separate endeavours, and that the measures have tended to emerge from distinct research areas. Furthermore, some empirical studies suggest that rumination and worry have

differing effects on psychological and physical wellbeing suggesting that they may represent distinct processes (e.g. [112, 146-148].

On the other hand, worry and rumination are at least moderately correlated e.g.[146, 148, 149] and are frequently comorbid[150]. Ehring & Watkins[114] note three key features common to both rumination and worry: they are repetitive, relatively uncontrollable, and focused on negative content. Others have suggested that while the content of ruminative and worrisome thoughts may vary the processes involved are alike[114, 146, 150]. Results of correlational and experimental studies show that both rumination and worry are involved in depression and anxiety in clinical and non-clinical samples (e.g.[146, 148, 151-158]), and that they both are linked with a wide range of psychiatric conditions suggesting they may be transdiagnostic phenomena[114, 159]. Research using confirmatory factor analyses and structural equation modelling to investigate if measures of rumination and worry load on to single or separate factors provides some evidence to suggest that the similarities between rumination and worry may be greater than the differences[130, 146].

1.2.4.4 Association of perseverative negative thinking with psychopathology

Although there is some overlap with clinical symptoms perseverative negative thinking, such as in rumination and worry, is a common, everyday phenomenon. However, there is evidence that when it becomes excessive and chronic perseverative negative thinking is associated with the exacerbation and maintenance of adverse mental health outcomes such as depression and anxiety[113, 125].

A number of strands of evidence suggest that perseverative negative thinking is associated with negative effects on mood in otherwise healthy samples. First, perseverative negative thinking is elevated in people at greater risk for depression e.g. it is higher in females compared to males[160, 161] and in individuals with a history of depression compared to those without[162].

Second, a large number of empirical studies show that there are cross-sectional and prospective associations between perseverative negative thinking and negative affect including the onset, maintenance and relapse of depression e.g.[118, 121, 122, 140, 146, 152, 163, 164] and increased anxiety e.g.[153, 165-167] (for reviews see[113, 168-171]). While cross-sectional studies strongly support the association between

perseverative negative thinking and adverse mental health outcomes such as depression and anxiety the findings of prospective studies which would allow tentative causal inferences to be made have been more mixed (e.g. [169]), although the majority of such studies still support an association. Narrative and systematic reviews have suggested that some of the variability in findings may be explained by characteristics of the population (e.g. gender, psychopathology[168, 170]), 'intrapersonal context' (e.g. self-efficacy, dysfunctional attitudes[113]) and by aspects of perseverative negative thinking itself (e.g. valence and content of thoughts[113]). A meta-analysis of the association of emotion regulation strategies with different classes of psychopathology showed that associations of rumination with depression and anxiety were strongest in clinical samples compared to non-clinical participants[168].

Third, experimental studies have shown that inducing rumination and/or worry or allowing participants to ruminate increases both depressed and anxious mood[145, 157, 158, 172, 173].

Thus, a large body of converging evidence is strongly suggestive of an association between perseverative negative thinking with changes in mood, depression and anxiety. However, the majority of previous research has focused on physically healthy populations.

1.2.4.4.1 Perseverative negative thinking and psychopathology in people with LTCs

Cross-sectional studies in people with LTCs show that perseverative negative thinking is correlated with adverse mental health outcomes. For example, Schroevers et al. (2008) investigated associations among goal adjustment, cognitive emotion regulation strategies and positive/negative affect in 108 mixed cancer patients an average of 7 years post-diagnosis. Rumination and catastrophizing were measured using the self-report Cognitive Emotion Regulation Questionnaire (CERQ; [174]) and positive and negative affect with the positive and negative affect schedule (PANAS; [175]). Rumination (r=0.37) and catastrophizing (r=0.40) were significantly correlated with negative affect, and the associations remained significant after controlling for age and time since diagnosis[176].

Dickens et al. (2012) examined the strength of associations of perseverative negative cognitive processes (worry, thought suppression, and avoidance of undesirable thoughts) with depression in 190 outpatients with heart disease, diabetes, rheumatoid arthritis and chronic obstructive pulmonary disease. A tertile split of self-report worry scores (Penn State Worry Questionnaire, PSWQ; [133]) was used to categorise participants according to trait tendency to worry. Those in the top tertile (compared to the lower tertile) were 20 times more likely to have Hospital Anxiety and Depression Scale (HADS; [177]) scores indicative of possible depression (after controlling for age, sex, education, marital and work status, and type and duration of LTC). This study also showed (a non-significant trend) that severity of depression was associated with worry[178].

Other cross-sectional studies in people with LTCs have found that rumination and catastrophizing are associated with symptoms of depression and anxiety in people with visual impairments[179], hearing loss[180], and peripheral arterial disease[181]. These studies demonstrate that perseverative negative thinking is associated with depression and anxiety, although they are limited by their cross-sectional design since it does not allow the direction of the association to be established.

Prospective studies would allow tentative causal inferences to be made, although few such studies have been conducted to date in people with LTCs including CHD. Exceptions include a small study by Garnefski et al. (2010) in post-MI patients that investigated the association of rumination and catastrophizing with depressive symptoms at 1 year follow-up[182], and a larger study by Denton et al. (2012) in which the effects of rumination and psychosocial vulnerabilities immediately post-ACS on depression at 3 month follow-up were investigated[183].

Garnefski et al. (2010) recruited 160 patients (88 available for follow-up) who had experienced an MI in the preceding 3 to 12 months. They took self-report measures of rumination and catastrophizing (CERQ) and depressive symptoms (HADS) at initial assessment and again 1 year later. Rumination (r=0.43) and catastrophizing (r=0.45) at baseline were significantly correlated with depressive symptoms at follow-up, and these associations remained significant after controlling for sex, age, and physical limitations.

Denton et al. (2012) selected patients with Beck Depression Inventory (BDI; [184]) scores of 0 to 4 or >10 within 1 week of hospital admission for ACS (387 available for follow-up). Self-report assessments of psychosocial vulnerabilities for depression (including dyadic adjustment, engagement in pleasant events and dysfunctional attitudes), rumination (Ruminative Responses Scale;[118]) and depression were completed at baseline and repeated 3 months later. Rumination at baseline predicted depression severity both independently and in interaction with other psychosocial vulnerabilities at 3 months, after adjusting for confounding variables including age, sex and baseline depression. The association was strongest in patients who were depressed at baseline.

The findings of these studies are consistent with a prospective association of rumination and catastrophizing with subsequent depression in people with CHD. However, these studies are limited by a large amount of attrition and selection of participants based on a subset of depression scores which could affect the generalisability of findings. The findings are also limited to the associations between rumination and catastrophizing with depression.

Thus, there is emerging empirical evidence that suggests perseverative negative thinking is associated with depression in people with LTCs including CHD, although this remains to be confirmed in high quality prospective studies.

1.2.4.5 Mechanisms of the association between perseverative negative thinking and psychopathology

Within vulnerability-stress frameworks perseverative negative thinking has been conceptualised as a maladaptive response to stressful life events that amplifies and maintains the effect of a stressor leading to the development and maintenance of depressive and anxious symptoms (e.g.[123, 185]).

Several specific mechanisms have been suggested by which perseverative negative thinking, specifically rumination, may contribute to depression. These include (1) erosion of social support, (2) impaired problem solving, (3) reduced motivation to perform instrumental behaviours, and (4) negative cognitive biases[120, 186]. These mechanisms are unlikely to be independent.

1.2.4.5.1 Reduced social support

Low perceived social support correlates with depression in the general population (e.g.[187]) and in people with CHD the inability to form and maintain close relationships due to the burden of a medical condition, low perceived availability of social support, and the number of close network members have been associated with depression, anxiety and worse quality of life[71, 188-193]. Importantly, lack of a close confidant has also been shown to predict further cardiac events over 12 months after myocardial infarction[194]. Social support may be protective because a partner could encourage faster treatment seeking[195] and better adherence to treatment[196].

High levels of support seeking, low perceived availability of social support and social friction are correlated with elevated rumination and worry[120, 197] and ruminators appear to erode social support by engaging in behaviours that are detrimental to their relationships. For example by placing high emotional and practical demands on members of their social network[198], excessive reassurance-seeking[199], and by creating conflict and disturbances in their interpersonal relationships due to social support discontent[200].

1.2.4.5.2 Impaired problem solving

Social problem solving is defined as a "cognitive-behavioural process by which a person attempts to identify or discover effective or adaptive solutions for specific problems encountered in the course of everyday living"[201]. Studies in healthy participants have shown that poor problem solving is prospectively associated with depressive and anxious symptoms[202-204] and that it mediates the association of stressful life events with depression and anxiety[205].

Rumination appears to interfere with multiple aspects of problem solving ability: problem solving confidence, generation of effective solutions, and ability or motivation to implement problem solutions. Ruminators, compared to non-ruminators, lack confidence in the quality of their problem solutions[206, 207] and following rumination induction dysphoric and depressed indivduals appraise their problems as overwhelming and unsolvable[208, 209]. Rumination inductions in individuals with dysphoria, current depression or a history of depression lead to the generation of fewer effective problem solutions[208-211]. Ruminators are also less

likely to implement problem solutions, even when they generate effective solutions[206, 207].

1.2.4.5.3 Inhibition of instrumental behaviours

Lack of interest and reduced engagement in pleasant activities is a symptom of depression[11], and depressed mood has been correlated with lower frequency of engagement in pleasant events[212]. In a sample of ACS patients Denton et al. (2012) found that both depression and rumination were associated with self-reported infrequency of engagement in pleasant events[183].

Rumination may contribute to depression by sapping motivation to engage in constructive behaviours. Additionally, persistent focus on negative mood could act to convince the individual that they lack the self-efficacy to initiate potentially mood-alleviating activities. Lyubomirsky & Nolen-Hoeksema (1993) found that following a rumination induction dysphoric individuals were less willing to engage in a number of pleasant activities, despite believing that the activities would be pleasant. Ruminators also indicated that they perceived value in their rumination (e.g. gaining insight) and so were encouraged to continue ruminating rather than engaging in pleasant activities[213].

1.2.4.5.4 Negative cognitive biases

Negative biases in processing emotional information are central to cognitive theories of depression[214, 215] and include the tendency to interpret ambiguous stimuli as negative[216, 217], selectively allocate attention to negative material[218], difficulty disengaging attention from negative material[219] and preferential memory for self-relevant negative over positive material[220]. Impaired cognitive control accounts of depression[221] and rumination [222] suggest that deficits in cognitive control are responsible for these biases.

Rumination is associated with the tendency to view past, present and future events more negatively. For example, dysphoric individuals induced to ruminate will recall more negative events from the past, will spontaneously talk about their concerns, and have low expectations for future positive events[208, 209, 223].

1.2.4.6 Association of perseverative negative thinking with physical outcomes

Perseverative negative thinking may be associated with adverse physical as well as mental health outcomes. For example, trait and experimentally induced perseverative negative thinking has been associated with: impaired wound healing following routine surgery[224], immune dysfunction following a stressful event[225], changes in cortisol levels in response to exam stress[226] and changes in physiological measurements such as raised blood pressure and increased heart rate[227]. In addition, worry has been shown to predict incident heart disease over 20 year follow-up in a longitudinal cohort study of men who were free of known chronic disease at entry to the study[228].

Thayer and colleagues have proposed the 'perseverative cognition hypothesis' that might explain the association between perseverative negative thinking and adverse physical outcomes[229, 230]. Perseverative cognition ("the repeated or chronic activation of the cognitive representation of one or more psychological stressors") is conceptualised as the core feature of processes involving repetitive thought (such as rumination and worry). Perseverative cognition is said to occur in anticipation of, or as a reaction to, an acute stressor and maintains a cognitive representation of that stressor. In turn, the prolonged cognitive representation is associated with chronic low level physiological activation of stress-related systems including cardiovascular, hypothalamic–pituitary–adrenal and immune systems (a state of 'action readiness'), which can lead to somatic and health consequences. The perseverative cognition hypothesis is consistent with allostatic load models of stress that suggest biological reactivity to stress is adaptive in the short term, but over longer durations causes wear and tear on physiological systems[231, 232]. In addition, an extended version of the model accounts for the association between CHD and depression. Larsen & Christenfeld (2009) suggest that perseverative cognition mediates the association of depression with subsequent cardiovascular health by delaying physiological recovery from acute stress[233]. Reviews of empirical studies showing that perseverative negative thinking is associated with adverse physiological changes such as elevated cortisol, altered immune response, increased heart rate and reduced heart rate variability[227, 229, 234] provide some support for the

perseverative cognition hypothesis. However, existing empirical evidence is limited largely to cross-sectional and experimental studies in healthy participants, and the longer term effects in patients with CHD remain to be confirmed.

Finally, a behavioural pathway has recently been suggested through which perseverative negative thinking may also impact on worse health outcomes. Clancy et al. (2016) conducted a systematic review and meta-analysis of studies investigating the association of perseverative negative thinking with health behaviours that may directly or indirectly influence health outcomes. They found that perseverative negative thinking was associated with increased health risk behaviours e.g. substance use, alcohol consumption, unhealthy eating, and smoking[235].

1.2.4.7 Existing treatments for depression involving perseverative negative thinking

Behavioural activation (BA), rumination-focused cognitive behavioural therapy (RFCBT) and mindfulness-based cognitive behavioural therapy (MCBT) are current psychological treatment approaches for depression that contain components that target rumination.

BA explicitly focuses on reducing rumination using functional analysis and self-monitoring to help patients identify when they are ruminating, to identify triggers for rumination and to find alternative strategies with which to replace rumination[236]. RFCBT uses the same function-analytical approach but also incorporates a novel element that focuses on shifting thinking style to increase concrete, process-focused thinking styles and reduce abstract and judgemental thinking[237]. MCBT could interfere with ruminative thoughts by teaching patients to shift their attention to the present moment and to relate to their thoughts in a more detached and less judgemental way[238]. Beneficial effects of these treatment approaches have been demonstrated in patients with depression (e.g. [237, 239-242]) although evidence of their acceptability and efficacy in treating depression in CHD populations is currently lacking.

1.3 Summary

Depression is common in people with LTCs including CHD and is associated with worse physical outcomes. A large body of work is highly suggestive of a link between

depression and CHD and a variety of plausible mechanisms have been suggested. However the nature of the causal association between depression and CHD is not fully understood, and the mechanism underpinning the association between depression and poor medical outcomes remains unclear.

Depression is under-recognised and undertreated in people with CHD, and the effectiveness of antidepressant drugs and psychological interventions appear limited. Furthermore trials have failed to demonstrate convincingly that improving depression also improves physical health outcomes, meaning proof that depression causes poor physical health outcomes among people with CHD is currently lacking.

Cognitive processes could be linked with depression and reduced quality of life in people with CHD. The tendency to dwell persistently on negative thoughts (i.e. perseverative negative thinking) could act to maintain and prolong the effect of stressors in the context of chronic physical illness. Perseverative negative thinking might therefore explain the observed association between depression and poor medical outcomes. In otherwise healthy populations, perseverative negative thinking has been strongly associated with the onset and maintenance of depression in healthy and psychiatric populations, and also predicts adverse medical outcomes. Most previous prospective research investigating the association of perseverative negative thinking with depression has focused on physically healthy populations, however.

Therefore, the nature of the association and the mechanisms by which perseverative negative thinking may impact on both mood and physical health outcomes in people with CHD are unclear. Better understanding the factors that contribute to the development of depression in people with CHD and the mechanisms that explain the association of depression with increased mortality and morbidity could (a) help predict which patients are at increased risk of developing depression and, as a consequence, are at increased risk of adverse medical outcomes, (b) facilitate personalisation of treatment based on risk of developing depression, and (c) inform the development of novel interventions that could target processes which might improve both physical and mental health outcomes.

1.4 Aims

This thesis seeks to (a) clarify the association of perseverative negative thinking with depression, anxiety and health-related quality of life in people with CHD, and (b) explore factors that may mediate the association of perseverative negative thinking with subsequent depression, anxiety and health-related quality of life in people with CHD.

The main aims of this thesis will be addressed by:

i. Conducting a systematic review to identify, synthesise and evaluate existing empirical evidence of the prospective association of perseverative negative thinking with depression, anxiety and emotional distress in people with LTCs.

ii. Conducting an observational prospective cohort study to investigate whether rumination and worry are prospectively associated with depression, anxiety and worse health-related quality of life over 6 months in people with recent CHD. In addition, the study will explore potential mechanisms by which perseverative negative thinking may impact on mood and worse physical health outcomes in people with CHD.

1.5 Thesis structure

This thesis is presented in chapters to address various aspects of the aims described above. This section outlines the content of each of the remaining chapters.

Chapter 2: Systematic review

Chapter 2 presents a systematic review and narrative synthesis of studies investigating the prospective association of perseverative negative thinking with depression, anxiety and emotional distress in people with LTCs. Since the majority of previous prospective research in this area has focused on physically healthy individuals, the aim of this review was to evaluate and synthesise the existing empirical evidence in people with LTCs. The characteristics, quality and findings of existing studies are appraised and summarised, and implications for future work are drawn out.

Chapter 3: Methods

Chapter 3 outlines the methods of a prospective observational cohort study that forms the basis of the results chapters that follow. Recruitment, inclusion and exclusion criteria, selection of questionnaires and measures, procedural methods, data collection and data management are described. Generic statistical methods are described in this chapter, although details of methods specific to addressing the aims of each chapter are presented in the relevant chapter. Specific hypotheses are set out at the start of each of the relevant results chapters.

Chapter 4: Results Part I (Prospective association of rumination and worry with depression, anxiety and quality of life)

Chapter 4 presents the results of a series of multiple regression analyses to investigate whether baseline rumination and worry predict 6 month depression, anxiety and quality of life in people with ACS. Additionally, prospective associations were also explored using longitudinal multilevel (repeated measures) models to take account of within-participant correlations due to repeated measurements, and the findings of these models are also presented in this chapter.

Chapter 5: Results Part II (Mechanisms of the association between rumination and worry with depression and quality of life)

Chapter 5 presents the results of a series of mediation analyses to explore whether low social support, impaired problem solving, reduced instrumental behaviours and negative cognitive biases may represent mechanisms that explain the associations of perseverative negative thinking with depression and quality of life found in the preceding chapter. A causal steps approach to mediation was used combined with a bootstrapping test of indirect effects. Predictors of depression and quality of life, and possible mediators the association between rumination and worry with depression and quality of life, are identified.

Chapter 6: General discussion

Chapter 6 is divided into sections providing a brief re-statement of background and aims, summary of findings, discussion of strengths and limitations, and an integrated discussion of the findings from the thesis as a whole with reference to

existing literature. Implications of the findings are considered and suggestions for future work are made.

Chapter 2 The association of perseverative negative thinking with depression, anxiety and emotional distress in people with LTCs: A systematic review

2.1 Chapter outline

The primary aim of this systematic review was to identify, synthesise and evaluate existing empirical evidence of the prospective association of perseverative negative thinking with depression, anxiety and emotional distress in people with long term conditions (LTCs).

This chapter presents:

i. A description of the methods used to identify, select, evaluate and synthesise relevant studies.
ii. Detailed findings and a summary of results.
iii. Discussion of the methods and findings with reference to strengths, weaknesses and comparison with existing literature.

2.2 Methods

This review was conducted following the guidance of the University of York Centre for Reviews and Dissemination[243] and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[244]. The review protocol was not registered with a database such as PROSPERO as the review did not fit within the scope of these registers, however the protocol was published[245] in the interests of transparency.

2.2.1 Inclusion/exclusion criteria

Studies were included if they investigated among people with LTCs the prospective association between perseverative negative thinking, on the one hand, and depression, anxiety and emotional distress, on the other. To clarify the temporal relationship, studies examining the prospective association between perseverative negative thinking and subsequent depression, anxiety or emotional distress, or the

reverse association, i.e. depression, anxiety or emotional distress predicting perseverative negative thinking, were included.

Perseverative negative thinking was defined as repetitive, prolonged and recurrent negative thoughts about oneself and one's concerns (including worry, rumination, perseverative cognition, counterfactual thinking, mind wandering, post-event processing, habitual negative self-thinking and catastrophizing [113, 246, 247]). Studies with measures of constructive repetitive thought such as reflection, rehearsal, planning, and problem solving were not included. The terms depression, anxiety and emotional distress were used to refer to symptoms of mood disorders and negative emotional states including negative mood. We defined LTCs broadly, as conditions which cannot be cured but which can be managed with treatment[2].

Studies meeting the following criteria were included:

i. ***Population*** Studies in adults (>16 years) with any LTC.

ii. ***Interventions & Comparators*** Use of an intervention and comparator was not a requirement.

iii. ***Outcomes*** Studies including a standardised measure of perseverative negative thinking *and* a standardised measure of depression, anxiety or emotional distress (including negative mood and negative affect). Data were extracted on physical outcomes as well as depression, anxiety or emotional distress, where available.

iv. ***Study design*** Observational, prospective studies, and experimental or quasi-experimental studies. It was anticipated that findings from such studies would clarify temporal relationships between perseverative negative thinking and depression, anxiety or emotional distress, enabling tentative causal inferences to be drawn. Cross-sectional and other study designs that would not allow such inferences were excluded.

v. ***Other limiters*** No date or language restrictions were applied. Studies published as papers in peer reviewed journals, conference proceedings and dissertations were included.

2.2.2 Information sources and search strategy

MEDLINE, EMBASE, PsycINFO, and CINAHL databases were searched on 4th June 2013, and searches repeated on 19th June 2015 and 7th Sept 2016. Search terms included subject headings and free text words relevant to: (1) depression, anxiety, emotional and psychological distress, (2) perseverative negative thinking, and (3) prospective study design (see Appendix 1 for search strategy). As there is no comprehensive and definitive list of LTCs available, studies of people with LTCs were not searched using electronic search terms; suitable studies of people with LTCs were identified by hand-searching papers meeting criteria 1-3 above, to maximise sensitivity of our search strategy. Backward and forward citation searches of eligible studies were undertaken, and authors of included studies were contacted to identify any additional unpublished studies.

2.2.3 Study selection

Eligibility screening of titles and abstracts, and then of full text records, was completed independently by two reviewers. Agreement between reviewers was 80% at title/abstract screening stage, and 94% at full text screening. Disagreements were resolved by discussion, with the involvement of a third reviewer where agreement could not be reached. Findings from single, independent studies presented in multiple reports/publications were presented only once, to avoid double counting studies.

2.2.4 Data extraction

Data from included studies was extracted independently by two reviewers and included characteristics of the study (design, participants, measures, timing of assessments, physical health/medical outcomes included, statistical methods) and the study findings (covariates controlled, strength of association). Agreement between reviewers for the primary outcome of bivariate associations was 93%, with disagreements resolved by discussion. Authors were contacted for further data in cases where suitable measures were taken but outcomes of interest were not presented in the published papers.

2.2.5 Risk of bias

Risk of bias within each study was independently evaluated by two reviewers using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool[248]. Ratings were made for six components (selection bias, study design, confounders, blinding, data collection methods, and withdrawals). Each component was rated strong, moderate or weak, and additionally these ratings were combined into a global quality score, such that globally strong studies had at least 4 strong and no weak ratings, moderate studies had 1 weak rating, and weak studies had more than 1 weak rating.

Minor adaptions to the confounders and blinding components of the EPHPP tool were necessary due to the design of the included studies. First, the confounders component is intended to evaluate whether there were important differences between study groups prior to an intervention. However, as there were no group comparisons in the included studies (or data related to group comparisons was not extracted because it was not relevant) we evaluated 'Were any relevant confounders controlled for, in the design of the study or in the analysis?'. Relevant confounders were defined as age, sex and baseline depression as these are all known to be associated with depression. Studies were rated strong where all three of these confounders were controlled for, moderate where some of these confounders were controlled for, and weak where no confounders (or others not listed) were controlled for. Second, the blinding component is intended to evaluate whether outcome assessors were aware of the intervention or exposure status of participants. However, as participants were not allocated to groups or conditions in the included studies (or if they were, data relating to groups or conditions was not extracted because it was not relevant) the blinding component evaluated: (a) 'was the researcher exposed to information about the participant that could lead to bias?' For example, was the researcher aware of participants' previous responses when administering questionnaires, or did researchers have access to participant data from previous or other assessments when scoring questionnaires, and (b) 'was the participant aware of the research question?'.

Agreement between reviewers for global quality ratings was 73%, with disagreements resolved by discussion.

2.2.6 Data synthesis

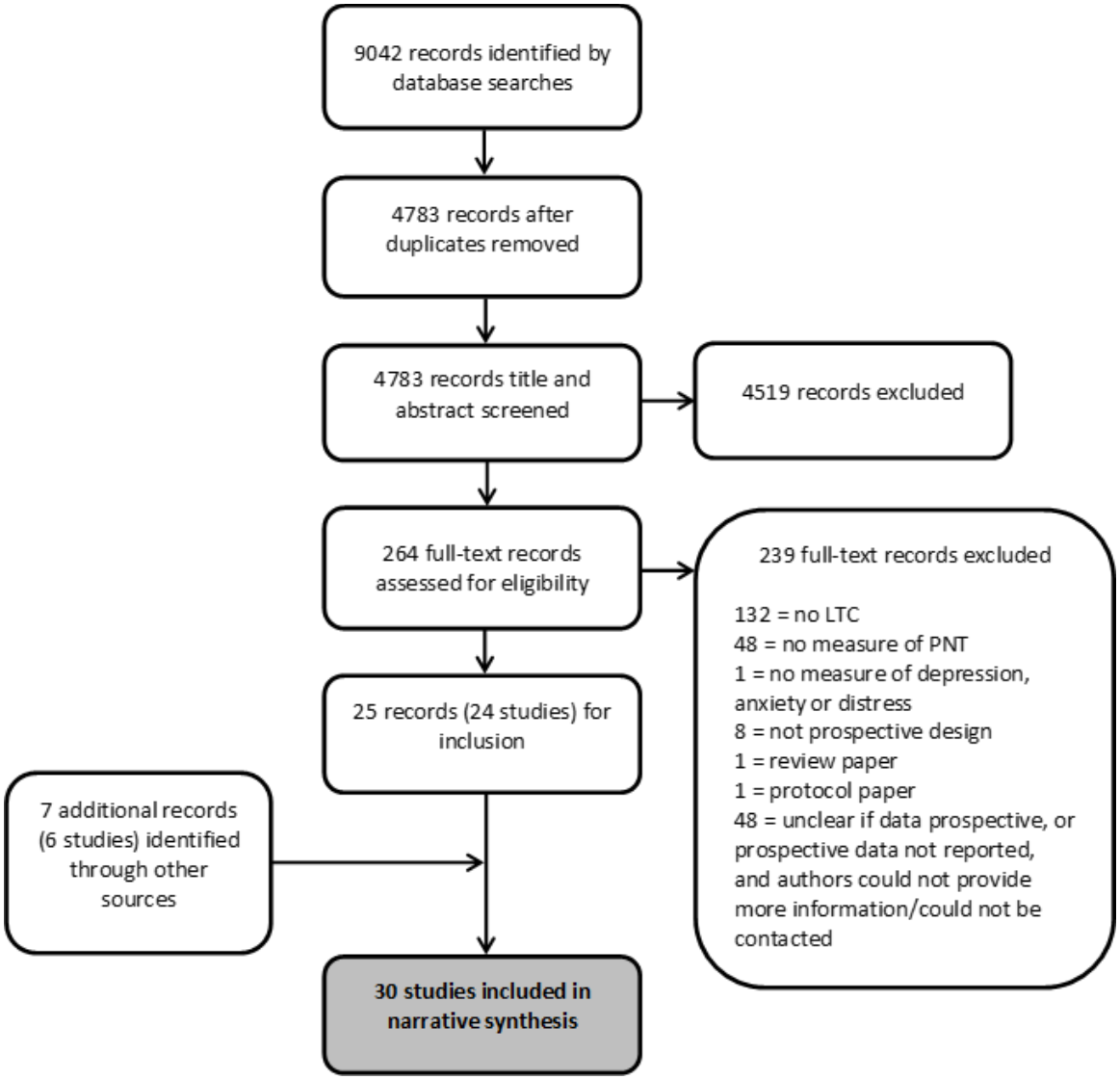
Characteristics and findings of included studies are summarised in tables. Findings are narratively synthesized (informed by the guidelines of the ESRC methods programme[249] where possible) based on grouping studies according to: i) type of perseverative negative thinking measured, ii) type of psychological outcome measured (i.e. depression, anxiety or emotional distress), iii) timing of follow-up (6 months or less versus more than 6 months), iv) type of LTC, and v) type of analysis conducted (bivariate versus multivariable).

2.3 Results

2.3.1 Study selection

Details of study selection are shown in Figure 2.1. Thirty eligible studies were included in the review [182, 183, 250-279]. Authors of a further 46 potentially eligible studies were contacted for additional data; authors of 15 studies were unable to provide additional data, and authors of 31 did not respond. It was not possible to contact authors of a further 2 studies for additional information and these studies were therefore excluded.

Figure 2.1: PRISMA flowchart



2.3.2 Study characteristics

There were 26 observational cohort studies, 3 prospective evaluations of an intervention, and 1 randomised controlled trial. Characteristics of all included studies are given in Table 2.1.

2.3.2.1 Samples

Sample sizes ranged between n=22 to n=560 in relevant prospective analyses (median n=99). Mean age ranged between 24.3 to 70.1 years, with subjects ranging from 0% to 100% female.

There were 5 studies in people with vascular disease [182, 183, 251, 253, 270, 273]), 4 in rheumatoid arthritis[260, 266-268], 10 in cancer[250, 252, 254, 255, 263, 264, 271, 272, 275, 278], 2 in individuals experiencing infertility[261, 262], 2 in muscular dystrophy or cerebral palsy[258, 265], and 7 in chronic pain-related conditions[257, 259, 269, 274, 276, 277, 279].

2.3.2.2 Measures

Included studies measured five types of perseverative negative thinking (rumination, catastrophizing, worry, anxious pre-occupation and preoccupation with death) using a total of 15 different measures. Six types of psychological outcome were identified (depression, anxiety, psychological distress, psychological functioning, negative affect and negative mood) measured using 15 different scales.

2.3.2.3 Timing of assessments

Duration of LTC at baseline assessment was up to 1 month in 6 studies, up to 1 year in 3 studies, more than one year in 12 studies (maximum 16.5 years), and unclear in 9 studies. Median duration of LTC was 12.6 months. In 16 studies there was one follow-up assessment, in 12 studies there were between 2 and 5 follow-ups, and in 2 studies follow-ups took the form of daily diary measures completed over 14 – 30 days. The median number of follow-up assessments was 1. Follow-up assessments took place within 1 month (8 studies), between 1 and 6 months (17 studies), 6 months to 1 year (11 studies), and 1 to 2 years (5 studies). The median time to follow-up was 6 months.

Table 2.1: Characteristics of included studies

ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
1	Denton et al. (2012, 2011)	Acute coronary syndrome	457 (387)	61.1	58.6	Eligible patients on coronary care and cardiac step-down units of three hospitals; USA	T1=within 1 week of index event, T2=3 months post-ACS	Ruminative responses scale of the Response Styles Questionnaire @ T1 and T2	Beck Depression Inventory @ T1 and T2
2	Garnefski & Kraaij (2010)	Myocardial infarction	160 (88)	56.0	80.7	Patients aged <70 years from cardiology outpatient clinic database who had received PCI in the previous 3-12 months; Netherlands	T1=within 3-12 months following PCI, T2=12 months later	Rumination and catastrophizing subscales of the Cognitive Emotion Regulation Questionnaire @ T1	Hospital Anxiety & Depression Scale @ T1 and T2 (depression subscale)
3	Vogele et al. (2012)	Myocardial infarction	36 (24[c])	57.6	89	Patients with acute first MI contacted in hospital; Germany	T1=5-15 days post-MI, T2=6-8 weeks post-MI, T3=6 months post-MI	Rumination subscale of the Trierer Skalen zur Krankheitbewaltigung (Coping questionnaire) @ T1	Centre for Epidemiologic Studies Depression Scale @ T1, T2, and T3
4	Baker (2014)	Coronary heart disease	101 (85)	66 – 75 modal range	76.2	Inpatients or outpatients presenting for cardiac care at hospital; UK	T1=after attendance at inpatient or outpatient cardiology service, T2=3 months later	Ruminative Responses Scale of the Response Styles Questionnaire @ T1 and T2	Patient Health Questionnaire-9 (depression) @ T1 and T2
5	Xiao et al. (2011)	Hypertension	650 (560)	55.4	51.8	Randomly selected from 1200 hypertension patients at one hospital; China	T1=following at least 1 year of hypertension, T2=6 months later	Rumination and catastrophizing subscales of the Cognitive Emotion Regulation Questionnaire @ T1	Centre for Epidemiologic Studies Depression Scale @ T1 and T2
6	Keefe et al. (1989)	Rheumatoid arthritis	Unclear (223)	52.7	25	Patients identified by rheumatology practices; USA	T1=within 7 years of diagnosis, T2=6 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1 and T2	Centre for Epidemiologic Studies Depression Scale @ T1 and T2

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ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
7	Sturgeon & Zautra (2013)	Rheumatoid arthritis	231 (93% completion of diaries)	55.0	30.4	Patients invited to participate at health fairs, Arthritis Foundation members, local physicians offices, Veterans Administration Hospital; USA	Daily diary for 30 days (once per day), starting an average of 13.6 years post-diagnosis	2 items from the catastrophizing subscale of the Coping Strategies Questionnaire @ daily	Positive and Negative Affect Schedule; depressive symptoms @ daily
8	Schiaffano & Revenson (1995)	Rheumatoid arthritis	101 (64)	NR	20	Eligible patients from hospital outpatient clinic, or from rheumatology practices; USA	T1=within 2 years of diagnosis, T2=18 months later	5-point Likert scale of rumination @ T2	Centre for Epidemiologic Studies Depression Scale @ T1 and T2
9	Sharpe et al. (2001)	Rheumatoid arthritis	53 (22)	55.1	30	Consecutive patients at rheumatology clinics of three general hospitals, enrolled into RCT; UK	T1=within 2 years of diagnosis,T2=3 months , T3=6 months, T4=9 months, T5=15 months, T6=21 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3, T4, T5 and T6	Hospital Anxiety & Depression Scale @ T1, T2, T3, T4, T5 and T6
10	Wang et al. (2014)	Breast cancer	509 (504)	48.3	0	Eligible women who had undergone surgery for breast cancer at two hospitals; China	T1=approx. 1 week post-diagnosis (5-7 days post-surgery), T2=1 month later	Rumination and catastrophizing subscales of the Cognitive Emotion Regulation Questionnaire @ T1	Centre for Epidemiologic Studies Depression Scale @ T1 and T2
11	Andreu et al. (2012)	Breast cancer	174[d] (102)	50.5	0	Consecutive patients attending pre-operative visit at department of surgery at oncology clinic; Spain	T1=pre-surgery (at preliminary diagnosis), T2=2-7 days post-surgery, T3=at definitive diagnosis, T4=at chemotherapy	Anxious preoccupation subscale of the Mental Adjustment to Cancer Scale @ T4	Brief Symptom Inventory 18 (distress) @ T1, T2, T3 and T4
12	Ferrero et al. (1994)	Breast cancer	68 (66)	53.0	0	Consecutive newly diagnosed patients attending hospital oncology clinic; Spain	T1=after diagnosis (approx. 1 month post-surgery), T2=4 months post-surgery, T3=7 months post-surgery	Anxious preoccupation subscale of the Mental Adjustment to Cancer Scale @ T1, T2 and T3	Breast Cancer Quality of Life Questionnaire (psychological distress subscale) @ T1, T2 and T3

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ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
13	Groarke et al. (2013)	Breast cancer	355 (221)	24.3	0	Consecutive eligible patients attending a breast symptomatic unit at a University-affiliated hospital; Ireland	T1=within 1 week of diagnosis, T2=4 months later	Anxious preoccupation subscale of the Mental Adjustment to Cancer Scale @ T1 and T2	Hospital Anxiety & Depression Scale; Positive and Negative Affect Schedule @ T1 and T2
14	Lam et al. (2013)	Advanced breast cancer	228 (192)	53.5	0	Hospital outpatients identified from clinic lists of 6 breast/oncology clinics; China	T1=post- diagnosis (awaiting or receiving initial chemotherapy), T2=6 weeks, T3=3 months, T4=6 months, T5=12 months later	Cancer-related Rumination Scale @T1	Hospital Anxiety & Depression Scale @ T1, T2 and T5
15	Thomsen et al. (2013)	Colon cancer	67 (54)	63.5	54	Patients referred for chemotherapy at hospital oncology department; Denmark	T1=1-7 months post-diagnosis (mean 72 days), T2=8 months later	Rumination-Reflection Questionnaire @ T1 and T2	Beck Depression Inventory @ T1 and T2
16	Couper et al. (2010)	Early and advanced prostate cancer	367 (265)	66.2 early; 70.1 advanced	100	Consecutive patients recruited by their oncologist/urologist from public hospitals and practices; Australia	T1=after diagnosis, at beginning treatment (early) or after patients informed disease metastatic (advanced), T2=12 months later	Anxious preoccupation subscale of the Mental Adjustment to Cancer Scale @ T1 and T2	Brief Symptom Inventory 53 (anxiety and depression) @ T1 and T2
17	Lehto & Cimprich (2009)	Suspected lung cancer	52 (42)	64.0	64.3	Patients undergoing surgical evaluation for lung cancer at a comprehensive cancer center; USA	T1=at diagnosis (14 days prior to surgery), T2=5-6 weeks later	Penn State Worry Questionnaire @ T1 and T2	State-Trait Anxiety Inventory @ T1 and T2
18	Lampic et al. (1994)	Mixed cancer	197 (121)	61.0	37	Consecutive patients scheduled for hospital appointment at oncology clinic; Sweden	T1=at clinic appointment (median 6 yrs from diagnosis), T2=few days after appointment, T3=3 weeks after appointment	Anxious preoccupation subscale of the Mental Adjustment to Cancer Scale @ T2; Cancer-related worry @ T1, T2, and T3	Visual analogue ratings of anxiety @ T1, T2 and T3

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ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
19	Vollmer et al. (2011)	Haematologic malignancy	102[e] (45)	46.7	51.6	Consecutively enrolled patients with haematologic malignancies identified from weekly lists of inpatients; Germany	T1=within 7 days post-admission, T2=at least 4 weeks later	Preoccupation with death subscale of the Subjective Assessment of the Course of Disease & Death @ T1 and T2	Hospital Anxiety & Depression Scale @ T1 and T2
20	Kraaij et al. (2008)	Definitive infertility	169 (99)	41.0	38	Individuals with definitive infertility responding to announcements in local media and online self-help groups; Netherlands	T1=average 5 years post-diagnosis, T2=2 years later	Rumination and catastrophizing subscales of the Cognitive Emotion Regulation Questionnaire @ T1 and T2	Depression subscale of the Symptom Check List @ T1 and T2
21	Kraaij et al. (2010)	Infertility	313 (139)	35.0	22	Patients who had attended an infertility clinic for treatment within the previous 4 months; Netherlands	T1=within 4 months of most recent treatment, T2=9 months later	Rumination and catastrophizing subscales of the Cognitive Emotion Regulation Questionnaire @ T1	Hospital Anxiety & Depression Scale @ T1 and T2
22	Nieto et al. (2012)	Muscular dystrophy	395[f] (107)	50.2	43	Participants identified from National Registry of Myotonic Dystrophy & Facioscapulohumeral Muscular Dystrophy Patients & Family Members, and from neuromuscular disease clinic; USA	T1=average 16.5 years post-diagnosis, T2=24 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1; Pain Catastrophizing Scale @ T2	5 item SF-36 mental health scale (psychological functioning) @ T1 and T2
23	Jensen et al. (2006)	Cerebral palsy	48 (48)	40.1	50	Patients who participated in a previous cross-sectional study; USA	T1=after previous study (pain duration ≥3 months) , T2=6 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1 and T2	Centre for Epidemiologic Studies Depression Scale @ T1 and T2

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ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
24	Turner et al. (2004)	Tempromandibular disorder	110 (100)	38.8	13	Patients evaluated at a TMD clinic and enrolled in a RCT; USA	T1= prior to enrolment in RCT, where facial pain ≥3 months, T2= daily diary for next 14 days (3 times per day)	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1; brief daily diary measure of catastrophizing/ruminatio n (3 Likert-style items) @ T2	Beck Depression Inventory @ T1; brief daily diary measure of negative mood ('unhappy', 'annoyed', 'anxious') @ T2
25	Hanley et al. (2004), Jensen et al. (2002)	Phantom limb pain	89 (70[g])	44.7	73	Consecutive admissions at Department of Orthopaedic Surgery for lower limb amputation invited to participate in RCT; USA	T1=1 month post-amputation, T2=6 months post-amputation, T3=12 months post-amputation, T4=24 months post-amputation	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3 and T4	Centre for Epidemiologic Studies Depression Scale @ T1, T2, T3 and T4
26	Jensen et al. (2001)	Chronic pain (mixed primary sites)	197 (141)	44.7	49	Patients enrolled in multidisciplinary pain management program; USA	T1=pre-treatment (mean pain duration 3.2 years), T2=post-treatment (approx. 3 weeks later), T3=6 months later, T4=12 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3 and T4	Centre for Epidemiologic Studies Depression Scale @ T1, T2, T3 and T4
27	Sparkes et al. (2015)	Mixed pain conditions	75 (56)	47.4	44.6	Consecutive patients assessed by a multidisciplinary team at a secondary care centre and referred for a spinal cord stimulation (SCS) trial; UK	T1= 1 week before SCS trial (mean pain duration 8.2 years), T2=6 months post-SCS, T3=12 months post-SCS	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3	Hospital Anxiety & Depression Scale @ T1, T2, T3
28	Mehlsen et al. (2015)	Chronic pain	87 (73)	52	15	Patients Invited to attend a pain self-management course by local health care and social work professionals (pain duration >3 months); Denmark	T1= 2-14 days before course; T2=1-3 weeks after course, T3=5-6 months after course	Pain Catastrophizing Scale @ T1, T2, T3	Depression and anxiety subscales of the Common Mental Disorders Questionnaire @ T1, T2, T3

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ID	Authors and date	Condition	Sample size Recruited (Analysed)[a]	Mean age (years)[b]	Males (%)[b]	Sample	Assessments	PNT measure	Anxiety, depression or distress measure
29	Bourgault et al. (2015)	Fibromyalgia syndrome	58 (37)	50	7.1	Patients recruited via newspaper adverts for a fibromyalgia self-management intervention (mean duration of pain >10 years); Canada	T1=prior to intervention, T2=post-intervention (~11 weeks), T3=3 months, T4=6 months, T5=12 months later	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3, T4, T5	Beck Depression Inventory @ T1, T2, T3, T4, T5
30	Rzewuska et al. (2015)	Musculo-skeletal pain	502 (502[h])	64.8	38.6	Consecutive older adults presenting with musculoskeletal pain in five general practices; UK	T1=following GP consultation, T2=3 months, T3=6 months, T4=12 months	Catastrophizing subscale of the Coping Strategies Questionnaire @ T1, T2, T3, T4	Hospital Anxiety & Depression Scale @ T1, T2, T3, T4

[a]Where more than one follow-up, '(Analysed)' refers to N included in appropriate analyses at final time point.
[b]Demographics (age and sex) of whole sample at baseline.
[c]Refers to Pearsons correlations, for partial correlations n=17.
[d]126 met inclusion criteria.
[e]Does not include 33 controls who participated at T1 but were not required to participate at T2.
[f]279 met inclusion criteria.
[g]61 at T2.
[h]392 completers at T4, but all cases who completed at least one assessment were included in analyses.
Abbreviations: PNT = perseverative negative thinking, PCI = percutaneous coronary intervention, MI=myocardial infarction, T1 = time 1 (baseline), T2 = time 2 (follow-up), T3 = time 3 (follow-up), T4 = time 4 (follow-up), T5 = time 5 (follow-up), T6 = time 6 (follow-up).

2.3.3 Perseverative negative thinking and negative psychological outcomes

Findings from all included studies are summarised in Table 2.2.

2.3.3.1 Bivariate analyses

Prospective, bivariate correlations between perseverative negative thinking and subsequent depression, anxiety or emotional distress were reported in 20 of the 30 studies identified. The most commonly studied associations were of rumination (7 studies) and catastrophizing (9 studies) with depression. Eighteen studies found a significant association between perseverative negative thinking at one assessment time with depression, anxiety or emotional distress at a subsequent time. One of these studies[254] found mixed evidence of an association (3 out of 4 correlations significant). The 2 studies that did not find a significant association had particularly low sample sizes at follow-up (n=24[270] and n=22[267]). Bivariate effect sizes ranged between r=.23 and r=.73, representing small to moderate effects.

The significant associations did not appear to be influenced by type/measure of perseverative negative thinking, type/measure of depression, anxiety or emotional distress, or whether follow-ups took place at less than or greater than 6 months (median time to follow-up) after baseline.

2.3.3.1.1 Reverse-associations

7 of the 30 identified studies reported bivariate correlations between baseline depression, anxiety or emotional distress with subsequent perseverative negative thinking, and 6 of these found a significant positive association.

2.3.3.2 Multivariable analyses

Multivariable analyses of the association between perseverative negative thinking with subsequent depression, anxiety or emotional distress were available for 25 of the 30 included studies and included partial correlations (4 studies), multiple regression (19 studies), and latent growth models combined with logistic regression to predict trajectories of depression and anxiety (2 studies). Consistent with bivariate analyses the most commonly studied associations were of rumination with depression (8 studies) and catastrophizing with depression (10 studies).

Age, sex and baseline depression (or anxiety, as appropriate) were the variables most commonly controlled for (15, 14 and 17 studies, respectively). Only 8 studies controlled for all three of these confounders (and 2 studies in entirely female samples controlled for both age and baseline depression). A variety of other demographic, disease, physical and psychosocial factors were also controlled for.

Ten studies found significant positive associations between measures of perseverative negative thinking and subsequent depression, anxiety or emotional distress, and a further 5 showed mixed results, i.e. some associations significant but some not. Five of these studies controlled for age, sex and baseline depression, and 3 studies controlled for baseline depression alone. One study found a negative association, i.e. where high catastrophization at baseline predicted greater improvement in depression over the subsequent period.

Significant multivariable associations were found more often in studies that measured the effect of catastrophizing on subsequent depression, anxiety or emotional distress compared to studies that measured the effect of rumination. However, associations did not appear to be influenced by the measure of depression, anxiety or emotional distress used. In addition, associations did not vary according to whether follow-ups took place before or after the median time to follow-up (6 months), although significant effects were found less often in studies with particularly short (up to 1 month) and long (>1 year) follow-ups and most frequently among studies with follow-up periods between 1 month and 1 year (although there were fewer studies with particularly short or long follow-ups).

A variety of effect sizes and coefficients were reported. Partial correlations ranged from r=.23 to r=.35. For multiple regression analyses, the contribution of perseverative negative thinking to subsequent depression, anxiety or emotional distress was indicated using ΔR^2 (range=.01 to .083), β (range=.21 to .53), or B (range=.0865 to .62). Odds ratios (range=1.15 to 8.75) were given for logistic regression analyses. In studies that controlled for baseline depression, anxiety or emotional distress, the range of partial correlations, ΔR^2 and odds ratios were unchanged, however the range of B was higher (range=.61 to .62; but based on only 2 observations) and β was available for only one study with a value of .21.

2.3.3.2.1 Reverse-associations

Only 2 studies reported multivariable analyses (multiple regression in both cases) of the association of depression, anxiety or emotional distress with subsequent perseverative negative thinking, and neither found a significant association.

Table 2.2: Findings of included studies

ID	Authors and date	Bivariate findings	Multivariable findings	Variables controlled for
1	Denton et al. (2012; 2011)	T1 rumination correlates with T2 depression (r=.49, p<.001); T1 depression correlates with T2 rumination (r=.52, p<.001)	T1 rumination predicts T2 depression independently (ΔR^2=.01, ΔF=9.21, p=.003) and in interaction with poor dyadic adjustment (ΔR^2=.01, ΔF=2.67, p=.03) In patients depressed at baseline T1 rumination independently predicts T2 depression (ΔR^2 =.03, ΔF=6.65, p=0.01) In patients non-depressed at baseline T1 rumination does not independently predict T2 depression (ΔR^2=.002, ΔF=.80, p=.37), but T1 rumination predicts T2 depression in interaction with poor dyadic adjustment (ΔR^2=.06, ΔF=5.31, p<0.001)	Age, sex, partner, years of schooling, work status, ethnicity, baseline depression, Charlson comorbidity index, cardiac disease severity
2	Garnefski & Kraaij (2010)	T1 rumination correlates with T2 depression (r=.43, p<.001); T1 catastrophizing correlates with T2 depression (r=.45, p<.001)	T1 rumination/catastrophizing predicts T2 depression (β=.35, p<.001)	Sex, age, physical limitations
3	Vogele et al. (2012)	T1 rumination does not correlate with depression at T2 (r=.01, ns) or T3 (r=.14, ns)	T1 rumination does not correlate with depression at T2 (r=.10, ns) or T3 (r=.24, ns)	Baseline depression
4	Baker (2014)	T1 rumination correlates with T2 depression (r=.73, p=.01); T1 depression correlates with T2 rumination (r=.70, p=.01)	T1 rumination predicts T2 depression (β=.46, B=.202, SE=.043, t=4.705, p<.001, R^2=.083)	Baseline depression, cardiac quality of life, age, sex, body mass index, social support
5	Xiao et al. (2011)	Greater rumination at T1 correlates with greater depression at T2 (r=.38, p<.001); greater catastrophizing at T1 correlates with greater depression at T2 (r=.37, p<.001)	Higher T1 rumination (B=.62, t=0.18, p<.001) and T1 catastrophizing (B=.61, t=.18, p<.001) predicts increases in T2 depressive symptoms	Sex, baseline depression, smoking, alcohol use, coffee consumption
6	Keefe et al. (1989)	T1 catastrophizing correlates with T2 depression (r=.62, p<.01)	T1 catastrophizing predicts T2 depression (sr^2=.043, F=20.87, p=<.001)	Baseline depression, age, SES, sex, disability support status, duration of disease
7	Sturgeon & Zautra (2013)	Bivariate analyses not reported	Previous day catastrophizing predicts subsequent day depressive symptoms (B=.0865, p<.05) but not negative affect (B=.0016, ns)	Age, sex, neuroticism, positive affect (negative affect analysis only)
8	Schiaffano & Revenson (1995)	T1 depression correlates with T2 rumination (r=.30, p<.05)	T1 depression does not predict T2 rumination (β=.22, ΔR^2=.05, F=2.84, p<.10)	Education
9	Sharpe et al. (2001)[b]	T1 catastrophizing does not correlate with T2 depression(r=.18, p=.461), T6 depression (r=.03, p=.891), T2 anxiety (r=.32, p=.177) or T6 anxiety (r=.12, p=.607)	T1 catastrophizing does not correlate with T2 depression (r=.11, p=.671) or anxiety (r=.34, p=.17)	Age, baseline depression, baseline anxiety
10	Wang et al. (2014)	Bivariate analyses not reported	T1 rumination (β=.09, SE=0.12, ns) and catastrophizing (β=.26, SE=.15, ns) do not predict T2 depression	Age, place of residence, marital status, years of schooling, employment status, disease severity, baseline depression
11	Andreu et al. (2012)	T4 anxious preoccupation does not correlate with T1 (-.08, ns), T2 (-.04, ns) or T3 (.02, ns) distress	Multivariable analyses not reported	None

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ID	Authors and date	Bivariate findings	Multivariable findings	Variables controlled for
12	Ferrero et al. (1994)	T1 anxious preoccupation does not correlate with T2 distress (r=.21, ns) but does correlate with T3 distress (r=.40, p<.001); T2 anxious preoccupation correlates with T3 distress (r=.32, p<.01)	T1 anxious preoccupation does not predict T2 or T3 distress (relevant regression statistics not reported) T2 anxious preoccupation predicts T3 distress (full model R^2=.428, p<.001, including predictors MAC 'fighting spirit', 'fatalism', and 'denial' , and T1 psychological distress and physical symptoms)	Baseline distress, physical symptoms
13	Groarke et al. (2013)[b]	T1 anxious preoccupation correlates with T2 depression (r=.23, p <.001) and T2 anxiety (r=.35, <.001)	T1 anxious preoccupation does not predict T2 depression (β=.014, B=.010, SE(B)=.048, t=.216, ΔR^2 =.000, ΔF=.046, p=.830), T2 anxiety (β=.038, B=.036, SE(B)=.058, t=.617, ΔR^2 =.001, ΔF=.381, p=.538) or T2 negative affect (β=.022, B=.041, SE(B)=.121, t=.340, ΔR^2 =.000, ΔF=.115, p=.734)	Baseline depression/anxiety, age, disease severity, type of surgery
14	Lam et al. (2013)	Bivariate analyses not reported	Four coping-related factors including negative cancer-related rumination differentiated depression ($\chi2(8)$=132.83, p<.001, R^2=.52) and anxiety ($\chi2(12)$=107.00, p<.001, R^2=.45) trajectories. T1 rumination greater in 'High-stable/high-recovering' (OR=1.38 (95% CI=1.18-1.61), p<.001) and 'Recovering' (OR =1.15 (95% CI=1.03-1.30), p=.017) trajectories compared to low-depression referent group. T1 rumination greater in 'High-stable' (OR =1.22 (95% CI=1.06-1.39), p=.005) and 'Recovering' (OR = 1.18 (95% CI=1.04-1.34), p=.012), but not 'Intermediate', trajectories compared to low-anxiety referent group.	Radiation therapy and occupational status (depression model only)
15	Thomsen et al. (2013)	T1 rumination correlates with T2 depression (r=.32, p<.05.); T1 depression correlates with T2 rumination (r=.37, p<.05.)	T1 rumination does not predict T2 depression (β=.07, ns)	Age, baseline depression
16	Couper et al. (2010)	Bivariate analyses not reported	T1 anxious preoccupation does not predict T2 depression (early β=NR, ns; advanced β=.15, ns) T1 anxious preoccupation does not predict T2 anxiety in early (β=NR, ns), but does predict anxiety in late prostate cancer (β=.21, p<.001)	Baseline depression, health-related quality of life
17	Lehto & Cimprich (2009)[b]	Worry at T1 correlates with state anxiety at T2 (r=.34, p=.027)	Multivariable analyses not reported	None
18	Lampic et al. (1994)	T2 anxious preoccupation correlates with T3 anxiety (r=.31, p<.01)	Multivariable analyses not reported	None
19	Vollmer et al. (2011)[a]	T1 preoccupation with death correlates with T2 depression (r=.37, p=.013) and anxiety (r=.38, p=.012); T1 depression (r=.42, p=.009) and anxiety (r=.44, p=.006) correlates with T2 preoccupation with death	T1 preoccupation with death does not predict T2 depression (ΔR^2=.004, ΔF=.301, p=.586) or T2 anxiety (ΔR^2=.010, ΔF=.670, p=.418) T1 depression (ΔR^2=.002, ΔF=.114, p=.738) and T1 anxiety (ΔR^2<.000, ΔF=.021, p=.887) does not predict T2 preoccupation with death (after controlling for age, sex, and T1 preoccupation with death)	Age, sex, baseline depression (or anxiety as appropriate)
20	Kraaij et al. (2008)	T1 rumination correlates with T2 depression (r=.29, p<.001); T1 catastrophizing correlates with T2 depression (r=.31, p<.001)	T1 rumination does not predict T2 depressive symptoms (test statistics not reported) T1 catastrophizing predicts increased depressive symptoms at T2 (β=.26, p<.05)	Sex, wish to have children
21	Kraaij et al. (2010)	T1 rumination / catastrophizing correlates with depression (r=.37, p<.001) and anxiety (r=.40, p<.001) at T2	T1 rumination/catastrophizing predicts T2 depression (β=.26, p<.05) and T2 anxiety (β=.24, p<.05)	Sex, number of children, time since treatment, success of treatment

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ID	Authors and date	Bivariate findings	Multivariable findings	Variables controlled for
22	Nieto et al. (2012)	Change (T2-T1) in catastrophizing correlates with change in psychological functioning (r=.25, p<.01)	Change (T2-T1) in catastrophizing does not predict change in psychological functioning (β=.18, ns)	Pain intensity
23	Jensen et al. (2006)	Change (T2-T1) in catastrophizing correlates with change in depression (r=.49, p<.001)	No relevant multivariable analyses reported	None
24	Turner et al. (2004)	T1 depression correlates with T2 catastrophizing/rumination (r=.39, p<.0001)	Daily catastrophizing/rumination at previous time point does not predict daily negative mood at subsequent time point (B=.05, ns)	Baseline negative mood
25	Hanley et al. (2004), Jensen et al. (2002)	Bivariate analyses not reported	Greater T1 catastrophizing predicts improvements in depression from T1 to T2 (β =.53, p<.001), from T1 to T3; β=.46, p<.01) and from T1 to T4; β=.43, p<.05)	Pain intensity, age, sex
26	Jensen et al. (2001)	Change in catastrophizing correlates with change in depression (T1-T2 r=.64, p<.001; T1-T3 r=.61, p<.001; T1-T4 r=.53, p<.001)	Change in catastrophizing predicts change in depression (T1-T2 β =.44, p<.001; T1-T3 β =.48, p<.001; T1-T4 β =.38, p<.001)	Baseline pain intensity
27	Sparkes et al. (2015)[b]	T1 catastrophizing correlates with T2 (r=.55, p<.01) and T3 (r=.57, p<.01) depression, and with T2 (r=.51, p<.01) and T3 (r=.42, p<.01) anxiety	T1 catastrophizing correlates with T2 depression (r=.30, p=.026), T3 depression (r=.35, p=.009), T2 anxiety (r=.31, p=.02) but not T3 anxiety (r=.21, p=.119)	Age, gender, baseline depression
28	Mehlsen et al. (2015)[b]	Bivariate analyses not reported	T1 catastrophizing correlated with T2 (r=.23, p=.018) and T3 (r=.24, p=.014) depression, and with T2 (r=.24, p=.015) and T3 (r=.31, p=.001) anxiety	Age, gender, baseline depression
29	Bourgault et al. (2015)[b]	T1 catastrophizing correlates with T2 (r=.27, p=.0002) and T3 (r=.29, p=.0002) depression	T1 catastrophizing does not predict T2 (β=.35, p=.3562) or T3 (β=-.04, p=. 9231) depression	Age, gender, baseline depression, treatment arm
30	Rzewuska et al. (2015)	Bivariate analyses not reported	T1 catastrophizing differentiated depression- and anxiety-related trajectories over 12 months. T1 catastrophizing greater in 'persistent depression' group compared to 'no depression' referent group (adj. OR=3.20 (95% CI=1.53-6.66)). No significant difference between 'depression symptom recovery' group and 'no depression' referent group. T1 catastrophizing greater in 'persistent anxiety' (adj. OR=8.75 (95% CI=3.66-20.89)) and 'transient anxiety' (adj. OR=4.09 (95% CI=1.38-12.13)) groups compared to 'no anxiety' referent group.	Age (depression model only), gender, baseline depression/anxiety, coping strategies, emotional support, pain-related variables

[a]Based on additional data provided by the authors.

[b]Based on additional analyses provided by the authors.

Abbreviations: SES=socioeconomic status, T1 = time 1 (baseline), T2 = time 2 (follow-up), T3 = time 3 (follow-up), T4 = time 4 (follow-up), T5 = time 5 (follow-up), T6 = time 6 (follow-up), NR=not reported.

2.3.4 Long term conditions

Studies reporting multivariable associations were grouped according to LTC (see Appendix 2).

In heart disease and chronic pain the majority of studies reported significant associations between perseverative negative thinking and depression, anxiety or emotional distress. In rheumatoid arthritis and infertility there was mixed evidence of an association between perseverative negative thinking and depression, anxiety or emotional distress. The majority of studies in cancer patients did not find an association between perseverative negative thinking and depression, anxiety or emotional distress. In one small study there was no evidence of an association between perseverative negative thinking and depression, anxiety or emotional distress in patients with muscular dystrophy.

2.3.5 Physical outcomes

Associations between perseverative negative thinking and physical outcomes (such as health-related quality of life, functional limitations, pain intensity and pain interference) were reported in 9 studies[251, 256-260, 265, 266, 268, 269]. Four studies found evidence of an association, 1 study found mixed evidence, and 4 studies found no evidence of an association. Rumination was not related to subsequent quality of life or functional disability. Catastrophizing was associated with impairments in physical outcomes, improvements in physical outcomes, and in some studies was not associated with physical outcomes.

2.3.6 Reporting bias

23 studies reported the results of bivariate analyses, and of those multivariable analyses were also available for 19 studies. Significant bivariate associations were found in 89% of the 19 studies for which both types of analyses were available, and ranged between r=.23 to r=.73. In the 4 studies for which multivariable findings were not available, significant bivariate associations were found less frequently (75% of the studies) and the range of effect sizes was smaller (r=.31 to r=.49). This hints at a possible bias toward reporting multivariable analyses where significant or large

associations were most likely to be found, although this suggestion is based on only 4 observations.

2.3.7 Risk of bias

Component and global risk of bias ratings for each study are presented in Table 2.3. Based on global ratings, 23 of the included studies were moderate quality and 7 were weak quality. Studies with overall moderate ratings were not all equivalent; 5 studies were assigned 3 strong component ratings and these were comparatively good quality[183, 251, 272, 273, 276] with particular strengths in retention of participants at follow-up (>80%), control for appropriate confounders, and reliability/validity of data collection methods. Four of these 5 studies found significant associations between perseverative negative thinking and subsequent depression, anxiety or emotional distress after controlling for relevant confounders including baseline depression.

Among the overall weak quality studies, selection bias and retention of participants were identified as areas of concern. In multivariable analyses associations between perseverative negative thinking and subsequent depression, anxiety or emotional distress were found less often in studies of weak methodological quality.

In heart disease and chronic pain, studies which did not find an effect had small sample sizes at follow-up [270, 274], or used unusual methods to collect or analyse data (time series data and use of change scores[269]).

In rheumatoid arthritis, where evidence of an association was weak, studies tended to be of weak quality due to low sample sizes, high numbers of withdrawals at follow-up, and limited reliability of measures. Similarly, there was weak evidence of an association in people experiencing infertility and these studies tended to be weak quality due to use of self-selected samples and high numbers of withdrawals.

Studies in cancer patients, in whom evidence of an association between perseverative negative thinking and depression, anxiety or emotional distress was weak, recruited quite heterogeneous participants and, unlike other studies, focused on ‘anxious preoccupation’ and ‘preoccupation with death’, which may have influenced findings.

Table 2.3: Risk of bias/quality assessment

ID	Authors and date	Selection bias	Design[a]	Confounding	Blinding[b]	Data collection	Withdrawals	**Global rating**
1	Denton et al. (2012, 2011)	2	2	1	2	1	1	**2**
2	Garnefski & Kraaij (2010)	2	2	2	2	1	3	**2**
3	Vogele et al. (2012)	3	2	2	2	1	3	**3**
4	Baker (2014)	2	2	1	2	1	1	**2**
5	Xiao et al. (2011)	1	2	2	2	1	1	**2**
6	Keefe et al. (1989)	3	2	1	2	1	3	**3**
7	Sturgeon & Zautra (2013)	3	2	2	2	3	3	**3**
8	Schiaffano & Revenson (1995)	2	2	3	2	3	2	**3**
9	Sharpe et al. (2001)	2	2	2	2	1	3	**2**
10	Wang et al. (2014)	2	2	1	2	1	1	**2**
11	Andreu et al. (2012)	2	2	3	2	1	1	**2**
12	Ferrero et al. (1994)	2	2	2	2	1	1	**2**
13	Groarke et al.(2013)	3	2	1	2	1	2	**2**
14	Lam et al. (2013)	2	2	3	2	1	1	**2**
15	Thomsen et al. (2013)	2	2	2	2	1	1	**2**
16	Couper et al. (2010)	2	2	2	2	1	2	**2**
17	Lehto & Cimprich (2009)	2	2	3	2	1	1	**2**
18	Lampic et al. (1994)	2	2	3	2	1	2	**2**
19	Vollmer et al. (2011)	2	2	1	2	1	3	**2**
20	Kraaij et al. (2008)	3	2	2	2	1	3	**3**
21	Kraaij et al. (2010)	3	2	2	2	1	3	**3**
22	Nieto et al. (2012)	3	2	3	2	1	3	**3**
23	Jensen et al. (2006)	2	2	3	2	1	1	**2**
24	Turner et al. (2004)	3	2	2	2	1	1	**2**

Table continues on following page…

ID	Authors and date	Selection bias	Design[a]	Confounding	Blinding[b]	Data collection	Withdrawals	**Global rating**
25	Hanley et al. (2004), Jensen et al. (2002)	2	2	2[c]	2	1	2	**2**
26	Jensen et al. (2001)	2	2	3	2	1	2	**2**
27	Sparkes et al. (2015)	2	2	1	2	1	2	**2**
28	Mehlsen et al. (2015)	2	2	1	2	1	1	**2**
29	Bourgault et al. (2015)	3	2	1	2	1	2	**2**
30	Rzewuska et al. (2015)	2	2	3	2	1	2	**2**

1=strong, 2=moderate and 3=weak.

[a]All studies were rated as moderate quality on the study design component. There was 1 RCT[274] which would have qualified for a strong quality rating, however because the data extracted for this review related to changes in the whole cohort over several assessment times this study was treated as a cohort study for the purpose of quality assessment for this component.

[b]The blinding component was modified to be more suitable for the included study designs, although it remained difficult to assign ratings for this component and all studies were rated as moderate quality as it was not possible to tell if the researcher was exposed to information about the participant that could lead to bias, or if the participants were aware of the research question.

[c]Jensen et al. = 3 (no control for confounders at 6 month follow-up), and Hanley et al. = 2 (control for some confounders at 12 and 24 months follow-up).

2.4 Discussion

The aim of this systematic review was to clarify among people with LTCs the temporal relationship between perseverative negative thinking, on the one hand, and depression, anxiety or emotional distress, on the other, and to determine the strength of the prospective associations. Findings were limited mainly to the association of rumination and/or catastrophizing with subsequent depression. The majority of uncontrolled studies showed an association between measures of perseverative negative thinking and subsequent depression, anxiety or emotional distress. Studies controlling for the effects of covariates, including depression at baseline, using multivariable analysis showed more mixed results, though the majority of studies (15 / 25 studies) still supported a significant association, with effects being small in magnitude.

Strongest associations were observed in studies measuring catastrophizing. The strength of association between perseverative negative thinking and subsequent depression, anxiety or emotional distress appeared to vary across studies of different LTCs, with greatest effects seen in people with heart disease and chronic pain. Whilst degrees of perseverative negative thinking and of depression, anxiety or emotional distress might reasonably be expected to vary across long term conditions, it isn't immediately obvious why the relationship between such thinking and depression, anxiety or emotional distress should vary between LTCs. It is possible that some of the variability between LTCs could be due to the use of different perseverative negative thinking constructs in the different samples (e.g. studies in pain conditions tended to measure pain catastrophizing, studies in cancer patients tended to measure anxious preoccupation and preoccupation with death). The different measures are likely to reflect different dimensions of repetitive thinking, suggesting that some dimensions are important predictors of depression, anxiety or emotional distress while others are not.

Contrary to expectation, one study found that greater catastrophizing at baseline predicted improvements in depression from baseline to 6, 12 and 24 month follow-ups. Baseline catastrophizing was concurrently associated with higher levels of

depression in this study, as might be expected. Since the authors did not control for the effects of depression at baseline, this counter-intuitive finding may have arisen because individuals with high levels of catastrophizing (and therefore also depression) at baseline had more potential for improvement in depression during follow-up.

Too few studies investigated the association of baseline depression, anxiety or emotional distress with subsequent perseverative negative thinking to be able to draw firm conclusions about the reverse association. Among the studies identified, few included measures of physical health outcomes, and findings from those studies were very mixed.

The quality of studies identified was highly variable, with no "strong" studies being identified. Quality was most frequently low due to studies failing to control adequately for potential confounding variables or due to high numbers of participants dropping-out, which reduced the generalisability of findings. Interestingly, we found significant associations least frequently in the studies rated as weak compared to studies rated moderate, suggesting that poor control for confounders did not increase the likelihood of an association being found in studies identified for this review. A number of studies had small sample sizes and the majority of such studies failed to find an association between perseverative negative thinking and subsequent depression, anxiety or emotional distress. There was significant variation in study quality across LTCs.

This systematic review is the first to investigate the prospective association of perseverative negative thinking with subsequent depression, anxiety or emotional distress specifically in people with LTCs. The main strengths of this review are that it adhered to established guidelines[243, 244] to ensure rigorous methods were used. A comprehensive search strategy was used, combined with supplementary backward and forward citation searches of included papers. In addition, we are confident that our strategy of hand-searching records for LTCs ensured that all studies containing relevant samples were identified. *A priori* restrictions were not applied to the definition of LTCs. The group of conditions identified was heterogeneous and this may have contributed to the heterogeneity of findings although it is unclear whether variations in study quality across different LTC groups may explain this observation.

Eligibility screening, data extraction and quality assessment were undertaken by two reviewers to minimise bias and maximise reliability. To clarify the temporal relationships between perseverative negative thinking and depression, anxiety or emotional distress, studies investigating prospective associations in either direction were included.

There are some limitations of this systematic review. First, the majority of this review is based on published journal articles so the conclusions are vulnerable to the effects of publication bias. There was some suggestion of publication bias, in that studies presenting multivariable findings were more likely to have larger bivariate associations, compared to those that did not present multivariable findings. Second, meta-analysis was not performed due to the multitude of measures of both perseverative negative thinking and depression, anxiety or emotional distress, and also due to heterogeneity in research methods used (including variables controlled for, and study quality). Rather, findings were synthesized using vote counts, which is a crude method of synthesis and does not take account of the effect sizes or precision of individual studies. Conducting a meta-analysis using only studies presenting bivariate analyses would have allowed synthesis of a subset of more comparable studies. However this would have led to an overestimate of the associations since important confounding variables would not have been controlled for. Third, findings were presented for associations of perseverative negative thinking with physical health outcomes, such as quality of life, where these were presented within the eligible papers. However, we acknowledge that our searches were not designed to identify all such studies, since investigating the impact on physical health outcomes was not a primary objective of our review. There are likely to be other studies relevant to this objective that were not identified by our search processes. As a consequence, no firm conclusion on the association of perseverative negative affect and physical health outcomes can be drawn from our review.

The findings of this review are interpreted as indicating that perseverative negative thinking (particularly catastrophizing) is prospectively associated with a range of subsequent negative affective states among people with LTCs, even after controlling for important covariates such as depression at baseline. Evidence of perseverative

negative thinking predicting subsequent adverse medical outcomes in the studies identified was too mixed to enable firm conclusions. There was no convincing evidence that depression, anxiety or emotional distress predicted subsequent perseverative negative thinking, particularly after controlling for covariates.

The findings are consistent with perseverative negative thinking causing depression, anxiety or emotional distress among people with LTCs, but current evidence falls short of proving causation. Perseverative negative thinking has been described within the context of a number of theoretical models, and these models offer either overt or implicit suggestions as to how perseverative negative thinking could lead to depression. The response styles theory[120] posits that perseverative negative thinking (in particular depressive rumination) could lead to depression via several mechanisms including focusing attention on and elaboration of negative thoughts, interfering with problem solving, reducing motivation to engage in constructive behaviours, and eroding social support. On the other hand control theory approaches[115, 119] emphasize managing discrepancies between actual and desired states. This suggests that perseverative negative thinking could lead to depression when it is not possible to reduce such discrepancies (either by making progress toward, or changing, the desired state) because the discrepancy focuses attention on the unresolved issue and makes it more salient. These models of perseverative negative thinking were not developed specifically with people with chronic physical illnesses in mind, and previous research has tended to focus on otherwise healthy individuals, and so it is unclear to what extent these models apply to people with LTCs.

There did not appear to be any variation in findings based on whether follow-up took place before or after the median follow-up time of 6 months. However, closer inspection suggested that effects were identified more often in studies with intermediate length follow-up. This variation with length of follow-up could be due to significant changes in the status of the LTC or due to fluctuations in levels of perseverative negative thinking over time. Future studies should carefully consider the length of follow-up or risk missing a true association. It seems most likely that a follow-up between 1 and 12 months would be most appropriate.

The results of this review are consistent with the findings of previous narrative ([113, 169, 171]) and systematic ([168, 170]) reviews focused on physically healthy individuals. Similar to ours, these previous reviews noted that, compared to the results of cross-sectional studies, the findings from prospective research are more mixed although the majority of such studies did support an association. In these previous reviews, moderators of the association between perseverative negative thinking and subsequent symptoms of depression and anxiety or negative affect that relate to characteristics of the population (e.g. gender, psychopathology) and to aspects of repetitive thinking itself (e.g. valence, content) have been suggested to explain some of the variability in findings.

Further high quality research is required to clarify the association of perseverative negative thinking, on the one hand, with psychological and other medical outcomes such as quality of life, morbidity and mortality, on the other. Experimental studies in which perseverative negative thinking is induced or interrupted, with effects on depression, anxiety or emotional distress monitored, would provide good evidence of a causal association and indicate that perseverative negative thinking is a relevant target for treatment of depression and other psychological outcomes in people with LTCs. Future prospective and experimental research should investigate differences of associations of perseverative negative thinking with depression, anxiety or emotional distress in groups of individuals with different LTCs. In addition, attempts should be made to clarify mechanisms that might explain how and why perseverative negative thinking contributes to depression, anxiety and emotional distress. A number of possible mechanisms have been suggested in the research literature, including via a reduction in social support, impairment of problem solving, reduced motivation to perform positive instrumental behaviours and increased negative thinking[113, 120]. These mechanisms could also provide potential targets for intervention aimed at improving depression and also physical health outcomes.

Chapter 3 Methods

3.1 Chapter outline

This chapter outlines the methods of a prospective observational cohort study to investigate the role of rumination and worry in predicting depression, anxiety and quality of life in people with acute coronary syndrome (ACS). The findings of this study form the basis of the results chapters that follow.

This chapter provides an overview of:

i. The methodological approach chosen and explains how previous literature has informed the design of the current research.
ii. The procedural methods including recruitment, inclusion and exclusion criteria, description of measures and questionnaires.
iii. Generic statistical methods (details of statistical analyses specific to addressing the aims of each of the results chapters are presented in the relevant chapter).

3.2 General methodology

3.2.1 Design

An observational prospective cohort design was used. This study design requires the outcome to be measured after the exposure (i.e. variables of interest are measured in chronological order) meaning that tentative inferences about causality can be made on the basis of demonstrating temporal precedence (although temporal precedence alone is not a sufficient condition to demonstrate causality). Other advantages of this type of longitudinal study design are that observation of within-subject changes in responses over time controls for confounds related to individual differences[280] and mechanisms of changes in responses can be studied[281].

Cross-sectional studies in people with chronic physical illnesses including coronary heart disease (CHD) have shown a strong association between depression and perseverative negative thinking (e.g. [176, 178]). However the design of these

studies leaves open 3 possibilities: (1) that depression causes perseverative negative thinking, (2) perseverative negative thinking causes depression, or (3) both depression and perseverative negative thinking are related to a third, measured or unmeasured, factor. A prospective study can establish whether one variable precedes another, increasing confidence in the direction of the association, but cannot rule out the involvement of a third factor. Five previous prospective studies in people with CHD were identified in the systematic review presented in Chapter 2. These studies all measured the association of rumination with subsequent depression within the first year after CHD, and follow-ups took place once or twice within 6 weeks to 1 year later. Some studies were limited by small sample size[270], a large number of dropouts[182, 270] and inadequate or incomplete control for confounders. Samples were selected in some studies according to pre-defined criteria related to depression scores[183] or age[182].

The current study was designed to extend the previous research in the following ways:

i. A representative sample of ACS patients, based in the UK, at various stages of treatment, were invited to participate.
ii. Confounding variables known to be associated with depression (age, sex, socioeconomic status, history of depression, social support, severity of cardiac disease) were controlled.
iii. Worry was assessed in addition to rumination, to investigate the association of a broader range of perseverative negative thinking with depression.
iv. Since depression and anxiety are highly comorbid, (and both predict cardiac morbidity e.g.[282]) anxiety was included as an additional outcome measure.
v. To investigate whether perseverative negative thinking is prospectively associated with worse physical health outcomes as well as depression in people with CHD, health-related quality of life was included as an additional outcome measure.

vi. Mechanisms that could explain why rumination is associated with depression in people with CHD were explored (low social support, poor problem solving, reduced instrumental behaviours and negative cognitive biases).

3.2.2 Self-report measures

Consistent with previous research in this area, this study relied on the use of self-report measures of the main predictors and main outcome variables. Despite the disadvantages associated with self-report methods (including incomplete or missing data and response biases, for example) self-report measures were the preferred option because (a) it was not feasible to use other appropriate alternatives e.g. clinician ratings of depression and anxiety, experience sampling measures of rumination and worry[283, 284], and (b) participant burden was minimised by using self-report measures. In addition, the use of self-report measures of quality of life was an advantage because they allowed a more nuanced assessment of physical health status than 'hard' outcomes such as mortality might[285-287].

Self-report measures with demonstrated reliability and validity and that had previously been used in a CHD population were selected where possible (details are given in Section 3.3.2.2).

3.2.3 Timing of follow-up assessments

Assessments were completed by each participant on three occasions: (1) baseline assessments within 6 months of hospitalisation for ACS, (2) follow-up at 2 months after baseline, and (3) follow-up at 6 months after baseline.

How the temporal relationship between depression and CHD evolves is unclear[33, 288] although elevated prevalence of depression has been reported both immediately after and in the year post-MI[289-292]. Therefore, participants for this study were recruited within 6 months of their hospital admission in order that follow-up assessments could be completed within the first year post-ACS.

3.2.4 Reporting

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement makes specific recommendations on the content that should be included in an accurate and complete published report of an observational study[293]. Where possible reporting of the observational prospective cohort study described in this thesis follows STROBE recommendations, with adaptations made to accommodate the thesis-format.

3.3 Procedural methods

3.3.1 Participants

Patients attending specialist inpatient and outpatient cardiology services at the Royal Devon & Exeter hospital between September 2014 and May 2015 were recruited following admission for ACS.

ACS is subcategory of coronary heart disease (CHD) that refers to disorders caused by sudden loss of blood flow to the heart and includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).

The Royal Devon & Exeter hospital is a teaching hospital with over 800 beds that provides specialist and emergency services to a population of approximately 500,000 people in Exeter, East, Mid and North Devon. The hospital employs 7000 staff and manages 100,000 emergency department attendances, 300,000 outpatient attendances, and over 115,000 day case or inpatient admissions per year. There are three cardiology wards including a coronary care unit (CCU), and 7 consultant cardiologists who provide diagnostic and interventional cardiology services including a 24 hour primary angioplasty service.

Patients with suspected ACS access cardiology services at the Royal Devon & Exeter hospital from home or from primary care through two main routes: (i) by emergency admission to the CCU, acute medical unit or cardiology ward, or (ii) by outpatient appointment at a chest pain clinic (Rapid Access Chest Pain Clinic; RACPC).

Patients admitted with a STEMI are transferred directly to the cardiac catheterisation laboratory for percutaneous coronary intervention (PCI) immediately. Those admitted with a NSTEMI or unstable angina undergo angiography, usually within 7 days of admission, and approximately 50% undergo coronary revascularization with PCI. Approximately 30% do not undergo PCI but are managed medically (i.e. receive drug treatments only), and the remainder are transferred to another hospital, locally or nationally, to consider surgical revascularisation with coronary artery bypass graft (CABG) surgery. Patients with STEMI are discharged within 3 days of admission, on average, and other ACS patients are generally discharged the day following PCI. On discharge, patients are typically prescribed drug treatments for secondary prevention that include antiplatelet therapy (e.g. aspirin), beta-blockers, ACE-inhibitors and statins, as per current clinical guidelines[294]. Approximately one third of the patients who enter cardiology services via the RACPC outpatient clinic have angina requiring PCI, and are admitted to a day case cardiology ward for an elective procedure (PCI) approximately 3 months after their outpatient clinic appointment.

ACS patients receive information about their condition, treatment and recovery from a cardiac rehabilitation nurse before discharge from hospital. In addition, all patients who live locally are invited to participate in a community-based cardiac rehabilitation programme which takes place on average 4 to 8 weeks after discharge from hospital. Approximately 50% of patients attend a cardiac rehabilitation programme, consistent with UK participation rates[295].

3.3.1.1 Inclusion criteria

In order to be included in the study participants had to:

i. Be aged 18 years or over.

ii. Have been diagnosed with ACS (including unstable angina or myocardial infarction - MI) within the previous 6 months.

3.3.1.2 Exclusion criteria

Participants were excluded from the study if:

i. For reasons of physical frailty or cognitive impairment it was considered inappropriate to involve them in this research (either by the patients themselves, a carer or a member of the clinical team).

ii. They suffered from severe mental illness (including severe depression with significant suicide risk, or psychosis).

3.3.1.3 Sample size

A sample size calculation indicated that a sample of 113 participants assessed at baseline, 2 months and 6 months would provide 90% power to detect an association of r=0.30 the p=0.05 significance level. An effect size of r=0.30 was chosen since this represents a small degree of association and because levels of association r< 0.30 can often occur by chance alone. A similar previous study in ACS patients found a correlation of r=0.49 between baseline brooding and depression at 3 month follow-up[183] and so r=0.30 represents a conservative estimate. Participants who dropped out were not replaced, therefore a target sample size of 142 participants was chosen to allow for up to 20% attrition during follow-up whilst retaining adequate power.

3.3.2 Measures

3.3.2.1 Sample characteristics

The following background details were collected in order to describe the study population and to allow for statistical control of confounders.

3.3.2.1.1 Socio-demographics

Demographic and lifestyle details were collected using a custom-designed questionnaire. Participants were asked to self-report: age, sex, employment status, occupation, years of education, relationship status, whether they lived alone, smoking status, alcohol use, recreational drug use and frequency of exercise.

3.3.2.1.1.1 Age and sex

Age and sex were recorded from medical notes at the time of recruitment and confirmed with self-reports. Age was collected as a continuous variable and sex as a binary categorical variable. Both were used unchanged in all summary statistics and analyses.

3.3.2.1.1.2 Employment status

Response options for employment status consisted of employed full-time, employed part-time, self-employed, unemployed, retired, homemaker and other. This was collapsed into a binary variable for use in summary statistics by creating two categories: 'in employment' (consisting of employed full-time, employed part-time, self-employed and homemaker) and 'not in employment' (consisting of unemployed, retired and other).

3.3.2.1.1.3 Socioeconomic status

Index of Multiple Deprivation (IMD)[296] decile was derived from the participants current postcode and used as a proxy of socioeconomic status. IMD ranks each of 32,844 small areas or neighbourhoods in England according to their relative level of deprivation. The rank is based on 7 weighted dimensions of deprivation: income, employment, education/skills/training, health and disability, crime, barriers to housing and services, and living environment. The ranks do not quantify the absolute level of deprivation in a small area, but rather provide a means for comparison among areas. The ranks are split into deciles of most to least deprived areas to facilitate this, with lower scores indicating greater deprivation.

For summary statistics the IMD decile was collapsed into a binary variable based on creating two even groups using a median split (median decile = 6). Two categories were created: most deprived (consisting of deciles 1 to 6) and least deprived (consisting of deciles 7 to 10). For regression analyses and multilevel (repeated measures) models the IMD decile was entered to represent socioeconomic status, which was an ordinal variable with a possible range of scores between 1 to 10 (where lower scores indicated greater deprivation).

3.3.2.1.1.4 Years of education

Participants were asked to report an integer to represent the number of years spent in education. For summary statistics years of education was collapsed into two categories consisting of participants who reported 11 or less years of education (equivalent to completion of secondary education or less) or more than 11 years of education (equivalent to further or higher education).

3.3.2.1.1.5 Relationship status

Response options for relationship status consisted of single, married, co-habiting, civil partnership, widowed, divorced/separated and other. This was collapsed into a binary variable for summary statistics by creating two categories: 'in a relationship' (consisting of married, co-habiting and civil partnership) and 'not in a relationship' (consisting of single, divorced/separated, widowed and other).

In addition, a binary response ('yes'/'no') was required to indicate whether a participant lived alone.

3.3.2.1.1.6 Smoking status

Response options for smoking status were yes, no and quitting. For summary statistics these responses were coded into a binary variable ('smoker'/'non-smoker'). Since there were few smokers and few participants attempting to quit smoking if quitting was endorsed this was coded as 'smoker'.

3.3.2.1.1.7 Alcohol use, recreational drug use and frequency of exercise

Response options for alcohol use, drug use and exercise frequency were never, monthly or less, 2-4 times a month, 2-3 times a week, and 4 or more times a week. For summary statistics these were collapsed into binary variables by creating two categories: 'never/infrequent' (consisting of never, monthly or less, and 2-4 times a month) and 'regular' (consisting of 2-3 times a week, and 4 or more times a week).

3.3.2.1.2 Medical and psychiatric history

Where available, objective measures of severity of cardiac disease assessed during hospitalisation were obtained from medical records in order to describe the sample at baseline. Paper and electronic medical records were interrogated to collect the following information: diagnosis (unstable angina/NSTEMI/STEMI), days since index event, severity of cardiac disease (number of diseased coronary vessels, left ventricular function, cardiac enzymes during hospitalisation, blood markers of inflammation during hospitalisation), pre-existing physical health conditions, current medication and history of depression.

3.3.2.1.2.1 Days since index event

The number of days between the admission date of the most recent hospitalisation for ACS prior to baseline assessments and the date baseline assessments were undertaken. For the majority of participants the date of index event was also the admission date of the most recent hospitalisation for ACS prior to recruitment into this study.

3.3.2.1.2.2 Number of diseased coronary vessels

The number of coronary vessels >50% occluded, ranging from 0 to 3, was recorded. There were 4 participants who met criteria for ACS but with all vessels ≤50% occluded. These participants were included in the study and the number of diseased coronary vessels was coded as 0. The medical records contained inconsistent information for 6 participants due to multiple admissions for ACS. For these participants the largest (most severe) number of occluded vessels was recorded.

3.3.2.1.2.3 Left ventricular function

Left ventricular function was represented using a categorical variable created from information contained within the cardiac catheterisation reports: (1) left ventricular ejection fraction (%), or (2) a clinical description of left ventricular function (good function, mild dysfunction, moderate dysfunction or severe dysfunction). Using a single data source for left ventricular function led to a large amount of missing data, so the sources described above were combined. The clinical description was used preferentially where available. Ejection fraction between 55-70% was considered good/normal function, 45-54% mild dysfunction, 36-44% moderate dysfunction and <35% severe dysfunction. This measure of left ventricular function was used for descriptive purposes only.

It was not possible to obtain a measure of left ventricular function from the medical records for 37 participants. In order to maximise the number of cases available for analyses the New York Heart Association (NYHA) functional status classification system[297] was used as an indicator of severity of heart disease in statistical analyses instead, since this was available for almost all participants. The NYHA classification system is a commonly used tool for assessing limitations of physical activity due to chest discomfort, palpitations, shortness of breath and fatigue. As a prognostic tool

the NYHA classification has been shown to predict mortality among patients with heart failure[298-300]. In addition, it has been used as a selection tool and as an outcome measure in clinical research[301], and a self-rated version has been shown to predict hospitalisations, quality of life and mortality[302].

The NYHA classification system consists of four possible response options that represent no limitations, slight limitations, moderate limitations or severe limitations. It was collapsed into a binary variable for summary statistics and analyses by creating two categories: 'no impairment' (consisting of no limitations) and 'some impairment' (consisting of mild, moderate or severe limitations).

3.3.2.1.2.4 Cardiac enzymes and blood markers of inflammation

Where available, blood levels of cardiac enzymes (troponin) during hospitalisation were recorded as measures of disease severity. Presence of troponin indicates injury to the heart muscle, and increasing concentrations of troponin have been associated with greater complexity and severity of coronary artery disease[303]. Where troponin was measured on more than one occasion during hospitalisation the highest value was recorded.

Blood markers of inflammation during hospitalisation (white cell count – WCC, and C-reactive protein - CRP) were also recorded. These markers have also been associated with worse outcomes in patients with coronary heart disease[304, 305]. In addition, inflammation is increasingly being implicated in the development of depression[306-309] including in patients with coronary heart disease[310]. For summary statistics WCC was collapsed into a binary variable consisting of the categories 'normal' ($<12 \times 10^9$/L) or 'raised' ($\geq 12 \times 10^9$/L). CRP was collapsed into a binary variable consisting of the categories 'inflammation present' (>10 mg/L) or 'inflammation absent' (<10 mg/L). Since there were some ambiguous values for CRP (e.g. <1 mg/L) which could not be used as a continuous value but could be categorised, collapsing this variable allowed more cases to be retained for analysis.

3.3.2.1.2.5 Comorbidities

Number and severity of comorbidities was assessed using the Charlson Co-morbidity Index[311, 312]. The index was developed as a prognostic indicator of short term mortality and is an indicator of disease burden[313]. The Charlson Co-morbidity

Index has been shown to predict mortality in patients with coronary artery disease[314]. Weighted scores are summed for 16 conditions, with higher scores indicating greater relative risk of death. One point is given for each of the following: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus without end organ damage and mild liver disease. Two points are given for: diabetes mellitus with end organ damage, moderate to severe kidney disease, hemiplegia, leukemia, malignant lymphoma and non-metastatic solid tumour. Three points are given for moderate to severe liver disease, and six points are given for metastatic solid tumour or AIDS.

The comorbidity score was obtained by harvesting information from the medical records regarding comorbid conditions. Comorbidity score was used for descriptive purposes only, and was collapsed into a binary variable consisting of the categories '1 or less' or '2 or more'.

3.3.2.1.2.6 History of depression

Medical records were inspected to ascertain whether participants had a history of depression (including current depression). Based on this information a binary variable ('yes'/'no') was created.

3.3.2.2 Questionnaire assessments of main predictor and outcome variables

All self-report assessments were combined into one questionnaire pack for ease of use. A copy of the baseline questionnaire pack is provided in Appendix 3.

Each scale was chosen based on its ability to reliably measure the construct of interest, ideally having previously been used in a cardiac population. Since there were multiple constructs of interest, brief versions of some scales were chosen in order to minimise participant burden.

The primary constructs of interest were the predictor variables rumination and worry, and the main outcome measure depression. Secondary outcome measures were anxiety and quality of life. Finally, possible explanatory variables were social support, problem solving, and engagement in instrumental behaviours.

Scale and subscale scores for the main predictors and outcome variables were prepared in accordance with standardised instructions from the authors if available, and are described below. In this section missing items refers to missing, incomplete or ambiguous responses (e.g. 2 response options endorsed).

3.3.2.2.1 The Ruminative Responses Scale – Brooding subscale

The Ruminative Responses Scale (RRS) of the Response Styles Questionnaire[140] is a 22-item self-report measure that assesses the degree to which individuals characteristically respond to depressed mood with ruminative thoughts, feelings and behaviours. The frequency of self-focused, symptom-focused and consequence-focused ruminative thoughts are rated using a 4-point Likert scale ranging from 1 ('almost never') to 4 ('almost always'). The RRS can be decomposed into 'brooding' and 'reflection' subscales. Brooding is a 5-item subscale characterised by 'moody pondering' and omits items that contain overlap with depression and 'neutral contemplation' (i.e. reflection). RRS brooding is the subscale is most often associated with depression. Scores range from 5 to 20, with higher scores indicating greater trait brooding. The RRS brooding subscale has been shown to have good internal consistency (Cronbach α=.77) and test-retest reliability (r=0.62)[315], and correlates with measures of negative mood and onset, maintenance and severity of depression (e.g. [121, 146, 152]) in samples including ACS patients[183].

RRS brooding score was obtained by summing items 5, 10, 13, 15 and 16 of the RRS. Missing items were not replaced, and if any items were missing RRS brooding was coded as missing for that assessment. Internal consistency of the RRS brooding subscale in this sample at baseline was Cronbach α=0.85.

3.3.2.2.2 Penn State Worry Questionnaire

The Penn State Worry Questionnaire (PSWQ)[133] is a 16-item trait measure of frequency, severity and perceived control over worry. Items are rated using a 5-point Likert scale ranging from 1 ('not at all typical of me') to 5 ('very typical of me'). Scores range from 16 to 80, with high scores reflecting high levels of worry. The PSWQ is positively correlated with other self-report and experimental measures of worry[133], and is able to discriminate patients with generalised anxiety disorder from non-anxious samples[316, 317] and from patients with social anxiety disorder[318]. The PSWQ has

good test-retest reliability and high internal consistency in undergraduates, community volunteers and older adults with anxiety disorders (r>0.90, α>0.88)[133, 316, 319]. The PSWQ has been shown to correlate with depression in patients with long term conditions including CHD[178].

Total PSWQ score was obtained by summing all items (with the negatively worded items 1, 3, 8 10 and 11 reverse scored). Missing items were replaced with the mean value of all completed items. If more than 2 items were missing PSWQ was coded as missing for that assessment. Internal consistency of the PSWQ in this sample at baseline was Cronbach α=0.91.

3.3.2.2.3 The Patient Health Questionnaire-8 item version

The 8 item Patient Health Questionnaire (PHQ-8)[320] is a brief self-rated diagnostic and severity measure of depression. The items of the PHQ-8 index the DSM-IV criteria for diagnosis of depressive disorders, but omits a ninth item addressing thoughts of death or self-harm. Respondents rate how often in the past two weeks they have experienced each of eight depressive symptoms, using a 4-point Likert scale ranging from 0 ('not at all') to 3 ('nearly every day'). Items are summed with the total score ranging between 0 to 24. Higher scores indicate greater severity of depression. A cut-point of ≥10 indicates current depression. The PHQ-8 has been used previously in a range of populations including those with CHD e.g.[48, 321].

The psychometric properties of the PHQ-8 are equivalent to the more commonly used 9 item version (PHQ-9), providing scores that are highly correlated (r=0.997) and identical cut-points on the receiver operating characteristics curve for indicating possible cases of depression to the PHQ-9. Sensitivity and specificity of 88% for detecting depressive disorders using the PHQ-8 have been reported[320, 322]. Sensitivity to change of the PHQ-9 has also been established, being comparable to the clinician-rated Hamilton Depression Rating Scale[322]. Internal consistency of the PHQ-8 is high (Cronbach α=0.86)[323]. The PHQ-8 is also recommended in medically ill patients, including CHD patients, since passive thoughts of death (unrelated to suicidal intent) may be more common among this group than in the general population meaning the ninth item may not represent an accurate suicide screen[321].

Total PHQ-8 score was obtained by summing all items. Missing items were replaced with the mean value of all completed items, unless more than 2 items were missing in which case PHQ-8 was coded as missing for that assessment. Internal consistency of the PHQ in this sample at baseline was Cronbach α=0.89.

3.3.2.2.4 Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) is a 21-item self-report measure of anxiety severity[324]. The items focus on somatic or autonomic symptoms of anxiety (such as trembling hands, nervousness, dizziness, sweating) and on subjective and panic-related aspects of anxiety (such as inability to relax, fear of the worst happening). Respondents rate how much they have been bothered by symptoms in the past four weeks on a 4-point Likert scale ranging from 0 ('not at all') to 3 ('severely'). Items are summed to give a single score ranging from 0 to 63. Scores of 10 - 18 represent mild to moderate anxiety, 19 – 29 moderate to severe anxiety, and 30 – 63 severe anxiety. BAI correlates with other measures of anxiety such as the Hamilton Anxiety Rating Scale (r=0.51), the State-Trait Anxiety Inventory (r=0.47 to 0.58) and the anxiety subscale of the Symptom Checklist-90 (r=0.81)[325, 326]. BAI is correlated with depression and negative attributions about the cause of illness in people with CHD[327]. Internal consistency is high (Cronbach α=0.90 to 0.94) and test-retest reliability of the BAI is good (r=0.62 to 0.93).

Among medical populations the somatic symptoms of anxiety may overlap with symptoms related to physical illness. However the BAI was selected for use in this study despite its focus on somatic symptoms due to its relative lack of items addressing cognitive aspects of anxiety (including worry). This is important because inclusion of items related to worry in the BAI could result in a spurious association between worry and anxiety.

Total BAI was obtained by summing all 21 item scores. Missing items were replaced with the mean value of all completed items, unless more than 2 items were missing in which case BAI was coded as missing for that assessment. Internal consistency of the BAI in this sample at baseline was Cronbach α=0.92.

3.3.2.2.5 EuroQol-5D

The EuroQol-5D (EQ5D) is a standardised self-report, assessment of generic health-related quality of life[328, 329]. Respondents are asked to indicate their perceived current health status in relation to difficulties in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a scale with five levels of severity (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems). Scores for each dimension can be reported individually, and an algorithm (based upon weights assigned to each response according to population norms) is provided to facilitate calculation of a single index value based on the profile of responses to the five dimensions[330]. In addition, respondents are asked to rate their current overall health using a 200mm vertical visual analogue scale (VAS), anchored at each end with 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). The EQ5D has been used extensively in cardiovascular research and its validity and reliability in this population is supported (e.g.[331-335]).

Individual EQ5D dimensions were scored from 1 ('no problems') to 5 ('extreme problems'), and if any items were missing the relevant dimension was coded as missing for that assessment. The dimensions were combined into a single index value using the interim UK EQ5D-5L crosswalk value set[330]. If any subscale scores were missing the index value could not be calculated and was coded as missing for that assessment. Index values range from -0.594 to +1 with higher positive values indicating better health state.

The EQ5D VAS required participants to mark a visual analogue scale labelled from 0 – 100 and to write the corresponding value into a box adjacent. If there was a discrepancy between the number marked on the VAS and the number entered in the box, the number entered in the box was used preferentially. If one of the values was missing, the value of the completed item was used. If both values were missing EQ5D VAS was coded as missing for that assessment.

3.3.2.2.6 Seattle Angina Questionnaire

The Seattle Angina Questionnaire (SAQ)[336] is a 19 item coronary disease specific self-report measure of health-related quality of life, including domains related

to both physical and emotional function. The scale is divided into five factors that assess physical limitations, frequency of angina, stability of angina, treatment satisfaction, and disease perception. Responses to all items are made using 5- or 6-point Likert scales, and scores for each of the five factors range from 0 to 100 with lower scores indicating worse health status. The psychometric properties of the SAQ have been established in patients with CHD: internal consistency (Cronbach $\alpha \geq 0.67$) and test-retest reliability is good ($r \geq 0.76$), the scale is responsive to small and large clinical changes (a change of 10 points equates to a change perceptible to patients) and SAQ scores are correlated with clinical measures such as hospitalisation for angina and nitroglycerin refills [336-339].

The SAQ subscales were scored in the following way:

i. *Physical limitations*. Items 1a to 1i were scored 1 to 5 (working from most to least limitations) and standardised using the formula 100*(Mean score – 1)/4. The items in this subscale are grouped into three levels of difficulty (lowest level = items 1a, 1b and 1c; middle level = items 1d, 1e, 1f; highest level = items 1g, 1h, 1i). Missing items were replaced with the mean of the other items of the same difficulty level. If all items of the lowest or highest difficulty level were missing they were replaced with the mean of the middle difficulty level. If all items of the middle difficulty level were missing they were replaced with the mean of the lower and higher difficulty levels. If response option 6 ('Limited or did not do for other reasons') was endorsed the item was treated as missing. If more than 4 items were missing the subscale was coded as missing for that assessment.

ii. *Angina frequency*. Items 3 and 4 were scored 1 to 6 (working from most to least frequent) and standardised using the formula 100*(Mean score – 1)/5. If one item was missing the subscale was calculated without that item.

iii. *Angina stability*. Item 2 was scored 1 to 5 (working from 'much more often' to 'much less often') and standardised using the formula 100*(Response - 1)/4. If response option 6 ('I've had no chest pain over the last 4 weeks') was endorsed the item was assigned a score of 3 (equivalent to response option 3 'About the same').

iv. *Treatment satisfaction*. Items 5, 6, 7 and 8 were scored from 1 to 5 (working from least satisfied to most satisfied) and standardised using the formula 100*(Mean score – 1)/4. For item 5 if response option 6 ('My doctor has not prescribed pills') was endorsed a score of 5 (equivalent to response option 5 'Not bothersome at all') was assigned. Missing items were replaced with the mean of completed items. If more than 2 items were missing the subscale was coded as missing for that assessment.

v. *Disease perception*. Items 9, 10 and 11 were scored 1 to 5 (working from worst to best perceptions) and standardised using the formula 100*(Mean score – 1)/4. Missing values were replaced with the mean of the completed items. If more than 1 item was missing the subscale was coded as missing for that assessment.

3.3.2.2.7 ENRICHD Social Support Inventory

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study Social Support Inventory (ESSI) is a seven-item self-report measure of the perceived availability of social support. The ESSI was designed for use in a trial of a psychosocial intervention for cardiac patients with depression and low social support[340]. The items do not differentiate between sources of support but instead focus on perceived availability of support from any social network member. Respondents rate the availability of support in three domains (emotional support, practical support and informational support) using a 5-point Likert scale ranging from 0 ('none of the time') to 4 ('all of the time'). Items are summed to give a single score, with higher scores indicating greater perceived support. The ESSI has been shown to correlate with the social functioning subscale of the Short Form-36, and ESSI scores were lower in cardiac patients with depression compared to those without depression[192]. Internal reliability (Cronbach α=0.88) and test-retest reliability (r=0.94) of the ESSI are good[192].

The ESSI was unique in this study in that it was the only questionnaire measure included as both a potential confounding variable (in the analyses presented in Chapter 4) and also as a potential mediator variable (in the analyses presented in Chapter 5). Total ESSI score was obtained by summing items 1 to 6. Missing items were

replaced with the mean of all completed items. If more than 1 item was missing ESSI was coded as missing.

3.3.2.2.8 Social Problem Solving Inventory

The Social Problem Solving Inventory-revised short version (SPSI-R:S) is a 25 item self-report scale which assesses 'real-world' problem solving[201]. Respondents rate 25 items describing typical ways in which they might respond when faced with an important problem, using a 5-point Likert scale ranging from 0 ('not at all true of me') to 4 ('extremely true of me'). The items relate to 2 problem solving processes: problem orientation and specific problem solving style. Problem orientation (positive problem orientation or negative problem orientation) refers to cognitive-emotional sets including appraisals, beliefs expectancies and emotional responses that involve the tendency to approach problems in a characteristic way. Problem solving styles (rational problem solving, impulsivity/carelessness style and avoidance style) describe the implementation of activities to solve a specific problem. Positive problem orientation and rational problem solving are constructive dimensions of problem solving, whereas negative problem orientation, impulsivity and avoidance are dysfunctional dimensions of problem solving. Internal consistency (Cronbach $\alpha \geq 0.80$) and test-retest reliability ($r=0.68$ to $r=0.91$) of the SPSI-R:S are good, and normative data is available for healthy adults and clinically depressed populations[201, 341]. SPSI-R:S has been associated with depression and anxiety in a community sample[205], and with severity of depression in a chronically depressed sample[342]. In addition, SPSI-R:S has been shown to correlate with pain intensity and pain frequency in patients with cardiac and non-cardiac chest pain[343].

SPSI-R:S subscale scores were calculated by summing the appropriate items: positive problem orientation=items 4, 5, 9, 13 and 15; rational problem solving=items 12, 16, 19, 21 and 23; negative problem orientation=items 1, 3, 7, 8, and 11; impulsivity-carelessness=items 2, 14, 20, 24 and 25; and avoidance=items 6, 10, 17, 18 and 22. Subscale scores range from 5 to 20 with higher scores indicating greater endorsement of the relative dimension. SPSI-R:S total score was calculated by summing the mean of each of the subscales (where negative problem orientation, impulsivity and avoidance were reversed) and higher scores indicate more

adaptive/positive problem solving. Missing items were replaced with the mean of all other items. If >2 items were missing, SPSI-R:S was coded as missing for that assessment. All SPSI subscales were used in analyses to identify particular areas of problem solving that might be related to both depression and rumination, although it was anticipated that associations with subscales indexing unconstructive aspects of problem solving (negative problem orientation, impulsivity and avoidance) would be strongest. For example, negative problem orientation (defined as a set of dysfunctional schemas that involve the tendency to view problems as threatening, to lack problem-solving confidence and to become easily frustrated when confronted with problems) has been prospectively associated with depressive symptoms[202, 203].

3.3.2.2.9 Pleasant Events Schedule for the elderly

The Pleasant Events Schedule for the elderly (PES-E) is a self-report 20-item short version of the original Pleasant Events Schedule[344] containing only items endorsed by respondents from the original validation sample aged over 50 years[345]. The scale assesses behavioural engagement by asking respondents to indicate on a 3-point scale how frequently they engaged in a variety of pleasant events over the past month (from 0='not at all' to 2='7+ times') and how pleasant they found the activities (from 0='not pleasant' to 2='very pleasant'). PES-E correlates well with the original long version of the Pleasant Events Schedule which has been shown to correlate with daily diary reports of activity (r=0.68 to 0.81) and depression scores[344]. PES-E measured post-MI has been associated with concurrent rumination and depression in a sample of acute coronary syndrome patients[183].

PES-E frequency items were scored 0 to 2 (working from least frequent to most frequent) and total frequency score was calculated as the mean of all completed frequency items (excluding missing items). Similarly, PES pleasantness items were scored 0 to 2 (working from least pleasant to most pleasant) and total pleasantness score was calculated as the mean of all completed pleasantness items (excluding missing items). The 'obtained pleasure' score for each item was obtained by multiplying the frequency x pleasantness ratings. Where relevant frequency or pleasantness items were missing, obtained pleasure was coded as missing for that item. Total obtained pleasure was calculated as the mean of all obtained pleasure

scores. Higher PES-E subscale scores indicated greater frequency and pleasantness of pleasant events, and greater obtained pleasure.

3.3.2.3 Assessment of negative cognitive biases

3.3.2.3.1 Memory bias

Preferential memory for self-referent negative information was assessed using an incidental recall task (based on that of Teasdale & Dent, 1987[346]). A list of 26 adjectives were read aloud and immediately after each adjective the participant was asked to rate whether the word was self-descriptive (answering 'yes' or 'no' for each adjective). Immediately afterwards, participants were given up to 3 minutes to verbally recall as many of the words as possible. Of the 26 adjectives, 12 referred to negative traits (deficient, failure, inadequate, incompetent, inferior, pathetic, stupid, unloved, unwanted, useless, weak, worthless), 12 referred to positive traits (capable, confident, dynamic, entertaining, important, optimistic, outgoing, respected, skilful, sociable, successful, valuable) and the first and last words were neutral filler words (ordinary, modern). Depressed individuals have been shown to endorse a higher number of negative adjectives and to recall more self-referent negative words using this task[346], in line with other research showing biased recall of negative over positive material in people with depression[220, 347, 348]. Recall of negative self-referential words has also been shown to predict depressive episodes in people with a history of recurrent major depression[349].

For descriptive purposes outcome measures were: (a) number of positive and negative adjectives endorsed, (b) number of positive and negative adjectives recalled, (c) number of negative adjectives recalled as a percentage of the total number recalled (excluding filler words), (d) number of endorsed (self-referential) positive words recalled, (e) number of endorsed (self-referential) negative words recalled, and (f) number of endorsed negative words recalled as a percentage of the total number of endorsed words recalled (excluding filler words). For statistical analyses the number of negative words endorsed, the percentage of negative words recalled and the percentage of endorsed negative words recalled were used.

3.3.2.3.2 Interpretation bias

A lexical ambiguity task based on that of Halberstadt et al. (1995)[350] was used to assess interpretation bias. A list of 19 adjectives was read aloud. Immediately following each adjective the participant was instructed first to give a brief sentence that included the word and then to verbally give the spelling of the word. Participants were encouraged to respond as quickly as possible after hearing each word, and to give the first answer that came to mind. The adjectives were homophones with one spelling related to a neutral meaning and another spelling related to an affective meaning. Affective meanings related to happiness (10 items: bridal-bridle, dear-deer, heal-heel, hymn-him, peace-piece, presents-presence, pride-pried, rose-rows, sweet-suite, won-one) or sadness (8 items: banned-band, bored-board, die-dye, fined-find, missed-mist, mourning-morning, pain-pane, poor-pore).

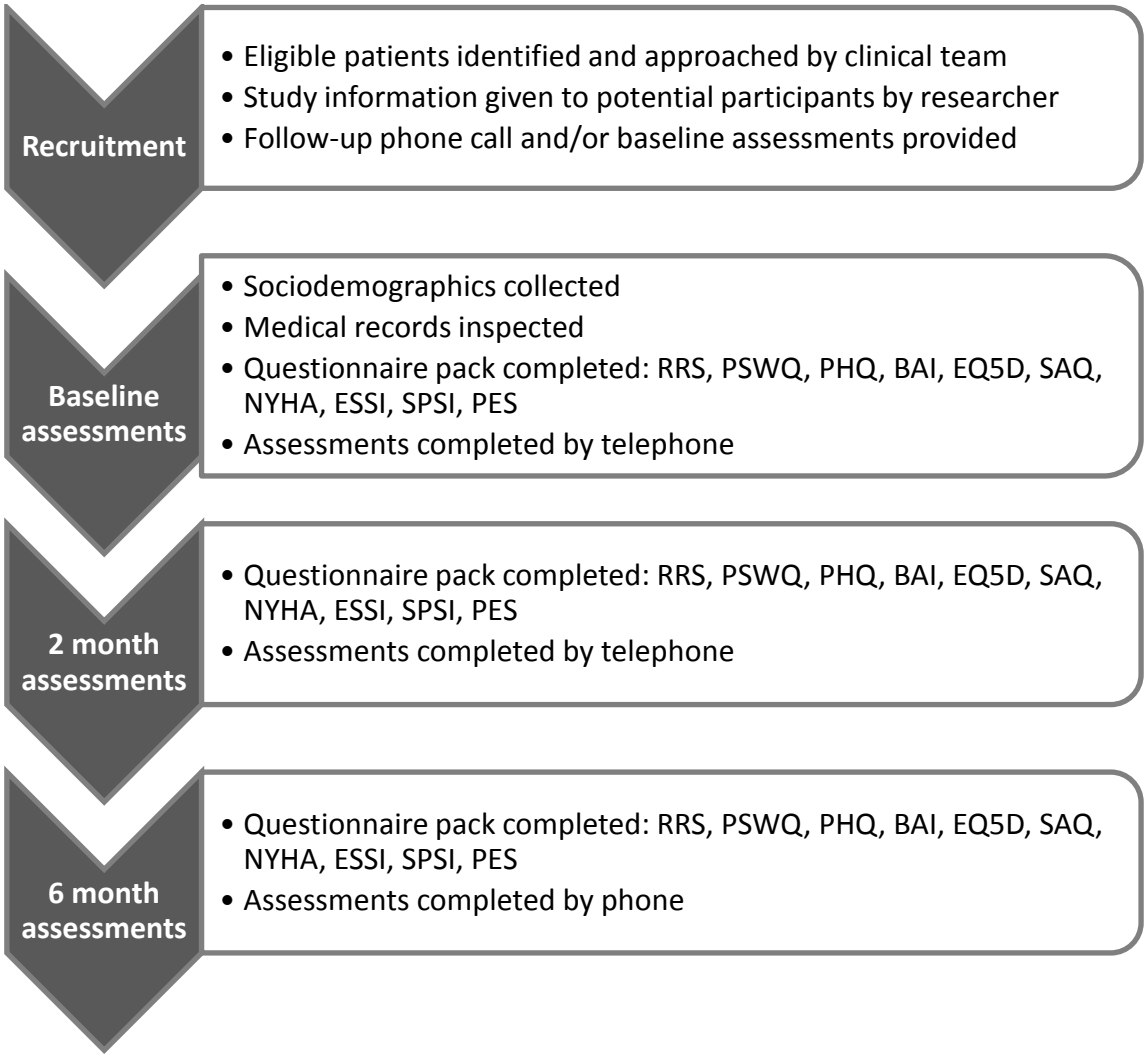
Each adjective was coded by the researcher according to whether the affective meaning or the neutral meaning had been accessed. If the definition and spelling given did not match the definition was preferentially used to code that adjective. If any answer was ambiguous that item was excluded. For descriptive purposes and statistical analyses the percentage of words for which the affective meaning was accessed (with reference to the percentage for which the neutral meaning was accessed) was calculated for both happy and sad homophones.

In a sample of healthy young adults a sad mood induction resulted in more affective meanings being accessed for sad homophones using this task[350].

3.3.3 Procedure

The flowchart in Figure 3.1 illustrates the main stages of the study.

Figure 3.1: Flowchart of study procedures



3.3.3.1 Identification of eligible patients

Eligible patients were identified by a member of the clinical team during inpatient admission for ACS or at outpatient follow-up with a member of the cardiac rehabilitation team. Eligible patients were initially approached by a member of the

clinical team, and asked to consent verbally to be contacted about the study by the researcher. If they agreed they were signposted to the researcher.[1]

Each signposted patient was contacted by the researcher in the cardiology department. A short verbal description of the study was provided along with a brief written information sheet introducing the researcher and the study (see Appendix 4). Patients were asked to provide their name and telephone number if they were willing to receive further information about the study.

Patients who agreed to receive further information about the study were contacted in the cardiology department if time and opportunity permitted or at home by telephone, and were given a verbal description of the study and opportunity to ask questions. Patients who expressed an interest in participating after the study had been fully explained to them were given an information sheet (Appendix 5), a consent form (Appendix 6), a questionnaire pack containing baseline assessments and a freepost envelope (for patients contacted by telephone arrangements were made to send these by post).

Where it was not possible to ask eligible patients to consent verbally to be contacted about the study (e.g. because they were admitted and discharged before a member of the clinical team was able to speak to them, or they were not well enough on the ward), a letter of invitation from the consultant cardiologist was posted and patients were asked to contact the researcher directly or to complete a reply slip indicating that they agreed to be contacted by telephone in order to receive details about the study.

3.3.3.2 Consent and participation

Patients who subsequently decided to participate in the study were asked to sign the consent form and return it with the pack of self-rated assessments in the freepost envelope provided. The date of completion was recorded on the front of the pack by the participant.

[1]The clinical team recorded age and sex of all participants approached to allow a crude comparison of the participants who participated and those who declined to participate.

Participants were encouraged to contact the researcher for assistance completing the consent form or assessments if needed. In the event that a participant who expressed an interest in participating did not return the consent form and self-rated assessments a reminder phone call was made after approximately two weeks, as agreed with the participant.

Once the consent form and questionnaire pack was received by the researcher, the participant was telephoned in order to complete the memory and interpretation bias tasks.

3.3.3.3 Follow-ups

At two months and six months after completion of the baseline assessments, another pack of self-rated assessments was sent to each participant by post. If a participant failed to return the self-rated assessments at either of these follow-ups a reminder phone call was made after approximately two weeks, as previously agreed with the participant. Once the 2 month and 6 month questionnaire packs were received by the researcher the participant was again contacted by telephone to complete the memory and interpretation bias tasks.

3.3.4 Ethical review and research site approval

This study was reviewed by the NRES Committee South West – Frenchay Research Ethics Committee, and received a favourable ethical opinion on 5th August 2014 (reference: 14/SW/0133).

Permission to recruit participants at the Royal Devon & Exeter hospital Cardiology department was granted by the Research & Development directorate of the Royal Devon & Exeter NHS Foundation Trust on 13th August 2014 (reference: 1502058).

3.4 Statistical methods

3.4.1 Data management

Raw data was checked for accuracy, completeness and legibility and prepared as described in Section 3.3.2. All analyses were conducted using Stata SE statistical

software release 14 (StataCorp. 2015; College Station, TX). Before any analyses were conducted, the following preliminary steps were taken.

3.4.1.1 Missing data analysis

Missing data at case and scale/subscale level was identified for all predictor, outcome and explanatory variables and summaries are presented in the relevant results chapters.

Methods for dealing with missing data in specific cases are described in the relevant results chapters. In general for correlations and other tests within a single assessment time pairwise deletion was used (i.e. available case analysis) in order to maximise the number of cases. For analyses that used data from multiple assessment times listwise deletion was used (i.e. data was included only for participants who completed all assessments).

3.4.1.2 Collapsing response options for categorical variables

In order to simplify the analysis of some categorical sociodemographic and disease variables with multiple response options, the levels of response were collapsed to create binary variables. Where relevant this is described in Section 3.3.2.

3.4.1.3 Detection of outliers

Minimum and maximum values of each variable at each assessment time were inspected, and a boxplot of each variable was produced to visually screen for potential outliers. For illustration purposes an example is included in Appendix 7 (boxplots for the main predictors and outcome variables at baseline). For the majority of plots there were a small number of values lying outside of the whiskers indicating potential outliers. Inspection of the individual data points indicated that these were plausible values for the relevant measure and in order to maximise the amount of data available for analyses these cases were retained.

3.4.1.4 Normality

The distribution of each variable was inspected using histograms and normal-probability plots. In addition, a Shapiro-Wilk test was conducted for each continuous variable to indicate whether the distribution was normal. Results of the Shapiro-Wilk

tests are summarised in Appendix 8. The majority of variables had a distribution that was significantly different from normal.

Several transformations were applied (square, square root, log, inverse, cubic) to correct the distributions, although none were successful. Therefore, non-parametric statistical tests were used for bivariate analyses. Since the multivariate statistical analyses used in this thesis rely upon normally distributed residuals rather than normally distributed raw scores, evaluation of the distribution of residuals is dealt with in the relevant results chapters.

3.4.2 Descriptive statistics

Overall descriptive statistics (mean and standard deviation, median and interquartile range, or number and percentages, as appropriate) were prepared for all sociodemographic and disease variables, predictors (rumination and worry), outcome variables (depression, anxiety and quality of life) and explanatory variables (social support, problem solving, instrumental behaviours, memory bias and interpretation bias). These are presented in the relevant results chapters.

3.4.3 Inferential statistics

Statistical analyses are described in detail in the relevant results chapters. Briefly, the key analyses are summarised below:

i. Chapter 4 presents a series of staged multivariable and ordered logistic regression analyses investigating prospective associations of rumination and worry with subsequent depression, anxiety and quality of life. These analyses are extended with the use of multilevel mixed-effects linear regression analyses (multilevel (repeated measures) models) in order to account for the nested structure of the longitudinal data involved.
ii. Chapter 5 presents a series of mediation analyses exploring social support, problem solving, instrumental behaviours and cognitive biases as potential mechanisms of the prospective association between rumination and worry with subsequent depression, anxiety and health-related quality of life. Mediation was tested by evaluating causal steps with multiple regression analyses, and

was combined with a bootstrapping approach to test the significance of indirect effects.

Chapter 4 Cohort study results - Part I: Prospective association of rumination and worry with depression, anxiety and worse quality of life

4.1 Chapter outline

The primary aim of this observational prospective cohort study was to investigate whether perseverative negative thinking predicts the development of depression, anxiety and poor physical health outcomes in people with coronary heart disease (CHD).

Detailed methods were presented in Chapter 3. This data chapter presents:

i. The hypotheses under test that pertain to the main aims of the study.
ii. A description of the statistical methods used.
iii. Detailed results.
iv. A brief summary of findings.

Discussion of the methods and findings with reference to strengths, weaknesses, comparison with existing literature and implications for future research is combined with that relating to the next results chapter (Chapter 5), and is presented in the general discussion chapter (Chapter 6).

4.2 Hypotheses

The primary hypotheses are that:

i. In patients with recent acute coronary syndrome (ACS), rumination and worry measured following hospitalisation will predict depression at six month follow-up, after controlling for other confounding variables including baseline levels of depression.
ii. In patients with recent ACS, rumination and worry at a previous assessment time (*t*) will predict depression at the next assessment time (*t*+1), after controlling for other confounding variables.

The secondary hypotheses are that:

iii. In patients with recent ACS, rumination and worry measured following hospitalisation will predict anxiety and worse quality of life at six month follow-up, after controlling for other confounding variables including baseline levels of anxiety and worse quality of life.

iv. In patients with recent ACS, rumination and worry at a previous assessment time (*t*) will predict anxiety and worse quality of life at the next assessment time (*t*+1), after controlling for other confounding variables.

A note on abbreviations

The measures used to assess predictors, outcomes and covariates of interest were described fully in Chapter 3. Throughout this chapter the following abbreviations will be used: brooding ('RRS brooding'), worry ('PSWQ'), depression ('PHQ'), anxiety ('BAI'), general health-related quality of life ('EQ5D'), cardiac disease-specific quality of life ('SAQ'), social support ('ESSI'), socioeconomic status ('IMD').

4.3 Statistical analysis

4.3.1 Sample characteristics

The number of participants, demographic variables (age, sex, years of education, employment status, relationship status, whether the participant lives alone, socioeconomic status, history of depression, smoking status, alcohol use, recreational drug use, exercise frequency, and perceived availability of social support) and disease-related sample characteristics (diagnosis, days since index event, left ventricular function, New York Heart Association (NYHA) functional classification, number of diseased vessels, comorbidity score, troponin, C-reactive protein and white cell count) were summarised using descriptive statistics.

Age and sex of individuals who participated in the study were compared to those who declined to participate using the Mann-Whitney U test for age, and the Chi-Square test for sex. Differences in sample characteristics according to depression status at baseline were explored in a similar way to allow inferences about the

representativeness of the sample according to features related to depression to be made (where depressed PHQ≥10 and non-depressed PHQ<10).

4.3.2 Description of baseline data

The main predictor variables (RRS brooding and PSWQ) and main outcome variables (PHQ, BAI, EQ5D visual analogue scale - VAS, EQ5D index value, EQ5D subscales mobility, self-care, usual activities, pain, anxiety/depression and SAQ subscales physical limitations, angina frequency, angina stability, treatment satisfaction, disease perception) at baseline were summarised using descriptive statistics. Missing data were summarised, and key characteristics (age, sex, baseline PHQ) of cases with and without missing data were compared using Mann Whitney U or Chi-Square tests.

Differences between predictor variables and main outcomes according to depression status at baseline were explored using Mann Whitney U or Chi-Square tests (depressed PHQ≥10, non-depressed PHQ<10).

Spearman's rho or Kendall's Tau-b correlations, as appropriate, were used to explore bivariate associations among baseline sample characteristics with main predictors (RRS brooding and PSWQ) and main outcome variables (PHQ, BAI, EQ5D and SAQ). For dichotomous variables related to sample characteristics, Mann-Whitney U tests were used instead to look at differences in predictor and outcome variables at different levels of the sample characteristics.

Spearman's rho or Kendall's Tau-b correlations were also used to explore bivariate associations among main predictors (RRS brooding and PSWQ) and main outcome variables (PHQ, BAI, EQ5D and SAQ) at baseline.

4.3.3 Description of 2 month and 6 month data

Timing of 2 month assessments were described using number of days from baseline assessments. The number of participants who completed (or did not complete) 2 month assessments were noted, and reasons for non-completion were listed.

Sample characteristics at baseline along with main predictor and outcome variables at baseline, of completers compared to non-completers at 2 months, were compared using Mann-Whitney U or Chi-Square tests as appropriate.

Similar to baseline assessments, the main predictor variables and main outcome variables at 2 months were summarised using descriptive statistics, and missing data was described. Key characteristics (age, sex, baseline PHQ) of cases with and without missing data at 2 months were compared using Mann Whitney U or Chi-Square tests.

Data pertaining to 6 month assessments were treated in the same way as data pertaining to 2 month assessments, as described above.

4.3.4 Changes in main predictors and outcomes over time

To investigate changes over time in each of the main predictors and outcome variables a series of Friedman's tests with assessment time as the independent variable were used, combined with Wilcoxon's tests for post-hoc exploration of significant main effects.

4.3.5 Prospective associations of baseline predictors with 6 month outcomes

To investigate if baseline brooding or worry predicted depression, anxiety or worse quality of life at 6 months a series of simple correlations, simple regression analyses and staged multivariable regression analyses were conducted. Bivariate correlations and simple regression analyses were conducted first to directly investigate the associations of interest, and staged multivariable models were conducted next in order to explore the impact of adding important covariates to the models.

4.3.5.1 Correlation of baseline predictors with 6 month outcomes

Spearman's rho or Kendall's tau correlations, as appropriate, were used to explore bivariate associations between the predictor variables (RRS brooding and PSWQ) at baseline, with the main outcome variables (PHQ, BAI, EQ5D and SAQ) at 6 months.

Since some attrition was anticipated during the study a sensitivity analysis was conducted by comparing bivariate correlations between the predictors and main outcomes at baseline for the participants who remained in the study at 6 months with baseline correlations for the participants who did not complete the study, in order to provide some indication whether there were any systematic differences in the strength or direction of observed associations between completers and non-completers.

4.3.5.2 Prospective associations using multiple regression

First, in simple regression models, baseline RRS brooding or baseline PSWQ (as appropriate depending on the model) was entered as the predictor variable, and in separate models the outcome variables were 6 month depression (PHQ), anxiety (BAI), general health-related quality of life (EQ5D VAS and EQ5D index value) and cardiac disease-specific quality of life (SAQ subscales physical limitations, angina frequency, angina stability, treatment satisfaction, disease perception). Equivalent simple ordered logistic regression analyses were conducted for the EQ5D subscales mobility, self-care, usual activities, pain and anxiety/depression.

Next, in separate staged multivariable regression models the outcome variables were 6 month depression (PHQ), anxiety (BAI), general health-related quality of life (EQ5D VAS and EQ5D index value) and cardiac disease-specific quality of life (SAQ subscales physical limitations, angina frequency, angina stability, treatment satisfaction, disease perception). Predictors were entered in blocks in successive steps. In order to control for the effects of demographic and other variables known to be associated with depression (age, sex, socioeconomic status, perceived availability of social support, history of depression[2], severity of cardiac disease[3]) these were entered in the first step. These variables were chosen as covariates because they have been shown to predict depression in people with coronary heart disease (e.g. [30, 71, 192]). Baseline scores for the outcome variable (e.g. baseline depression) were entered separately into the second step of the model in order to control for them and to isolate the extent to which baseline scores on the outcome variable would predict subsequent scores on the same variable at 6 months. Finally, baseline brooding (RRS brooding) or baseline worry (PSWQ), in separate models, was entered as a predictor variable in the third step. Equivalent ordered logistic multiple regression models were used as an alternative to staged multivariable regression for the EQ5D subscales mobility, self-care, usual activities, pain and anxiety/depression.

Raw or prepared scores (as described in Chapter 3) for continuous predictor and outcome variables (RRS brooding, PSWQ, PHQ, BAI, EQ5D VAS, EQ5D index value,

[2]History of depression was omitted from models where quality of life was the outcome measure.
[3]Using baseline NYHA classification in preference over left ventricular function, as more data was available for NYHA therefore allowing number of complete data sets for analysis to be maximised.

SAQ subscales, age, social support[4]) were used in the models. Binary categorical variables (sex, history of depression, NYHA functional classification) were entered as 0/1. Index of multiple deprivation (IMD) decile was entered to represent socioeconomic status.

The user-written Stata command *hireg[351]* was used to perform staged multivariable regression. The 'nomiss' option was specified in order to ensure listwise deletion of cases with missing data (i.e. to ensure that all steps of a given model were estimated based on the same cases as all other steps).

4.3.5.3 Regression assumptions and diagnostics

Standard regression diagnostics were used to investigate compliance with test assumptions:

i. The distribution of standardised residuals for each model were inspected using histograms, and the Shapiro-Wilk test was used to detect deviations from normality.

ii. The Breusch-Pagan test was used to confirm that the variance of residuals at each level of the predictors were equal (homoscedasticity).

iii. The Durbin-Watson test was used to detect non-independence of residuals (autocorrelation). For samples in the region of N=100, Durbin-Watson <1.34 for a model with 9 predictor variables, or <1.36 for a model with 8 predictors, was taken to indicate no autocorrelation[352].

iv. Variance inflation factor (VIF) was calculated for all predictor variables in each model, and VIF >10 was taken to indicate multicollinearity[353].

Finally, the fit of each model to the sample data was evaluated. Studentized residuals were inspected using stem and leaf plots to detect potential outliers, plus >5% studentized residuals outside the range <-2 or >2 were taken to indicate that a model may contain outliers[354]. Cook's distance >1 was used to indicate influential cases[355].

[4]Assessed using the *ENRICHD* study Social Support Inventory (ESSI).

4.3.6 Prospective associations of predictors and outcomes at other assessment times

Prospective associations of baseline predictors with 6 month outcomes were deemed to be the most conservative hypothesis test owing to the greatest time elapsed between assessments. However, associations of baseline predictors with 2 month outcomes, and of 2 month predictors with 6 month outcomes were also investigated using the same methods as described in the previous section (Section 4.3.5), in order to explore the stability of prospective associations at other combinations of assessment times.

4.3.7 Prospective associations of predictors and outcomes using multilevel (repeated measures) models

Multilevel modelling is an extension of conventional regression that allows for the analysis of associations among data with nested structures, including from longitudinal studies where an individual contributes data at multiple times (i.e. data from different assessment times is nested within the individual). Acknowledging the nested structure of such data is an advantage because it could be argued that multiple observations from the same participant are correlated, which violates the assumption of independence of conventional regression approaches.

A further benefit of using multilevel models for the analysis of longitudinal data is that it maximises the amount of data available for analysis since, in contrast to other regression approaches that are based on the use of complete cases only, all available observations are included in the analysis even where there are missing data (e.g. because a participant missed an assessment, or withdrew from the study). Use of all cases increases power to detect effects, and improves the representativeness of the sample included in analyses.

To extend the staged multivariable regression models previously described, and to investigate if worry or brooding at one assessment time predicted depression, anxiety or worse quality of life at a subsequent assessment time, while properly allowing for the effects of within-participant correlations between outcome variables at each of the assessment times, a series of multilevel mixed-effects linear regression analyses (multilevel (repeated measures) models) were conducted.

Multilevel modelling was conducting using the Stata *mixed* command, and proceeded in the following steps:

i. Definition of data structure.

ii. Hypothesis tests for random intercept variance.

iii. Specification of random coefficients ('growth curve') models.

iv. Selection and evaluation of models.

4.3.7.1 Definition of data structure

The data structure was declared such that assessment time (baseline, 2 months, 6 months) was the level 1 variable (coded sequentially as assessment 1, 2 or 3) and participants were the level 2 clusters (since in theory each participant could contribute a value of the outcome variable at each assessment time).

4.3.7.2 Hypothesis test for random-intercept variance

If a model does not contain random intercepts (in this case, between-participant variance in means) then multilevel modelling is not necessary since all clusters can be treated as equivalent and a single level ('ordinary') regression model is adequate. Therefore, a series of variance components models were used to investigate whether multilevel (repeated measures) models were justified.

Participants were declared as random clusters with repeated measures of the relevant outcomes (PHQ, BAI, EQ5D and SAQ) as the outcome variable. The likelihood-ratio test was used to indicate whether there was significant between-subjects variance in means (i.e. random intercepts), and intra-class correlation coefficients (ICC) were used to estimate the amount of variance attributable to within-participant correlations. Further multilevel (repeated measures) models were specified only where the likelihood-ratio test of the variance components model was significant and ICC >10%.

4.3.7.3 Specification of random coefficients ('growth curve') models

Random coefficients models are multilevel (repeated measures) models that allow random slopes to be specified in addition to random intercepts. In longitudinal models where participants are declared as clusters nested within occasions these are known as 'growth curve' models, and allow for between-participant variation in trajectories of the outcome variable over time (random slopes).

A series of growth curve models of increasing complexity were used to investigate the prospective association of rumination or worry with subsequent depression, anxiety and worse health-related quality of life. Random intercepts and random slopes were specified in each of these models for the level 1 unit (assessment time) and level 2 clusters (participants). The models are described below, and represent the following questions:

i. Does the outcome variable at *t* predict the outcome variable at *t*+1?[5]
ii. Does the predictor variable at *t* predict the outcome variable at *t*+1, after controlling for previous responses on the outcome variable?
iii. Does the predictor variable at *t* predict the outcome variable at *t*+1, after controlling for previous responses on the outcome variable and other confounders?

In all of these models, since the focus of the research question was to investigate *prospective* associations between predictors at one assessment time with outcomes at a subsequent assessment time, autoregressive lag-1 variables (n-1, where the current response was regressed on the previous response) were incorporated.

The simplest models ('i', above) consisted of two fixed effects: time and a lag variable (n-1) to represent the previous response of the outcome variable. Similar to the staged multivariable regression models described previously, the outcome variables (in separate models) were PHQ, BAI, EQ5D and SAQ.

Next, these models were extended ('ii', above) to include a fixed lag variable (n-1) to represent the main predictor (RRS brooding or PSWQ) at the previous assessment time.

Finally, consistent with the staged multivariable regression models described earlier, other covariates (age, sex, socioeconomic status, social support, history of depression[6] and severity of cardiac disease) were added to the models as fixed variables ('iii', above). Patients were recruited from both inpatient and outpatient settings and there was a degree of variability in time between index event (defined here as the admission date of the most recent hospitalisation for ACS) and baseline

[5]Where *t* refers to assessment time.
[6]History of depression was omitted from models where quality of life was the outcome measure.

assessments. To investigate whether time from index event would predict any of the outcomes, the number of days from index event to baseline assessment was included as an additional covariate. In addition, in order to explore whether differences in the time from baseline to completion of 2 and 6 month assessments would predict any of the outcomes, a sensitivity analysis was performed whereby the fully adjusted multilevel (repeated measures) models were conducted both with and without the number of days from baseline as an additional covariate.

All multilevel (repeated measures) models assumed linear associations and were estimated using maximum likelihood estimation with the covariance structure set to unstructured.

In place of standard multilevel (repeated measures) models, random-coefficient proportional-odds models and random-intercept proportional-odds models were used for the EQ5D subscales mobility, self-care, usual activities, pain and anxiety/depression, proceeding in the same steps as described above for the continuous outcome variables and using the user-written Stata command *gllamm[356]*).

4.3.7.4 Selection and evaluation of multilevel (repeated measures) models

Estimates produced by the growth curve models described in the previous section were stored and in each case compared to estimates produced by an alternative, nested, model that omitted the random effect of assessment time (random intercept model). A likelihood ratio test was used to compare the two models, and in doing so to indicate whether the random slope for time was required. If the likelihood ratio test was significant the model with random slope for time (growth curve, or random coefficient model) was retained, and if the likelihood ratio test was not significant the random slope was deemed unnecessary and the alternative model with random intercept only (random intercept model) was used.

The overall significance of the selected model was assessed using the Wald test, and the significance of individual predictors was derived from z tests associated with each coefficient.

4.3.7.5 Assumptions of multilevel (repeated measures) models

Following estimation and selection of the preferred models, relevant assumption checks were performed. First, the distribution of level 1 and level 2

residuals were visually inspected using histograms, and normality was statistically assessed using the Shapiro-Wilk test. Second, homoscedasticity (homogeneity of residual variance) at all levels of the explanatory variables and within clusters (i.e. within participant) was assessed by visual inspection of residuals vs. fitted values plots.

4.3.8 Post-hoc analyses

In order to explore the findings in greater depth, the following post-hoc analyses were conducted:

i. Some previous studies suggest that the association of brooding with depression may be weaker in samples without elevated depressive symptoms e.g.[118, 183]. Since there were low levels of depression in this study this could explain the weak association in some analyses presented here between brooding and depression. An exploratory subgroup analysis was performed to compare the strength of bivariate correlations between brooding with PHQ in (a) participants with PHQ scores ≥10 at baseline (depressed subgroup), and (b) participants with PHQ scores of <10 at baseline (non-depressed subgroup).

ii. The association of rumination and depression could be bidirectional. In order to investigate the prospective reverse association (i.e. the association of baseline depression with 6 month brooding), first a simple regression analysis was conducted with baseline depression as the predictor and 6 month brooding as the outcome variable. Next, in order to control for covariates (age, sex, socioeconomic status, social support, history of depression, and severity of cardiac disease) a staged multivariable regression analysis was performed with the covariates entered in the first step, baseline brooding entered in the second step and baseline depression entered in the final step.

iii. Low perceived availability of social support was a strong predictor of the majority of outcomes including depression. The findings of multilevel (repeated measures) models showed that brooding was a significant predictor of subsequent depression. However after covariates including social support were entered into the model, the association of brooding

with subsequent depression became marginally non-significant. It is possible that social support could confound the association of brooding and depression. In order to better understand the association between brooding and social support, the multilevel (repeated measures) model with a lag variable for RRS brooding as the main predictor and PHQ as the outcome was repeated without including social support as a covariate (all other aspects of the model remained unchanged).

4.4 Results

4.4.1 Sample

The flow of participants through each stage of recruitment and participation in the study is summarised in Figure 4.1.

4.4.1.1 Characteristics of individuals invited to participate

A total of 397 individuals (163 inpatients, 169 outpatients, and 65 contacted by letter) were invited to participate in the study. The average age of those approached was 67.3 years (SD 12.6 years, range 25 – 96 years), and 74.5% were male (290 male, 100 female, 5 unknown). Females invited to participate were significantly older than males invited to participate (70.5 years vs. 66.2 years; z=-2.99, p=0.0028).

4.4.1.2 Characteristics of participants at baseline

169 individuals who met the inclusion criteria consented to participate and returned the baseline questionnaire measures. Demographic and disease variables for all participants who completed baseline questionnaire measures are summarised in Table 4.1.

The mean age of participants was 66.8 years and 77.5% were male. Females were significantly older than males (70.0 years vs. 65.9 years; z=-2.11, p=0.0353). Just over one quarter of participants had a diagnosis of angina, and the remaining three quarters had a diagnosis of myocardial infarction, split approximately evenly between ST-Elevation Myocardial Infarction (STEMI) and non-ST-Elevation Myocardial Infarction (NSTEMI). Clinical records indicated that approximately half of the sample had good left ventricular function, and approximately half of the sample reported no functional impairments related to ACS. Approximately three quarters of participants were in a

relationship and lived with another person, and almost two thirds were not in employment.

4.4.1.3 Comparison of participants with individuals who declined to participate

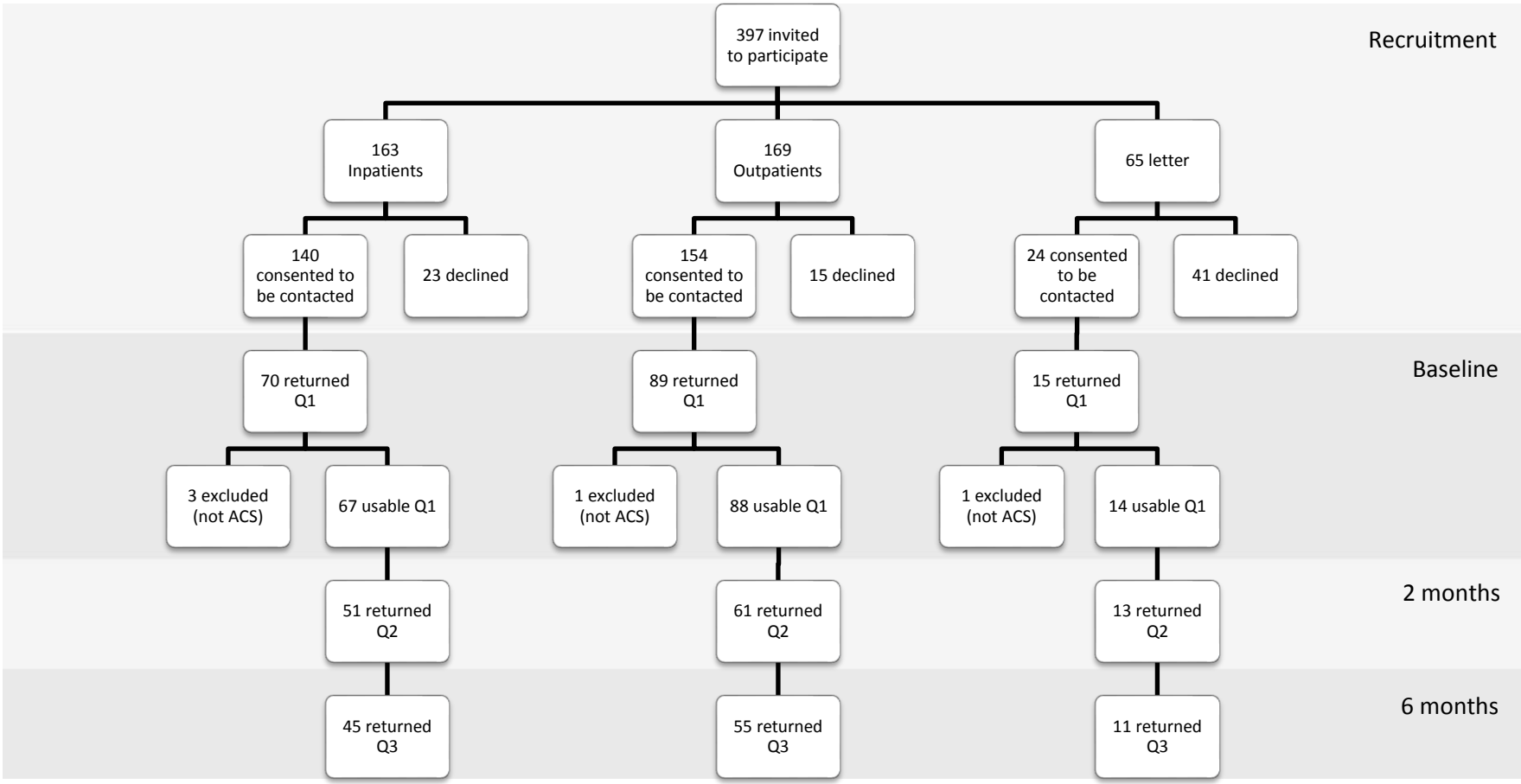
There was no difference in age between participants who returned the baseline questionnaire measures compared with individuals who were invited but did not participate in the study ($z=-0.68$, $p>0.05$). Similarly, there was no difference in the proportion of males and females who returned the baseline questionnaire measures compared with those who were invited but did not subsequently participate in the study ($\chi^2(1)=1.28$, $p>0.05$). Other comparisons were not possible because other sample characteristics at approach were unknown (this information could only be accessed if an individual consented to participate).

4.4.1.4 Comparison of depressed and non-depressed participants at baseline

There were 143 participants who were not depressed at baseline (PHQ<10) and 24 who were depressed at baseline (PHQ≥10) i.e. 14.4% of the sample were depressed at baseline.

Comparison of demographic variables showed that the subgroup of participants with depression at baseline were younger and more of them were not in a relationship, lived alone, had a history of depression, were smokers, exercised less frequently and had worse socioeconomic status than the group without depression at baseline (results of these analyses are summarised in Appendix 9). Comparison of disease related variables showed that there were no group differences in diagnosis, left ventricular function, days since index event, number of comorbidities, troponin, or white blood cell count. However, more of the subgroup of participants with depression had raised C-reactive protein (CRP) during hospital admission compared to those without depression (results of these analyses are summarised in Appendix 9).

Figure 4.1: Flow of participants through recruitment and study completion



Q1=baseline assessments, Q2=2 month assessments, Q3=6 month assessments.

Table 4.1: Sample characteristics at baseline

		Baseline sample n=169			
		N	%	Mean	SD
Demographic variables					
Age (years)		169		66.78	11.60
Sex	Male	131	77.51		
	Female	38	22.49		
Years of education	Secondary *(11 years or less)*	58	38.16		
	Higher *(more than 11 years)*	94	61.84		
Employment status	In employment *(full-time, part-time, self- employed, homemaker)*	65	38.46		
	Not in employment *(unemployed, retired, other)*	104	61.54		
Relationship status	In a relationship *(married, co-habiting, civil partnership)*	122	72.62		
	Not in a relationship *(single, divorced/separated, widowed, other)*	46	27.38		
Lives alone	Yes	125	25.60		
	No	43	74.40		
Index of multiple deprivation	Most deprived *(deciles 1 to 6)*	82	50.31		
	Least deprived *(deciles 7 to 10)*	81	49.69		
History of depression	Yes	16	9.47		
	No	153	90.53		
Smoking status	Smoker	18	10.71		
	Non-smoker	150	89.29		
Alcohol use	Never / infrequent *(once a week or less)*	95	57.23		
	Regular *(twice a week or more)*	71	42.77		
Drug use	Never / infrequent *(once a week or less)*	167	98.82		
	Regular *(twice a week or more)*	2	1.18		

Table continues on following page…

		Baseline sample n=169			
		N	%	Mean	SD
Exercise	Never / infrequent *(once a week or less)*	57	34.13		
	Regular *(twice a week or more)*	110	65.87		
ESSI social support		169		25.50	5.75
Disease variables					
Diagnosis	Angina	47	27.81		
	STEMI	63	37.28		
	NSTEMI	58	34.32		
	Unknown	1	0.59		
Days since index event*		161		110.63	75.38
Left ventricular function	Good / normal function	63	47.73		
	Mild dysfunction	42	31.82		
	Moderate dysfunction	21	15.91		
	Severe dysfunction	6	4.55		
NYHA functional classification	No impairment	78	46.99		
	Some impairment *(mild, moderate, severe)*	88	53.01		
Number of diseased vessels (>50% occluded)	0	4	2.37		
	1	70	41.42		
	2	53	31.36		
	3	42	24.85		
Comorbidity score	1 or less	121	71.60		
	2 or more	48	28.40		
Troponin		116		936.08	1858.85
C-reactive protein	Inflammation absent *(<10 mg/L)*	54	59.34		
	Inflammation present *(≥10 mg/L)*	37	40.66		
White cell count	Normal *(<12 x10^9/L)*	114	69.94		
	Raised *(≥12 x10^9/L)*	49	30.06		

*Index event = admission date of most recent hospitalisation for ACS prior to the baseline questionnaires being completed (for the majority of patients this was also the admission date of the most recent hospitalisation for ACS prior to recruitment).

4.4.2 Baseline assessments

4.4.2.1 Description of main predictors and outcomes at baseline

Summary statistics for RRS brooding, PSWQ, PHQ, BAI, EQ5D, and SAQ at baseline are presented in Table 4.2.

Comparison of baseline predictors and main outcomes between participants who were depressed at baseline and participants who were not depressed at baseline showed that depressed participants had higher brooding and worry scores, higher anxiety and worse general health and cardiac specific quality of life. Descriptive statistics and results of statistical tests are summarised in Appendix 10.

4.4.2.2 Missing data at baseline

The number of missing cases for any of the main predictors or outcome variables at baseline ranged from 0 to 13 (0% to 7.7% of cases, based on total n=169), and the total number of missing items for any multi-item variable at baseline ranged from 1 to 50 (0.1% to 5.1% of items). Missing data at case and scale/subscale level is summarised in Appendix 11.

For each main predictor and main outcome variable, characteristics (age, gender ratio, baseline PHQ) of respondents with missing data were compared to those for whom data was available. Cases with missing RRS brooding (z=-2.37, p=0.0179), PSWQ (z=-3.49, p=0.0005), and PHQ (z=-1.949, p=0.0513) data were older than cases for whom data was available. A greater number of cases with missing EQ5D VAS data were female ($\chi^2(1)=6.98$, p=0.050), and cases with missing SAQ frequency data had higher PHQ scores (z=-2.01, p=0.0444) compared to cases for whom data was available. These comparisons were based on between 2 and 7 missing cases.

4.4.2.3 Associations of sample characteristics with main predictors at baseline

There were significant but weak correlations between RRS brooding with lower age and less perceived availability of social support, and between PSWQ with lower age and less perceived availability of social support. All other correlations were non-significant, or correlation coefficients were of negligible magnitude (r<0.20). All correlations are summarised in Appendix 12.

In addition, results of difference tests showed that RRS brooding was significantly greater in smokers compared to non-smokers (RRS 9 vs. 7; z=-2.43, p=0.0153). PSWQ was significantly higher in participants with a history of depression

compared to those without a history of depression (PSWQ=49 vs. 35; z=-2.19, p=0.0286) and in participants who were employed compared to those who were unemployed (PSWQ=39 vs. 34; z=-2.12, p=0.0336).

Table 4.2: Main predictor variables and main outcomes at baseline

	N	Min	Max	Mean	SD	Median	IQR
Main predictors							
Total PSWQ	163	16.00	73.00	37.63	13.69	35.00	21.00
RRS Brooding	162	5.00	19.00	8.10	3.05	7.00	4.00
Main outcomes							
Total PHQ	167	0.00	20.00	4.25	4.90	2.00	5.00
Total BAI	167	0.00	41.00	8.70	9.21	5.53	10.00
EQ5D VAS	167	20.00	100.00	72.89	17.56	75.00	25.00
EQ5D Index value	165	-0.20	1.00	0.78	0.20	0.81	0.29
EQ5D Mobility	167	1.00	4.00	1.64	0.89	1.00	1.00
EQ5D Self-care	167	1.00	3.00	1.17	0.49	1.00	0.00
EQ5D Usual activities	166	1.00	5.00	1.81	1.08	1.00	1.00
EQ5D Pain	167	1.00	5.00	1.72	0.79	2.00	1.00
EQ5D Anxiety / depression	166	1.00	5.00	1.55	0.86	1.00	1.00
SAQ Physical limitations	162	8.33	100.00	73.90	24.30	80.56	41.72
SAQ Angina frequency	167	20.00	100.00	88.98	17.13	100.00	20.00
SAQ Angina stability	156	0.00	100.00	83.49	24.35	100.00	50.00
SAQ Treatment satisfaction	164	31.25	100.00	89.98	14.70	100.00	15.63
SAQ Disease perception	160	8.33	100.00	70.34	25.14	75.00	41.67

4.4.2.4 Associations of sample characteristics with main outcomes at baseline

There were small to medium sized correlations between NYHA functional classification with PHQ, BAI and the majority of EQ5D and SAQ subscales (r=0.18 to r=0.53), such that greater severity of cardiac disease was associated with greater depression and anxiety, and with poorer quality of life. Social support was weakly correlated with all outcome variables (r=0.16 to r=0.38) such that greater social support was associated with lower depression and anxiety and with better quality of life. Increasing age was weakly correlated with less depression, less anxiety, better EQ5D anxiety/depression and greater SAQ physical limitations (r=0.15 to r=0.31). Finally, number of comorbidities was significantly correlated with greater limitations in EQ5D mobility (r=0.42). Other correlations were non-significant or coefficients were of negligible magnitude. All correlations are summarised in Appendix 13.

In addition, results of difference tests showed that depression was greater in participants with a history of depression, smokers and participants who exercised infrequently. Anxiety was greater in participants who were smokers and who exercised infrequently. Quality of life was worse in participants who were female, in employment, not in a relationship, had a history of depression, were smokers, drank alcohol frequently and exercised infrequently. Significant results are summarised fully in Appendix 14.

4.4.2.5 Bivariate associations among main predictors and outcomes at baseline

The main predictor variables, RRS brooding and PSWQ, were moderately correlated at baseline (r=0.51, p<0.001). The majority of main outcome variables (PHQ, BAI, EQ5D and SAQ) were also significantly correlated with each other at baseline (see correlation matrix in Appendix 15).

Correlations between the main predictor variables (RRS brooding and PSWQ) and the main outcome variables (PHQ, BAI, EQ5D and SAQ) at baseline are presented in Table 4.3. There were small to medium correlations between both PSWQ and RRS brooding with the majority of outcome measures, with the exception that PSWQ was not correlated with the EQ5D mobility subscale, and neither RRS brooding nor PSWQ was correlated with the SAQ stability of angina subscale. The strongest associations were between RRS brooding with greater PHQ, BAI and EQ5D anxiety/depression

(r=0.53 to r=0.55), and between PSWQ with greater PHQ, BAI and EQ5D anxiety/depression (r=0.39 to r=0.50).

Table 4.3: Correlations between RRS brooding and PSWQ with main outcome variables at baseline

	RRS brooding		PSWQ	
	N	r	N	r
Total PHQ	162	0.55[a]	163	0.46[a]
Total BAI	162	0.53[a]	162	0.45[a]
EQ5D VAS	161	-0.31[a]	162	-0.29[a]
EQ5D Index value	160	-0.43[a]	160	-0.35[a]
EQ5D Mobility	160	0.17[c]	161	0.11
EQ5D Self-care	160	0.19[b]	161	0.14[c]
EQ5D Usual activities	160	0.27[a]	161	0.18[b]
EQ5D Pain	160	0.23[a]	161	0.24[a]
EQ5D Anxiety / depression	160	0.55[a]	160	0.39[a]
SAQ Physical limitations	156	-0.18[c]	156	-0.19[c]
SAQ Angina frequency	160	-0.27[a]	161	-0.26[a]
SAQ Angina stability	151	-0.06	151	-0.12
SAQ Treatment satisfaction	158	-0.27[a]	158	-0.21[b]
SAQ Disease perception	155	-0.41[a]	155	-0.37[a]

[a]p<0.001 [b]p≤0.01 [c]p≤0.05.

4.4.3 2 month assessments

4.4.3.1 Timing of 2 month assessments

Assessments at 2 months were conducted as close to 2 months after baseline assessments as possible. The actual number of days from baseline to 2 month assessments ranged from 55 to 210. The mean number of days between baseline and 2 month assessments was 95.6 (SD 29.9), and the median was 84.0 (IQR 32.0).

4.4.3.2 Attrition at 2 months

Of 169 participants who completed baseline assessments, 44 participants did not complete the 2 month questionnaire packs (i.e. 26.0%). Of these 1 was too unwell to continue, 4 did not wish to continue with the study, and 39 did not return the questionnaire pack and the reason for non-completion was unknown.

Compared to completers, non-completers at 2 months were significantly younger (62.4 years vs. 68.3 years; z=-2.41, p=0.0158) and had lower perceived social support (mean ESSI 24.8 vs. mean ESSI 25.7; z=-1.989, p=0.0467). More non-completers than completers had no partner (43.2% vs. 21.8%; $\chi^2(1)= 7.49$, p=0.006), lived alone (40.9% vs. 20.2%; $\chi^2(1)= 7.34$, p=0.007), lived in a higher deprivation postcode (68.4% vs. 44.8%; $\chi^2(1)= 6.50$, p=0.011), and received a diagnosis of STEMI (52.3% vs. 32.0%; $\chi^2(1)= 6.06$, p=0.048).

Characteristics of the sample that completed assessments at 2 months are summarised in Table 4.4, and compared with characteristics of the group that did not complete 2 month assessments.

4.4.3.3 Description of main predictors and outcomes at 2 months

Summary statistics for RRS brooding, PSWQ, PHQ, BAI, EQ5D and SAQ at 2 months are presented in Table 4.5.

4.4.3.4 Missing data at 2 months

The number of missing cases for any of the main predictors or outcome variables at 2 months ranged from 1 to 9 (0.8% to 7.2% of cases, based on total n=125), and the total number of missing items for any multi-item variable at 2 months ranged from 4 to 78 (0.6% to 7.2% of items). Missing data at case and scale/subscale level is summarised in Appendix 16.

For each main predictor and main outcome variable, characteristics (age, gender ratio, 2 month PHQ) of respondents with missing data were compared to those for whom data was available. There were no significant differences in characteristics of participants with and without missing data.

Table 4.4: Sample characteristics (measured at baseline) of participants remaining in the study at 2 months

		Completers n=125				Non-completers n=44			
		N	%	Mean	SD	N	%	Mean	SD
Demographic variables									
Age (years)*		125		68.33	9.63	44		62.41	15.23
Sex	Male	98	78.40			33	75.00		
	Female	27	21.60			11	25.00		
Years of education	Secondary	45	39.13			13	31.14		
	Higher	70	60.87			24	64.86		
Employment status	In employment	45	36.00			20	45.45		
	Not in employment	80	64.00			24	54.55		
Relationship status*	In a relationship	97	78.23			25	56.82		
	Not in a relationship	27	21.77			19	43.18		
Lives alone*	Yes	25	20.16			18	40.91		
	No	99	79.84			26	59.09		
Index of multiple deprivation*	Most deprived	56	44.80			26	68.42		
	Least deprived	69	55.20			12	31.58		
History of depression	Yes	12	9.60			4	9.09		
	No	113	90.40			40	90.91		
Smoking status	Smoker	10	8.00			8	18.60		
	Non-smoker	115	92.00			35	81.40		
Alcohol use	Never / infrequent	69	56.10			26	60.47		
	Regular	54	43.90			17	39.53		
Drug use	Never / infrequent	124	99.20			43	97.73		
	Regular	1	0.80			1	2.27		
Exercise	Never / infrequent	40	32.26			17	39.53		
	Regular	84	67.74			26	60.47		
ESSI social support*		125		25.74	5.92	44		24.81	5.23

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		Completers n=125				Non-completers n=44			
		N	%	Mean	SD	N	%	Mean	SD
Disease variables									
Diagnosis*	Angina	36	28.80			11	25.00		
	STEMI	40	32.00			23	52.27		
	NSTEMI	48	38.40			10	22.73		
	Unknown	1	0.80			0	0		
Days since index event		118		110.09	79.73			112.09	62.72
Left ventricular function	Good / normal function	47	48.96			16	44.44		
	Mild dysfunction	31	32.29			11	30.56		
	Moderate dysfunction	14	14.58			7	19.44		
	Severe dysfunction	4	4.17			2	5.56		
NYHA functional classification	No impairment	60	48.78			18	41.86		
	Some impairment	63	51.22			25	58.14		
Number of diseased vessels (>50% occluded)	0	2	1.60			2	4.55		
	1	50	40.00			20	45.45		
	2	38	30.40			15	34.09		
	3	35	28.00			7	15.91		
Comorbidity score	1 or less	90	72.00			31	70.45		
	2 or more	35	28.00			13	29.55		
Troponin		87		974.88	1878.35	29		819.69	1826.51
C-reactive protein	Inflammation absent	40	60.61			14	56.00		
	Inflammation present	26	39.39			11	44.00		
White cell count	Normal	90	74.38			24	57.14		
	Raised	31	26.45			18	42.86		

*Completers and dropouts significantly different**.**

Table 4.5: Main predictor variables and main outcomes at 2 months

	N	Min	Max	Mean	SD	Median	IQR
Main predictors							
Total PSWQ	124	16.00	76.00	36.03	13.44	34.50	18.50
RRS Brooding	124	5.00	17.00	7.68	2.88	7.00	3.00
Main outcomes							
Total PHQ	124	0.00	20.00	3.70	4.69	2.00	5.00
Total BAI	122	0.00	40.00	7.87	8.74	5.00	10.00
EQ5D VAS	124	7.00	100.00	74.74	19.18	80.00	20.00
EQ5D Index value	123	0.11	1.00	0.81	0.19	0.84	0.28
EQ5D Mobility	124	1.00	4.00	1.61	0.88	1.00	1.00
EQ5D Self-care	124	1.00	3.00	1.13	0.38	1.00	0.00
EQ5D Usual activities	124	1.00	5.00	1.57	0.85	1.00	1.00
EQ5D Pain	123	1.00	4.00	1.63	0.75	1.00	1.00
EQ5D Anxiety / depression	124	1.00	4.00	1.44	0.77	1.00	1.00
SAQ Physical limitations	120	5.56	100.00	77.94	22.21	83.33	35.42
SAQ Angina frequency	122	20.00	100.00	90.12	16.94	100.00	10.00
SAQ Angina stability	116	0.00	100.00	76.51	24.74	75.00	50.00
SAQ Treatment satisfaction	119	43.75	100.00	90.28	13.39	100.00	18.75
SAQ Disease perception	118	16.67	100.00	75.85	21.58	83.33	33.33

4.4.4 6 month assessments

4.4.4.1 Timing of 6 month assessments

Assessments at 6 months were conducted as close to 6 months after baseline assessments as possible. The actual number of days from baseline to 6 month assessments ranged from 158 to 384. The mean number of days between baseline and 6 month assessments was 200.6 (SD 31.8), and the median was 195.5, (IQR 31.5).

4.4.4.2 Attrition at 6 months

Of 169 participants who completed baseline assessments, 58 participants did not complete the 6 month questionnaire pack (i.e. 34.3%). Of these 3 were too unwell to continue, 4 did not wish to continue with the study, 2 died, and 49 did not return the questionnaire pack and the reason for non-completion was unknown.

Characteristics of the sample that completed assessments at 6 months are summarised in Table 4.6, and compared with characteristics of the group that did not complete 6 month assessments.

Compared to completers, more non-completers at 6 months had raised white cell count (41.1% vs. 24.3%; $\chi^2(1)= 4.92$, p= 0.027) and raised C-reactive protein (55.6% vs. 30.9%; $\chi^2(1)= 5.48$, p= 0.019) at hospital admission. There was no significant difference in PHQ scores at baseline between completers (mean=3.77, SD=4.38) and non-completers (mean=5.20, SD=5.70) (z=1.26, p=0.2091) at 6 months. However, fewer participants who were depressed at baseline completed the study (11 out of 24 i.e. 45.8%) compared to participants who were not depressed at baseline (99 out of 143 i.e. 69.2%; $\chi^2=5.00$, p=0.025).

4.4.4.3 Description of main predictors and outcomes at 6 months

Summary statistics for the RRS brooding, PSWQ, PHQ, BAI, EQ5D and SAQ at 6 months are presented in Table 4.7.

4.4.4.4 Missing data at 6 months

The number of missing cases for any of the main predictors or outcome variables at 6 months ranged from 0 to 6 (0.0% to 9.0% of cases, based on total n=111), and the total number of missing items for any multi-item variable at 6 months ranged from 0 to 85 (0.0% to 3.8% of items). Missing data at case and scale/subscale level is summarised in Appendix 17.

For each main predictor and main outcome variable, characteristics (age, gender ratio, 6 month PHQ) of respondents with missing data were compared to those for whom data was available. There were no significant differences in characteristics of participants with and without missing data.

Table 4.6: Sample characteristics (measured at baseline) of participants remaining in the study at 6 months

		Completers n=111				Non-completers n=58			
		N	%	Mean	SD	N	%	Mean	SD
Demographic variables									
Age (years)		111		68.26	9.07	58		63.97	15.02
Sex	Male	86	77.48			45	77.59		
	Female	25	22.52			13	22.41		
Years of education	Secondary	37	36.27			21	42.00		
	Higher	65	63.73			29	58.00		
Employment status	In employment	39	35.14			26	44.83		
	Not in employment	72	64.86			32	55.17		
Relationship status	In a relationship	84	76.36			38	44.82		
	Not in a relationship	26	23.64			20	34.48		
Lives alone	Yes	25	22.73			18	31.03		
	No	85	77.27			40	68.97		
Index of multiple deprivation	Most deprived	51	45.95			31	59.62		
	Least deprived	60	54.05			21	40.38		
History of depression	Yes	9	8.11			7	12.07		
	No	102	91.89			51	87.93		
Smoking status	Smoker	8	7.21			10	17.54		
	Non-smoker	103	92.79			47	82.46		
Alcohol use	Never / infrequent	64	58.72			31	54.39		
	Regular	45	41.28			26	45.61		
Drug use	Never / infrequent	111	100.00			56	96.55		
	Regular	0	0.00			2	3.45		
Exercise	Never / infrequent	35	31.82			22	38.60		
	Regular	75	68.18			35	61.40		
ESSI social support		111		25.59	6.07	58		25.32	5.13

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		Completers n=111				Non-completers n=58			
		N	%	Mean	SD	N	%	Mean	SD
Disease variables									
Diagnosis	Angina	30	27.03			17	29.31		
	STEMI	39	35.14			24	41.38		
	NSTEMI	42	37.84			16	27.59		
	Unknown	0	0.00			1	1.72		
Days since index event		107		110.45	81.20				
Left ventricular function	Good / normal function	44	51.76			19	40.43		
	Mild dysfunction	27	31.76			15	31.91		
	Moderate dysfunction	11	12.94			10	21.28		
	Severe dysfunction	3	3.53			3	6.38		
NYHA functional classification	No impairment	53	49.07			25	43.10		
	Some impairment	55	50.93			33	56.90		
Number of diseased vessels (>50% occluded)	0	2	1.80			2	3.45		
	1	46	41.11			24	41.38		
	2	35	31.53			18	31.03		
	3	28	25.23			14	24.14		
Comorbidity score	1 or less	84	75.68			37	63.79		
	2 or more	27	24.32			21	36.21		
Troponin		76		958.69	1898.69	40		893.13	1803.65
C-reactive protein*	Inflammation absent	38	69.09			16	44.44		
	Inflammation present	17	30.91			20	55.56		
White cell count*	Normal	81	75.70			33	58.93		
	Raised	26	24.30			23	41.07		

*Completers and dropouts significantly different.

Table 4.7: Main predictor variables and main outcomes at 6 months

	N	Min	Max	Mean	SD	Median	IQR
Main predictors							
Total PSWQ	110	16.00	76.00	35.17	13.86	34.00	18.00
RRS Brooding	108	5.00	18.00	7.70	2.82	7.00	3.00
Main outcomes							
Total PHQ	111	0.00	22.00	3.15	4.55	1.00	4.00
Total BAI	110	0.00	33.00	7.36	8.08	5.00	7.00
EQ5D VAS	110	20.00	100.00	76.67	18.25	80.00	20.00
EQ5D Index value	110	0.07	1.00	0.82	0.19	0.84	0.27
EQ5D Mobility	110	1.00	4.00	1.54	0.85	1.00	1.00
EQ5D Self-care	110	1.00	3.00	1.11	0.37	1.00	0.00
EQ5D Usual activities	110	1.00	4.00	1.49	0.75	1.00	1.00
EQ5D Pain	110	1.00	5.00	1.72	0.87	1.50	1.00
EQ5D Anxiety / depression	110	1.00	4.00	1.43	0.77	1.00	1.00
SAQ Physical limitations	107	13.89	100.00	79.13	23.47	88.89	33.33
SAQ Angina frequency	110	30.00	100.00	88.82	17.60	100.00	20.00
SAQ Angina stability	101	0.00	100.00	69.06	28.54	50.00	50.00
SAQ Treatment satisfaction	105	16.67	100.00	89.72	15.60	100.00	18.75
SAQ Disease perception	105	25.00	100.00	78.25	20.56	83.33	33.33

4.4.5 Changes in main predictors and outcomes over time

Friedman's test indicated that there was no significant change in the mean scores of predictor variables, RRS brooding and PSWQ, at any of the assessment times. There were large and highly significant correlations between RRS brooding at the three assessment times, and between PSWQ at the three assessment times (correlation coefficients are presented in Table 4.8).

There was also no significant change over time in the mean scores of main outcome variables related to depression (PHQ), anxiety (BAI) or quality of life (EQ5D or SAQ), with the exception that SAQ angina stability scores were significantly lower at each assessment compared to the previous one (F=8.24, p=0.0163; baseline vs. 2 months z=2.10, p=0.0356; baseline vs. 6 months z=3.76, p=0.0002; 2 months vs. 6 months z=2.33, p=0.0197).

Table 4.8: Correlations among RRS brooding at different assessment times and PSWQ at different assessment times

	Baseline RRS brooding		2 month RRS brooding	
	N	r	N	r
2 month RRS brooding	121	0.76[a]	-	-
6 month RRS brooding	106	0.78[a]	103	0.81[a]
	Baseline PSWQ		2 month PSWQ	
	N	r	N	r
2 month PSWQ	121	0.72[a]	-	-
6 month PSWQ	108	0.77[a]	104	0.77[a]

[a]p≤0.001 [b]p≤0.01 [c]p≤0.05.

4.4.6 Prospective associations of baseline predictors with 6 month outcomes

4.4.6.1 Correlation of baseline predictors with 6 month outcomes

Bivariate correlations between the main predictor variables at baseline (RRS brooding, PSWQ) and the main outcome variables at 6 months (PHQ, BAI, EQ5D and SAQ) are presented in Table 4.9.

There were small to medium sized correlations between baseline RRS brooding and PSWQ with all outcome measures related to depression and anxiety, and with the majority of outcomes related to quality of life. The strongest associations were between RRS brooding with PHQ, BAI, EQ5D anxiety/depression and SAQ disease perception (r=0.33 to r=0.47) (such that higher brooding was correlated with greater depression, greater anxiety and worse quality of life) and between PSWQ with PHQ, BAI, EQ5D index value, EQ5D anxiety/depression and SAQ disease perception (r=0.32 to r=0.38) (such that higher worry was correlated with greater depression, greater anxiety and worse quality of life).

4.4.6.1.1 Sensitivity analysis exploring differences in associations between completers and non-completers

Correlations between the main predictors and outcome variables at baseline for participants who completed assessments at 6 months were broadly similar to those for participants who did not complete assessments at 6 months (see Appendix 18), although correlations between brooding and overall quality of life appeared marginally stronger in non-completers compared to completers. This suggests that the associations of perseverative negative thinking with depression and anxiety, at least cross-sectionally, were not different for participants who completed the study compared to participants who withdrew from the study.

Table 4.9: Correlations between baseline PSWQ and RRS Brooding with main outcomes at 6 months

	Baseline RRS brooding		Baseline PSWQ	
	N	r	N	r
PHQ	108	0.47[a]	109	0.38[a]
BAI	108	0.37[a]	109	0.37[a]
EQ5D VAS	107	-0.18	108	-0.28[b]
EQ5D Index value	107	-0.19[c]	108	-0.32[a]
EQ5D Mobility	107	0.05	108	0.17[b]
EQ5D Self-care	107	0.15	108	0.14
EQ5D Usual activities	107	0.11	108	0.15[p=0.057]
EQ5D Pain	107	0.16[c]	108	0.22[b]
EQ5D Anxiety / depression	107	0.33[a]	108	0.33[a]
SAQ Physical limitations	104	-0.05	105	-0.16
SAQ Angina frequency	107	-0.23[b]	108	-0.19[c]
SAQ Angina stability	98	-0.07	99	-0.08
SAQ Treatment satisfaction	102	-0.15	103	-0.24[b]
SAQ Disease perception	102	-0.36[a]	103	-0.32[a]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

4.4.6.2 Predictors of depression at 6 months

Simple regression models showed that baseline RRS brooding ($F(1,106)=71.78$, $p<0.001$) and baseline PSWQ ($F(1,107)=32.16$, $p<0.001$) significantly predicted 6 month PHQ scores. Brooding and worry accounted for 40% and 22%, respectively, of variance in depression.

In a staged multivariable regression model with demographic variables entered in the first step, baseline depression entered in the second step and RRS brooding entered in the third step, the overall model was significant at each step with the full model accounting for 64% of the variance in 6 month depression (full results are reported in Table 4.10). Low perceived social support, baseline depression and baseline brooding were significant predictors of 6 month depression. At step 1 low social support explained 31% of the variance in 6 month depression, and in step 2 baseline PHQ explained an additional 30%. The addition of baseline brooding to the model in the final step accounted for a further 2% of variance in 6 month depression scores.

In a separate staged multivariable regression model with demographic details entered in the first step, baseline depression entered in the second step and PSWQ entered in the third step, the overall model was significant at each step with the full model accounting for 60% of the variance in 6 month depression (results of the regression model are reported in Table 4.11). Low social support and baseline depression were significant predictors of 6 month depression. In step 1 low social support explained 28% of the variance in 6 month depression scores, and in step 2 baseline PHQ explained an additional 30%. PSWQ was not a significant predictor of 6 month depression.

4.4.6.2.1 Subgroup analysis of depressed vs. non-depressed participants

Previous research suggests that the association of brooding with depression may be stronger in people with initially elevated depressive symptoms compared to those without. It was not possible to formally test this with depressed and non-depressed subgroups because only 24 participants (14.2%) were depressed at baseline (PHQ≥10) and 6 month assessments were only available for 11 of the 24. Exploratory bivariate correlations between baseline brooding and 6 month PHQ were conducted instead. The correlation for participants who were depressed at baseline (PHQ≥10) was $r=0.67$, $p=0.0228$ and the correlation for those who were not depressed at baseline (PHQ<10) was $r=0.32$, $p=0.0014$.

4.4.6.2.2 Reverse association

A sensitivity analysis was performed to investigate the reverse association i.e. the association of baseline depression with brooding at 6 months. A simple regression model showed that there was a significant association between baseline depression and 6 month brooding ($F(1, 106)=62.53$, $p<0.001$, $\beta=0.96$, $t=7.91$, $p<0.001$), although after controlling for baseline brooding (other covariates were not significant) the effect was no longer significant ($F(2, 103)=105.88$, $p<0.001$, $\beta=0.06$, $t=1.15$, $p=0.254$).

Table 4.10: Staged multivariable regression of baseline brooding with 6 month depression (N=106)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(6,99)=8.93[a]	0.31	
Age	-0.14	-0.07	0.04	-1.62			
Sex	0.01	0.06	0.96	0.06			
IMD	-0.02	-0.05	0.17	-0.27			
Q1 ESSI	-0.44	-0.34	0.07	-4.78[a]			
Q1 NYHA	0.16	1.48	0.80	1.83			
History of depression	0.12	2.01	1.43	1.41			
Step 2					F(7,98)= 26.20[a]	0.63	0.30 (F(1,98)=84.55[a])
Age	0.01	0.01	0.03	0.22			
Sex	0.10	1.16	0.72	1.62			
IMD	0.01	0.01	0.12	0.10			
Q1 ESSI	-0.23	-0.17	0.06	-3.14[b]			
Q1 NYHA	0.07	0.66	0.60	1.09			
History of depression	-0.03	-0.47	1.09	-0.43			
Q1 PHQ	0.68	0.71	0.08	9.20[a]			
Step 3					F(8,97)=24.68[a]	0.64	0.02 (F(1,97)=5.55[c])
Age	0.03	0.02	0.03	0.53			
Sex	0.09	1.04	0.70	1.48			
IMD	0.01	0.02	0.12	0.15			
Q1 ESSI	-0.23	-0.17	0.05	-3.22[b]			
Q1 NYHA	0.08	0.71	0.59	1.22			
History of depression	-0.03	-0.54	1.06	-0.51			
Q1 PHQ	0.55	0.57	0.10	5.90[a]			
Q1 RRS Brooding	0.20	0.29	0.12	2.36[c]			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.

Table 4.11: Staged multivariable regression of baseline worry with 6 month depression (N=107)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(6,100)=8.03[a]	0.28	
Age	-0.13	-0.07	0.04	-1.56			
Sex	-0.01	-0.16	0.97	-0.17			
IMD	-0.02	-0.03	0.17	-0.19			
Q1 ESSI	-0.41	-0.31	0.07	-4.37[a]			
Q1 NYHA	0.15	1.39	0.82	1.70			
History of depression	0.14	2.31	1.45	1.60			
Step 2					F(7,99)=23.90[a]	0.60	0.30 (F(1,99)=80.74[a])
Age	0.02	0.01	0.03	0.26			
Sex	0.09	0.96	0.73	1.32			
IMD	0.01	0.02	0.13	0.15			
Q1 ESSI	-0.19	-0.14	0.06	-2.55[b]			
Q1 NYHA	0.06	0.57	0.62	0.93			
History of depression	-0.01	-0.20	1.11	-0.18			
Q1 PHQ	0.69	0.72	0.08	8.99[a]			
Step 3					F(8,98)=20.83[a]	0.60	0.00 (F(1,98)=0.39)
Age	0.03	0.01	0.03	0.38			
Sex	0.08	0.94	0.74	1.28			
IMD	0.01	0.01	0.13	0.09			
Q1 ESSI	-0.19	-0.14	0.06	-2.55[b]			
Q1 NYHA	0.06	0.58	0.62	0.94			
History of depression	-0.01	-0.17	1.12	-0.15			
Q1 PHQ	0.66	0.69	0.09	7.41[a]			
Q1 PSWQ	0.05	0.02	0.03	0.63			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.

4.4.6.3 Predictors of anxiety at 6 months

Simple regression models showed that baseline RRS brooding ($F(1,106)=42.01$, $p<0.001$) and baseline PSWQ ($F(1,107)=26.52$, $p<0.001$) significantly predicted 6 month BAI scores. Brooding and worry accounted for 28% and 19%, respectively, of variance in anxiety.

In a staged multivariable regression model with demographic variables entered in the first step, baseline anxiety entered in the second step and RRS brooding entered in the third step, the overall model was significant at each step with the full model accounting for 60% of the variance in 6 month anxiety (full results are reported in Table 4.12). Low perceived availability of social support, greater severity of heart disease, and baseline anxiety were significant predictors 6 month anxiety. In step 1 social support and severity of heart disease together explained 38% of the variance in 6 month anxiety, and in step 2 baseline anxiety explained an additional 20%. Baseline brooding was not a significant predictor of 6 month anxiety.

In a separate staged multivariable model where PSWQ was entered in the third step instead of RRS brooding, the overall model was significant at each step with the full model accounting for 60% of the variance in 6 month anxiety (full results are reported in Table 4.13). In step 1 low social support and greater severity of heart disease were significant predictors and together explained 39% of the variance in 6 month anxiety. In step 2, where baseline anxiety was added to the model, low social support and baseline anxiety were significant predictors of 6 month anxiety (where baseline anxiety accounted for an additional 20% of the variance) although severity of heart disease was no longer a significant predictor at this step. In the final step, baseline PSWQ was not a significant predictor of 6 month anxiety.

Table 4.12: Staged multivariable regression of baseline brooding with 6 month anxiety (N=106)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(6,99)=11.88[a]	0.38	
Age	-0.12	-0.10	0.07	-1.44			
Sex	0.01	0.23	1.61	0.14			
IMD	0.03	0.09	0.28	0.33			
Q1 ESSI	-0.45	-0.61	0.12	-5.10[a]			
Q1 NYHA	0.27	4.34	1.35	3.21[b]			
History of depression	0.13	3.83	2.39	1.60			
Step 2					F(7,98)= 23.06[a]	0.60	0.20 (F(1,98)=52.84[a])
Age	-0.04	-0.03	0.06	-0.53			
Sex	0.11	2.11	1.33	1.59			
IMD	0.07	0.24	0.23	1.04			
Q1 ESSI	-0.30	-0.41	0.10	-4.14[a]			
Q1 NYHA	0.13	2.19	1.13	1.94			
History of depression	-0.04	-1.31	2.06	-0.63			
Q1 BAI	0.58	0.54	0.07	7.27[a]			
Step 3					F(8,97)=20.74[a]	0.60	0.01 (F(1,97)=3.32)
Age	-0.01	-0.01	0.06	-0.22			
Sex	0.10	1.97	1.32	1.49			
IMD	0.07	0.24	0.23	1.04			
Q1 ESSI	-0.30	-0.40	0.10	-4.05[a]			
Q1 NYHA	0.15	2.37	1.13	2.09[c]			
History of depression	-0.04	-1.25	2.05	-0.61			
Q1 BAI	0.50	0.47	0.09	5.31[a]			
Q1 RRS Brooding	0.13	0.33	0.22	1.52			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.

Table 4.13: Staged multivariable regression of baseline worry with 6 month anxiety (N=106)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(6,99)=12.33[a]	0.39	
Age	-0.14	-0.13	0.07	-1.77			
Sex	-0.00	-0.02	1.59	-0.01			
IMD	0.04	0.15	0.29	0.54			
Q1 ESSI	-0.46	-0.63	0.12	-5.34[a]			
Q1 NYHA	0.24	3.90	1.34	2.91[b]			
History of depression	0.13	3.70	2.38	1.55			
Step 2					F(7,98)=23.23[a]	0.60	0.20 (F(1,98)=51.14[a])
Age	-0.05	-0.04	0.06	-0.74			
Sex	0.10	1.96	1.33	1.47			
IMD	0.073	0.26	0.23	1.12			
Q1 ESSI	-0.31	-0.43	0.10	-4.26[a]			
Q1 NYHA	0.12	1.98	1.12	1.77			
History of depression	-0.05	-1.32	2.06	-0.64			
Q1 BAI	0.57	0.54	0.08	7.15[a]			
Step 3					F(8,97)=20.65[a]	0.60	0.01 (F(1,97)=1.59)
Age	-0.03	-0.02	0.06	-0.40			
Sex	0.09	1.87	1.32	1.41			
IMD	0.07	0.24	0.23	1.01			
Q1 ESSI	-0.31	-0.42	0.10	-4.22[a]			
Q1 NYHA	0.13	2.04	1.12	1.82			
History of depression	-0.04	-1.17	2.06	-0.57			
Q1 BAI	0.52	0.49	0.08	6.00[a]			
Q1 PSWQ	0.09	0.05	0.04	1.26			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Q1=baseline.

4.4.6.4 Predictors of general health-related quality of life (EQ5D) at 6 months

4.4.6.4.1 Predictors of EQ5D VAS at 6 months

Simple regression models showed that baseline RRS brooding ($F(1,105)=10.47$, $p=0.0016$, adj $R^2=0.08$) and baseline PSWQ ($F(1,106)=13.17$, $p=0.0004$, adj $R^2=0.10$) significantly predicted worse 6 month EQ5D VAS scores.

A staged multivariable model that included baseline RRS brooding as a predictor in step 3 was significant at each step with the full model accounting for 35% of the variance in 6 month EQ5D VAS (full results are reported in Table 4.14). In the final step of the model low social support and baseline EQ5D VAS were significant predictors of worse 6 month EQ5D VAS. Baseline brooding was not a significant predictor of 6 month EQ5D VAS.

Where the staged multivariable model included baseline PSWQ instead of RRS brooding in step 3, the model was significant at each step and the full model accounted for 35% of the variance in 6 month EQ5D VAS (full results are reported in Table 4.15). Consistent with the previous model, low perceived social support and baseline EQ5D VAS, in the final step, were significant predictors of worse 6 month EQ5D VAS. Baseline worry was not a significant predictor of 6 month EQ5D VAS.

4.4.6.4.2 Predictors of EQ5D index values at 6 months

Simple regression models showed that baseline RRS brooding ($F(1,105)=9.28$, $p=0.0029$, adj $R^2=0.07$) and baseline PSWQ ($F(1,107)=12.03$, $p=0.008$, adj $R^2=0.09$) significantly predicted worse 6 month EQ5D index values.

A staged multivariable model with baseline RRS brooding as a predictor in step 3 was significant at each step with the full model accounting for 44% of the variance in 6 month EQ5D index values (full results are reported in Table 4.16). In the final step of the model male sex, low perceived availability of social support and baseline EQ5D index values were significant predictors of worse 6 month EQ5D index values. Baseline brooding was not a significant predictor of 6 month EQ5D index values.

Where the staged multivariable model included baseline PSWQ as a predictor in step 3, the overall model was significant at each step with the full model accounting for 42% of the variance in 6 month EQ5D index values (full results are reported in Table 4.17). In the final step of the model male sex, low social support and baseline EQ5D

index values were significant predictors of worse 6 month EQ5D index values. Baseline worry was not a significant predictor of 6 month EQ5D index values.

Table 4.14: Staged multivariable regression of baseline brooding with 6 month quality of life (EQ5D VAS) (N=104)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,98)=6.91[a]	0.22	
Age	-0.03	-0.06	0.19	-0.32			
Sex	-0.05	-2.09	4.19	-0.50			
IMD	-0.15	-1.19	0.73	-1.62			
Q1 ESSI	0.42	1.30	0.29	4.48[a]			
Q1 NYHA	-0.18	-6.79	3.46	-1.96[c]			
Step 2					F(6,97)= 9.92[a]	0.34	0.12 (F(1,97)=18.73[a])
Age	-0.03	-0.06	0.17	-0.33			
Sex	-0.06	-2.73	3.86	-0.71			
IMD	-0.11	-0.88	0.68	-1.30			
Q1 ESSI	0.29	0.89	0.28	3.15[b]			
Q1 NYHA	-0.08	-2.78	3.32	-0.84			
Q1 EQ5D VAS	0.40	0.45	0.10	4.33[a]			
Step 3					F(7,96)=8.88[a]	0.35	0.01 (F(1,96)=2.01)
Age	-0.06	-0.13	0.18	-0.71			
Sex	-0.07	-2.95	3.84	-0.77			
IMD	-0.11	-0.92	0.68	-1.37			
Q1 ESSI	0.26	0.81	0.29	2.85[b]			
Q1 NYHA	-0.08	-2.87	3.30	-0.87			
Q1 EQ5D VAS	0.37	0.42	0.11	3.93[a]			
Q1 RRS Brooding	-0.13	-0.76	0.54	-1.42			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Table 4.15: Staged multivariable regression of baseline worry with 6 month quality of life (EQ5D VAS) (N=105)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,99)=6.17[a]	0.20	
Age	-0.02	-0.04	0.20	-0.19			
Sex	-0.03	-1.17	4.22	-0.28			
IMD	-0.17	-1.37	0.75	-1.82			
Q1 ESSI	0.39	1.18	0.29	4.14[a]			
Q1 NYHA	-0.17	-6.31	3.50	-1.80			
Step 2					F(6,98)=9.57[a]	0.33	0.13 (F(1,98)=20.52[a])
Age	-0.02	-0.04	0.18	-0.22			
Sex	-0.05	-2.10	3.86	-0.54			
IMD	-0.12	-1.00	0.69	-1.45			
Q1 ESSI	0.26	0.79	0.28	2.88[b]			
Q1 NYHA	-0.06	-2.26	3.32	-0.68			
Q1 EQ5D VAS	0.42	0.47	0.10	4.53[a]			
Step 3					F(7,97)=8.83[a]	0.35	0.02 (F(1,97)=3.14)
Age	-0.07	-0.15	0.19	-0.78			
Sex	-0.05	-2.39	3.82	-0.62			
IMD	-0.11	-0.93	0.69	-1.36			
Q1 ESSI	0.25	0.75	0.27	2.72[b]			
Q1 NYHA	-0.06	-2.26	3.28	-0.69			
Q1 EQ5D VAS	0.37	0.42	0.11	3.93[a]			
Q1 PSWQ	-0.16	-0.21	0.12	-1.77			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Table 4.16: Staged multivariable regression of baseline brooding with 6 month quality of life (EQ5D Index) (N=103)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,97)=10.15[a]	0.31	
Age	-0.09	-0.00	0.00	-1.10			
Sex	-0.20	-0.09	0.04	-2.33[c]			
IMD	-0.13	-0.01	0.01	-1.49			
Q1 ESSI	0.43	0.01	0.00	4.85[a]			
Q1 NYHA	-0.32	-0.12	0.03	-3.63[a]			
Step 2					F(6,96)= 14.61[a]	0.44	0.13 (F(1,96)=24.59[a])
Age	-0.14	-0.00	0.00	-1.83			
Sex	-0.19	-0.09	0.04	-2.39[c]			
IMD	-0.12	-0.01	0.01	-1.55			
Q1 ESSI	0.35	0.01	0.00	4.33[a]			
Q1 NYHA	-0.15	-0.06	0.03	-1.73			
Q1 EQ5D Index value	0.42	0.43	0.09	4.96[a]			
Step 3					F(7,95)=12.45[a]	0.44	0.01 (F(1,95)=0.22)
Age	-0.15	-0.00	0.00	-1.88			
Sex	-0.19	-0.09	0.04	-2.40[b]			
IMD	-0.12	-0.01	0.01	-1.57			
Q1 ESSI	0.34	0.01	0.00	4.12[a]			
Q1 NYHA	-0.16	-0.06	0.04	-1.77			
Q1 EQ5D Index value	0.41	0.42	0.09	4.41[a]			
Q1 RRS Brooding	-0.04	-0.00	0.01	-0.47			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Table 4.17: Staged multivariable regression of baseline worry with 6 month quality of life (EQ5D Index) (N=104)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,98)=8.27[a]	0.26	
Age	-0.08	0.00	0.00	-0.84			
Sex	-0.17	-0.08	0.04	-1.87			
IMD	-0.14	-0.01	0.01	-1.56			
Q1 ESSI	0.40	0.01	0.00	4.41[a]			
Q1 NYHA	-0.29	-0.11	0.04	-3.12[b]			
Step 2					F(6,97)=13.04[a]	0.41	0.15 (F(1,97)=26.26[a])
Age	-0.12	0.00	0.00	-1.55			
Sex	-0.16	-0.07	0.04	-1.95[c]			
IMD	-0.14	-0.01	0.01	-1.73			
Q1 ESSI	0.32	0.01	0.00	3.84[a]			
Q1 NYHA	-0.11	-0.04	0.03	-1.27			
Q1 EQ5D Index value	0.45	0.46	0.09	5.12[a]			
Step 3					F(7,96)=11.65[a]	0.42	0.01 (F(1,96)=2.30)
Age	-0.16	0.00	0.00	-1.92			
Sex	-0.16	-0.07	0.04	-2.02[c]			
IMD	-0.13	-0.01	0.01	-1.65			
Q1 ESSI	0.30	0.01	0.00	3.61[a]			
Q1 NYHA	-0.12	-0.05	0.03	-1.39			
Q1 EQ5D Index value	0.40	0.41	0.09	4.42[a]			
Q1 PSWQ	-0.13	0.00	0.00	-1.52			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

4.4.6.4.3 Predictors of EQ5D subscales at 6 months

Simple logistic regression models showed that baseline RRS brooding was a significant predictor of worse EQ5D self-care (LR $\chi^2(1)=4.70$, p=0.0302, pseudo $R^2=0.06$), pain (LR $\chi^2(1)=5.51$, p=0.0189, pseudo $R^2=0.02$) and anxiety/depression (LR $\chi^2(1)=18.76$, p<0.001, pseudo $R^2=0.10$) but not mobility or usual activities. In addition, baseline PSWQ significantly predicted worse 6 month EQ5D mobility (LR $\chi^2(1)=6.17$, p=0.0130, pseudo $R^2=0.03$), pain (LR $\chi^2(1)=6.77$, p=0.0093, pseudo $R^2=0.03$) and anxiety/depression (LR $\chi^2(1)=18.17$, p<0.001, pseudo $R^2=0.10$), but not self-care or usual activities.

In separate multiple ordered logistic regression models for each of the EQ5D subscales, baseline RRS brooding was not a significant predictor of any EQ5D subscales at 6 months. The full models were significant in all cases and the amount of variance explained ranged from 15% to 48%. In models that included baseline PSWQ instead of RRS brooding, PSWQ significantly predicted EQ5D mobility but none of the other subscales. The full models were significant in all cases and the amount of variance explained ranged from 14% to 47%.

Findings are summarised in Table 4.18 and results of the individual ordered logistic regression models are presented in Appendix 19 (RRS brooding models) and Appendix 20 (PSWQ models).

4.4.6.5 Predictors of cardiac disease-specific quality of life (SAQ) at 6 months

Simple regression models showed that baseline RRS brooding was a significant predictor of worse SAQ angina frequency ($F(1,105)=8.37$, p=0.0046, adj $R^2=0.07$) and disease perception ($F(1,100)=13.93$, p=.0046, adj $R^2=0.11$) but not physical limitations, angina stability or treatment satisfaction. In addition, baseline PSWQ significantly predicted worse 6 month SAQ treatment satisfaction ($F(1,101)=3.95$, p=0.0496, adj $R^2=0.03$) and disease perception ($F(1,101)=8.82$, p=0.0037, adj $R^2=0.07$), but not physical limitations, angina frequency or angina stability.

In separate staged multivariable regression models for each of the SAQ subscales that controlled for the effect of important covariates, neither baseline RRS brooding or baseline PSWQ were significant predictors of any SAQ subscale at 6 months. The full models were significant in all cases (with the exception of one model

where PSWQ at baseline was the main predictor variable and angina stability at 6 months was the outcome) and the amount of variance explained ranged from 10% to 47%. Combinations of low social support, worse severity of cardiac disease and baseline scores on the relevant SAQ subscale were significant predictors of 6 month quality of life in the final steps of the significant models. The findings are summarised in Table 4.19, and the results of individual regression models are provided in Appendix 21 (where RRS brooding was the main predictor) and in Appendix 22 (where PSWQ worry was the main predictor).

Table 4.18: Summary of ordered logistic regression models of baseline brooding and worry with 6 month quality of life (EQ5D subscales)

Brooding models	EQ5D Mobility	EQ5D Self-care	EQ5D Usual activities	EQ5D Pain	EQ5D Anxiety/ depression
Age			✓		
Sex					
IMD	✓				
Q1 ESSI	✓		✓	✓	✓
Q1 NYHA	✓		✓		✓
Q1 EQ5D	✓	✓	✓	✓	✓
Q1 RRS Brooding					

Worry models	EQ5D Mobility	EQ5D Self-care	EQ5D Usual activities	EQ5D Pain	EQ5D Anxiety/ depression
Age	✓		✓		
Sex					
IMD	✓				
Q1 ESSI			✓	✓	✓
Q1 NYHA	✓		✓		
Q1 EQ5D	✓	✓	✓	✓	✓
Q1 PSWQ	✓				

p≤0.05	p≤0.01	p≤0.001

Q1=baseline.

Table 4.19: Summary of staged multivariable regression models of baseline brooding and worry with 6 month quality of life (SAQ subscales)

Brooding models	SAQ Physical limitations	SAQ Angina frequency	SAQ Angina stability	SAQ Treatment satisfaction	SAQ Disease perception
Age					
Sex					
IMD					
Q1 ESSI	✓		✓	✓	✓
Q1 NYHA	✓	✓			
Q1 SAQ	✓	✓		✓	✓
Q1 RRS Brooding					

Worry models	SAQ Physical limitations	SAQ Angina frequency	SAQ Angina stability	SAQ Treatment satisfaction	SAQ Disease perception
Age	✓				
Sex					
IMD					
Q1 ESSI				✓	✓
Q1 NYHA	✓	✓			
Q1 SAQ	✓	✓		✓	✓
Q1 Total PSWQ					

p≤0.05	p≤0.01	p≤0.001

Q1=baseline.

4.4.6.6 Time since index event

Patients were recruited from inpatient and outpatient settings and there was a degree of variability in the interval between index event (i.e. cardiac event) and baseline assessments (baseline assessments were conducted on average 111 days post-ACS). A sensitivity analysis was performed to investigate if time since index event would predict any outcomes at 6 month follow-up. All staged multivariable regression models were repeated with the inclusion of time since index event as an additional covariate.

Time since index event was not a significant predictor of any outcome at 6 months. In addition, the inclusion of time since index event as a covariate did not alter the results of any of the staged multivariable regression models, with the exception

that in the fully adjusted model brooding at baseline was associated with depression at 6 months at trend level only (p=0.06).

Since the inclusion of time since index event as an additional covariate did not significantly predict any 6 month outcomes or substantially alter any of the results, all models are presented without time since index event included as a covariate.

4.4.6.7 Evaluation of regression assumptions

Results of tests to assess standard regression assumptions for all staged multivariable regression models are summarised in Appendix 23.

Shapiro-Wilk tests revealed that all but two of the staged multivariable regression models (with SAQ disease perception as the outcome variable) violated the assumption of normally distributed residuals. In addition, Breusch-Pagan tests indicated that the assumption of homoscedasticity was violated for 12 of the 18 staged multivariable regression models (including all models where PHQ, BAI, EQ5D VAS and SAQ physical limitations, angina frequency and disease perception were the outcome variables). Multivariable regression is relatively robust to violations of normality and homoscedasticity (e.g. [357]) and such findings are common with clinical indicators such as depression and anxiety scales.

Fit of the regression models to the sample data is summarised in Appendix 24. Cases containing possible outliers were identified in 8 out of 18 staged multivariable regression models, although Cook's distance for all cases in all models was <1 suggesting that influential cases were unlikely to pose a risk of bias in these models.

4.4.6.8 Summary of regression analyses of baseline predictors with 6 month outcomes

Significant baseline predictors of 6 month outcomes, based on simple regression analyses and on regression analyses that adjusted for confounders, are summarised in Table 4.20.

Table 4.20: Summary of significant baseline predictors of all 6 month outcomes based on simple and adjusted staged multivariable regression models

Outcome	Brooding (unadjusted)	Brooding (adjusted)	Worry (unadjusted)	Worry (adjusted)	Other predictors
PHQ Depression	✓	✓	✓		Baseline outcome, social support
BAI Anxiety	✓		✓		Baseline outcome, social support, severity of cardiac disease
EQ5D VAS	✓		✓		Baseline outcome, social support
EQ5D index	✓		✓		Baseline outcome, social support, sex
EQ5D Mobility			✓	✓	Baseline outcome, social support, severity of cardiac disease, index of multiple deprivation, age
EQ5D Self-care	✓				Baseline outcome
EQ5D Usual activities					Baseline outcome, social support, severity of cardiac disease, age
EQ5D Pain	✓		✓		Baseline outcome, social support
EQ5D Anxiety / depression	✓		✓		Baseline outcome, social support, severity of cardiac disease
SAQ Physical limitations					Baseline outcome, social support, severity of cardiac disease, age
SAQ Angina frequency	✓				Baseline outcome, severity of cardiac disease
SAQ Angina stability					Social support
SAQ Treatment satisfaction			✓		Baseline outcome, social support
SAQ Disease perception	✓		✓		Baseline outcome, social support

✓=significant predictor.
Green=significant predictor in brooding models only.
Red=significant predictor in worry models only.

4.4.7 Prospective associations of predictors and outcomes at other assessment times

4.4.7.1 Association of baseline predictors and 2 month outcomes

Bivariate correlations between baseline RRS brooding and PSWQ with the main outcome variables at 2 months are summarised in Appendix 25. The strongest associations were of RRS Brooding with PHQ, BAI, EQ5D index value, EQ5D anxiety/depression and SAQ disease perception (r=0.34 to r=0.51) and between PSWQ with PHQ, BAI, EQ5D index value, EQ5D anxiety/depression and SAQ disease perception (r=0.33 to r=0.50). These findings are consistent with correlations between baseline predictors and 6 month outcomes although, as expected due to the closer temporal spacing, equivalent correlations tended to be of slightly larger magnitude.

Simple regression analyses indicated that baseline RRS brooding and baseline PSWQ significantly predicted all 2 month outcomes, with the exceptions that RRS brooding did not predict stability of angina, and PSWQ did not predict physical limitations related to cardiac disease or problems with mobility.

Results of staged multivariable regression analyses that extended the simple models by controlling for the effects of potential confounding variables were broadly similar to those investigating the association of baseline predictors with 6 month outcomes, with the exception that baseline RRS brooding did not predict 2 month PHQ. The results are summarised in Appendix 26 (baseline RRS brooding with 2 month outcomes) and Appendix 27 (baseline PSWQ with 2 month outcomes).

4.4.7.2 Association of 2 month predictors and 6 month outcomes

Bivariate correlations between 2 month RRS brooding and PSWQ with the main outcome variables at 6 months are summarised in Appendix 28. The strongest associations were of RRS brooding with PHQ, BAI and SAQ disease perception (r=0.42 to r=0.52) and between PSWQ with PHQ, BAI, EQ5D index value, and EQ5D anxiety/depression (r=0.41 to r=0.49). Again, this is largely consistent with correlations between baseline predictors and 6 month outcomes.

Simple regression analyses showed that 2 month RRS brooding and 2 month PSWQ significantly predicted all 6 month outcomes, with the exceptions that RRS brooding did not predict stability of angina, and PSWQ did not predict physical limitations or stability of angina.

Staged multivariable regression analyses exploring associations of 2 month predictors with 6 month outcomes after controlling for possible confounding variables were largely consistent with those investigating the association of baseline predictors with 6 month outcomes. However, an additional finding was that 2 month PSWQ was a significant predictor of 6 month EQ5D VAS. The results are summarised in Appendix 29 (2 month RRS brooding with 6 month outcomes) and Appendix 30 (2 month PSWQ with 6 month outcomes).

4.4.8 Results of longitudinal multilevel (repeated measures) models

4.4.8.1 Between-participant variability in outcomes

Variance components models confirmed that there was significant between-cluster (i.e. between-participant) variability in the outcome variables representing depression, anxiety and quality of life (PHQ, BAI, EQ5D VAS, EQ5D index value and SAQ subscales).

Intra-class correlation coefficients indicated that between 27% and 81% of the total variance in these models was represented by cluster level (i.e. participant level) variation. Results are summarised in Appendix 31.

The variance component models indicated that it was appropriate to specify multilevel (repeated measures) models that included a term to represent participant level clusters for all continuous outcome variables.

4.4.8.2 Predictors of depression

A simple growth curve model with assessment time and depression at the previous assessment time as predictors (model i) showed that depression at a previous assessment time significantly predicted depression at the subsequent assessment time. The likelihood ratio test indicated that it was appropriate to include random slopes for assessment time, suggesting that trajectories of depression over time varied between participants. Results of these models, and the likelihood ratio test, are summarised in Appendix 32.

In an extension of the simple model that included RRS brooding at a previous assessment time as an additional predictor (model ii), both depression at the previous assessment time and RRS brooding at the previous assessment time significantly predicted depression at the subsequent assessment time. After inclusion of the

covariates age, sex, socioeconomic status, social support, history of depression, severity of cardiac disease and days since index event (model iii) depression at a previous assessment time and low social support were the only significant predictors of depression. There was a trend towards brooding at a previous assessment time predicting depression at the subsequent assessment time (p=0.065). Consistent with the simple models, likelihood ratio tests indicated it was appropriate to include random slopes for assessment time, suggesting that trajectories of depression over time varied between participants. Results of these models and likelihood ratio tests are reported in Table 4.21.

In a separate extension of the simple model that included PSWQ at a previous assessment time as an additional predictor (model ii), depression at the previous assessment time but not PSWQ at a previous assessment time predicted depression at the subsequent assessment time. In a model that included the covariates age, sex, index of multiple deprivation, social support, history of depression, severity of cardiac disease, and days since index event (model iii) previous depression and low social support were the only significant predictors of depression. Likelihood ratio tests indicated that trajectories of depression varied between participants. Results of these models and likelihood ratio tests are summarised in Table 4.22.

4.4.8.2.1 Sensitivity analysis without social support as a covariate

The stage iii model that included a lag variable for RRS brooding as the main predictor and PHQ as the outcome was repeated, but omitting social support as a covariate in order to assess the impact of brooding on depression independent of social support.

A random coefficient model failed to converge, and therefore a random intercept model was used instead. The results showed that after controlling for other confounders brooding at a previous assessment time was a significant predictor of depression at a subsequent assessment time (β=0.17, SE=0.09, z=1.98, p=0.048) i.e. brooding was a significant predictor of depression when social support was removed from the model. Other significant predictors were depression at a previous assessment time and greater severity of cardiac disease, consistent with the random intercept

model that included social support as a covariate. Results of this model are provided in Appendix 33.

Table 4.21: Multilevel (repeated measures) models of brooding with depression

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=225)							
Fixed							
Time	-0.09	0.44	-0.21	-0.08	0.37	-0.21	
Total PHQ (n-1 lag)	0.85	0.04	19.39[a]	0.74	0.05	13.53[a]	
RRS Brooding (n-1 lag)	0.16	0.07	2.25[c]	0.20	0.08	2.34[c]	
Random							$X^2(2)= 20.65^a$
Participant √ψ	10.97	94.36		0.00	0.00		
Participant √θ	1.48	53.90		2.78	0.13		
Time √ψ	4.29	37.17					
Overall model	Wald $\chi^2(3)=817.13^a$, Log likelihood=-538.97			Wald $\chi^2(3)=417.02^a$, Log likelihood=-549.30			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=212)							
Fixed							
Time	-0.05	0.45	-0.11	-0.03	0.37	-0.07	
Total PHQ (n-1 lag)	0.78	0.05	16.38[a]	0.64	0.06	10.35[a]	
RRS Brooding (n-1 lag)	0.12	0.07	1.85[p=0.065]	0.15	0.09	1.77[p=0.076]	
Age	-0.01	0.02	-0.57	-0.02	0.02	-0.76	
Sex	0.48	0.38	1.26	0.35	0.52	0.67	
IMD	0.01	0.06	0.17	0.01	0.09	0.13	
Q1 ESSI	-0.10	0.03	-3.62[a]	-0.11	0.04	-2.89[b]	$X^2(2)= 23.63^a$
Q1 NYHA	0.50	0.30	1.63	0.84	0.42	2.01[c]	
History of depression	-0.29	0.51	-0.57	0.36	0.69	0.52	
Days since index event	0.00	0.00	0.30	0.00	0.00	0.44	
Random							
Participant √ψ	12.06	11.50		0.00	0.00		
Participant √θ	0.30	35.84		2.69	0.13		
Time √ψ	4.66	4.57					
Overall model	Wald $\chi^2(10)=830.74^a$, Log likelihood=-498.45			Wald $\chi^2(10)=387.79^a$, Log likelihood=-510.27			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Table 4.22: Multilevel (repeated measures) models of worry with depression

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=226)							
Fixed							
Time	-0.13	0.44	-0.29	-0.12	0.38	-0.31	
Total PHQ (n-1 lag)	0.89	0.04	21.20[a]	0.80	0.05	15.67[a]	
Total PSWQ (n-1 lag)	0.01	0.01	0.66	0.01	0.02	0.81	
Random							$X^2(1)=18.84$[a]
Participant √ψ	11.32	0.90		0.00	0.00		
Participant √θ	-0.99	0.00		2.81	0.13		
Time √ψ	4.44	0.36					
Overall model	Wald $\chi^2(3)=773.35$[a], Log likelihood=-544.94			Wald $\chi^2(3)=403.59$[a], Log likelihood=-554.36			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=212)							
Fixed							
Time	0.00	0.45	0.00	0.00	0.38	0.01	
Total PHQ (n-1 lag)	0.83	0.05	16.61[a]	0.70	0.06	11.60[a]	
Total PSWQ (n-1 lag)	0.00	0.01	-0.08	0.00	0.02	0.08	
Age	-0.01	0.02	-0.79	-0.02	0.02	-1.03	
Sex	0.41	0.40	1.03	0.31	0.53	0.59	
IMD	0.02	0.07	0.31	0.02	0.09	0.24	
Q1 ESSI	-0.09	0.03	-3.21[a]	-0.10	0.04	-2.80[b]	$X^2(1)=18.35$[a]
Q1 NYHA	0.44	0.32	1.35	0.76	0.43	1.78	
History of depression	-0.15	0.54	-0.28	0.41	0.70	0.59	
Days since index event	0.00	0.00	0.42	0.00	0.00	0.52	
Random							
Participant √ψ	10.91	0.95		0.00	0.00		
Participant √θ	1.41	.		2.72	0.13		
Time √ψ	4.22	0.38					
Overall model	Wald $\chi^2(10)=729.42$[a], Log likelihood=-503.96			Wald $\chi^2(10)=372.50$[a], Log likelihood=-513.13			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

4.4.8.3 Predictors of anxiety

A simple random intercept model with assessment time and anxiety at the previous assessment time as predictors (model i) showed that anxiety at a previous assessment time significantly predicted anxiety at the subsequent assessment time. The equivalent random coefficient model including a random slope for assessment time failed to converge. Results of the random intercept model are summarised in Appendix 34.

In an extension of the simple random intercept model that included RRS brooding at a previous assessment time as an additional predictor (model ii), anxiety at the previous assessment time significantly predicted anxiety at the subsequent assessment time, but there was no significant effect of RRS brooding. After inclusion of the covariates age, sex, index of multiple deprivation, social support, history of depression, severity of cardiac disease, and days since index event (model iii) anxiety at a previous assessment time and low social support were the only significant predictors of anxiety. Likelihood ratio tests indicated it was appropriate to include random slopes for assessment time, suggesting that trajectories of anxiety over time varied between participants. Results of these models and likelihood ratio tests are reported in Table 4.23.

In a second extension of the simple model that included total PSWQ at the previous assessment time as an additional predictor (model ii), anxiety, but not PSWQ, at the previous assessment time predicted anxiety at the next assessment time. In a model that included the covariates age, sex, index of multiple deprivation, social support, history of depression, severity of cardiac disease and days since index event (model iii), anxiety at the previous assessment time and low social support were the only significant predictors of anxiety. Likelihood ratio tests indicated that trajectories of anxiety varied between participants. Results of these models and the likelihood ratio tests are summarised in Table 4.24.

Table 4.23: Multilevel (repeated measures) models of brooding with anxiety

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=221)							
Fixed							
Time	0.27	0.76	0.36	0.20	0.69	0.29	
Total BAI (n-1 lag)	0.77	0.05	17.08[a]	0.70	0.05	13.79[a]	
RRS Brooding (n-1 lag)	0.21	0.14	1.46	0.27	0.16	1.73[p=0.083]	
Random							$X^2(2)=9.18^b$
Participant √ψ	17.71	886.98		0.00	0.00		
Participant √θ	3.11	387.91		5.10	0.24		
Time √ψ	6.75	357.94					
Overall model	Wald $\chi^2(3)=585.91^a$, Log likelihood=-669.01			Wald $\chi^2(3)=398.73^a$, Log likelihood=-673.60			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=208)							
Fixed							
Time	0.17	0.74	0.23	0.11	0.67	0.16	
Total BAI (n-1 lag)	0.66	0.05	12.92[a]	0.57	0.06	10.05[a]	
RRS Brooding (n-1 lag)	0.11	0.14	0.75	0.18	0.16	1.11	
Age	-0.03	0.04	-0.82	-0.03	0.04	-0.64	
Sex	1.24	0.81	1.52	1.10	0.95	1.16	
IMD	0.15	0.14	1.09	0.13	0.16	0.80	
Q1 ESSI	-0.30	0.06	-4.66[a]	-0.33	0.07	-4.61[a]	$X^2(1)=7.73^b$
Q1 NYHA	1.14	0.68	1.69	1.43	0.78	$1.83^{p=0.067}$	
History of depression	-0.40	1.12	-0.36	0.46	1.27	0.37	
Days since index event	0.00	0.00	-0.35	0.00	0.00	-0.25	
Random							
Participant √ψ	14.88	2.91		0.00	0.00		
Participant √θ	3.65	0.45		4.82	0.24		
Time √ψ	5.59	1.16					
Overall model	Wald $\chi^2(10)=586.37^a$, Log likelihood=-618.75			Wald $\chi^2(10)=410.51^a$, Log likelihood=-622.62			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Table 4.24: Multilevel (repeated measures) models of worry with anxiety

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=220)							
Fixed							
Time	0.17	0.76	0.23	0.07	0.69	0.11	
Total BAI (n-1 lag)	0.79	0.04	19.32[a]	0.73	0.05	16.14[a]	
Total PSWQ (n-1 lag)	0.03	0.03	1.12	0.03	0.03	1.17	
Random							$X^2(1)=9.61$[b]
Participant √ψ	17.35	3.04		0.00	0.00		
Participant √θ	3.28	0.69		5.12	0.24		
Time √ψ	6.59	1.21					
Overall model	Wald $\chi^2(3)=585.12$[a], Log likelihood=-666.49			Wald $\chi^2(3)=397.58$[a], Log likelihood=-671.30			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=207)							
Fixed							
Time	0.14	0.74	0.19	0.04	0.68	0.06	
Total BAI (n-1 lag)	0.68	0.05	14.13[a]	0.60	0.05	11.41[a]	
Total PSWQ (n-1 lag)	0.01	0.03	0.34	0.01	0.03	0.40	
Age	-0.03	0.04	-0.89	-0.03	0.04	-0.75	
Sex	1.18	0.82	1.45	1.07	0.95	1.13	
IMD	0.14	0.14	1.00	0.11	0.16	0.70	
Q1 ESSI	-0.31	0.06	-4.82[a]	-0.35	0.07	-4.77[a]	$X^2(2)=8.13^c$
Q1 NYHA	0.96	0.67	1.42	1.22	0.78	1.57	
History of depression	-0.50	1.12	-0.44	0.35	1.27	0.27	
Days since index event	0.00	0.00	-0.34	0.00	0.00	-0.22	
Random							
Participant √ψ	18.25	43.49		0.00	0.00		
Participant √θ	2.23	27.34		4.85	0.24		
Time √ψ	6.95	17.58					
Overall model	Wald $\chi^2(10)=588.19^a$, Log likelihood=-616.38			Wald $\chi^2(10)=408.75^a$, Log likelihood=-620.45			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

4.4.8.4 Predictors of general health-related quality of life (EQ5D)

4.4.8.4.1 Predictors of EQ5D VAS

A simple random intercept model (model i) showed that EQ5D VAS at a previous assessment time significantly predicted EQ5D VAS at the next assessment time. The likelihood ratio test comparing this model with an equivalent random coefficient model indicated that trajectories of EQ5D VAS did not vary significantly between participants. These results are summarised in Appendix 35.

In an extension of the simple models that included RRS brooding as an additional predictor (model ii), both EQ5D VAS at the previous assessment time and RRS brooding at the previous assessment time significantly predicted EQ5D VAS at the subsequent assessment time. After inclusion of covariates (model iii) EQ5D VAS at the previous assessment time and low social support were the only significant predictors of EQ5D VAS. Trajectories of EQ5D VAS over time did not vary between participants. Results of these models are reported in Table 4.25.

In a second extension of the simple model that included total PSWQ as an additional predictor (model ii), EQ5D VAS at the previous assessment time and lower PSWQ at the previous assessment time predicted higher EQ5D VAS at the next assessment time. In a model that controlled for covariates (model iii), higher EQ5D VAS at the previous assessment time, lower PSWQ at the previous assessment time and low social support were significant predictors of higher EQ5D VAS. Trajectories of EQ5D VAS did not vary between participants. Results of these models are summarised in Table 4.26.

Table 4.25: Multilevel (repeated measures) models of brooding with EQ5D VAS

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=223)							
Fixed							
Time	0.32	2.05	0.16	0.37	1.89	0.20	
EQ5D VAS (n-1 lag)	0.70	0.05	13.64[a]	0.63	0.05	11.55[a]	
RRS Brooding (n-1 lag)	-0.75	0.32	-2.33[c]	-0.83	0.35	-2.40[c]	
Random							$X^2(2)=2.68$
Participant √ψ	35.61	238.40		0.00	0.00		
Participant √θ	11.82	55.21		14.02	0.66		
Time √ψ	14.00	93.26					
Overall model	Wald $\chi^2(3)=250.27$[a], Log likelihood=-903.84			Wald $\chi^2(3)=182.98$[a], Log likelihood=-905.17			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=211)							
Fixed							
Time	0.07	2.07	0.03	0.17	1.87	0.09	
EQ5D VAS (n-1 lag)	0.69	0.05	13.05[a]	0.61	0.06	10.43[a]	
RRS Brooding (n-1 lag)	-0.44	0.34	-1.28	-0.57	0.38	-1.50	
Age	-0.05	0.10	-0.53	-0.06	0.11	-0.49	
Sex	-3.00	2.27	-1.32	-3.04	2.61	-1.16	
IMD	-0.33	0.38	-0.89	-0.30	0.43	-0.69	
Q1 ESSI	0.48	0.16	3.03[b]	0.52	0.18	2.88[b]	$X^2(2)=5.55$
Q1 NYHA	-1.83	1.82	-1.00	-2.40	2.09	-1.15	
Days since index event	-0.01	0.01	-1.43	-0.01	0.01	-1.04	
Random							
Participant √ψ	49.64	131.37		0.00	0.00		
Participant √θ	6.48	77.37		13.47	0.66		
Time √ψ	19.30	51.99					
Overall model	Wald $\chi^2(9)=315.36$[a], Log likelihood=-845.37			Wald $\chi^2(9)=216.56$[a], Log likelihood=-848.15			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Table 4.26: Multilevel (repeated measures) models of worry with EQ5D VAS

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=224)							
Fixed							
Time	0.69	2.03	0.34	0.75	1.86	0.40	
EQ5D VAS (n-1 lag)	0.69	0.05	13.60[a]	0.62	0.05	11.42[a]	
Total PSWQ (n-1 lag)	-0.22	0.07	-3.32[a]	-0.24	0.07	-3.30[a]	
Random							$X^2(1)=3.17$
Participant √ψ	35.86	10.06		0.00	0.00		
Participant √θ	11.66	1.31		13.88	0.66		
Time √ψ	14.13	4.031					
Overall model	Wald $\chi^2(3)=263.84$[a], Log likelihood=-905.49			Wald $\chi^2(3)=190.02$[a], Log likelihood=-907.08			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=211)							
Fixed							
Time	0.05	2.06	0.02	0.23	1.86	0.12	
EQ5D VAS (n-1 lag)	0.68	0.05	12.97[a]	0.60	0.06	10.36[a]	
Total PSWQ (n-1 lag)	-0.14	0.07	-2.01[c]	-0.16	0.08	-2.06[c]	
Age	-0.05	0.10	-0.51	-0.05	0.11	-0.44	
Sex	-2.69	2.26	-1.19	-2.73	2.60	-1.05	
IMD	-0.32	0.38	-0.85	-0.28	0.43	-0.64	
Q1 ESSI	0.43	0.15	2.78[b]	0.48	0.18	2.72[b]	$X^2(2)=5.68$
Q1 NYHA	-1.95	1.82	-1.07	-2.57	2.09	-1.23	
Days since index event	-0.02	0.01	-1.56	-0.01	0.01	-1.17	
Random							
Participant √ψ	48.94	1071.86		0.00	0.00		
Participant √θ	6.72	600.10		13.42	0.65		
Time √ψ	19.06	423.50					
Overall model	Wald $\chi^2(9)=320.13$[a], Log likelihood=-844.43			Wald $\chi^2(9)=219.12$[a], Log likelihood=-847.27			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

4.4.8.4.2 Predictors of EQ5D index value

A simple random intercept model (model i) showed that EQ5D index value at a previous assessment time significantly predicted EQ5D index value at the next assessment time. The likelihood ratio test comparing this model with an equivalent random coefficient model that trajectories of EQ5D index value did not vary significantly between participants. Results are summarised in Appendix 36.

In an extension of the simple models that included RRS brooding as an additional predictor (model ii), EQ5D index value at the previous assessment time significantly predicted EQ5D index value at the subsequent assessment time, and there was a trend (p=0.057) toward higher RRS brooding at the previous assessment time also predicting worse EQ5D index value at the next assessment time. After inclusion of covariates (model iii) EQ5D index value at the previous assessment time, high RRS brooding at the previous assessment time, low social support and greater severity of cardiac disease were significant predictors of worse EQ5D index values. Trajectories of EQ5D index value did not vary between participants. Results are reported in Table 4.27.

In a second extension of the simple model that included total PSWQ as an additional predictor (model ii) EQ5D index value at the previous assessment time and higher PSWQ at the previous assessment time predicted worse EQ5D index values at the next assessment time. In a model that included covariates (model iii) EQ5D index value at the previous assessment time, low PSWQ at the previous assessment time, low social support and greater severity of cardiac disease were significant predictors of worse EQ5D index values. Trajectories of EQ5D index values did not vary between participants. These results are summarised in Table 4.28.

Table 4.27: Multilevel (repeated measures) models of brooding with EQ5D Index value

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=222)							
Fixed							
Time	-0.02	0.02	-1.39	-0.03	0.02	-1.44	
EQ5D Index value (n-1 lag)	0.73	0.05	14.13[a]	0.71	0.05	13.44[a]	
RRS Brooding (n-1 lag)	-0.01	0.00	-1.82[p=0.069]	-0.01	0.00	-1.91[p=0.057]	
Random							$X^2(2)=1.44$
Participant √ψ	0.31	-		0.00	0.00		
Participant √θ	0.10	0.01		0.13	0.01		
Time √ψ	0.13	0.01					
Overall model	Wald $\chi^2(3)=291.50^a$, Log likelihood=140.84			Wald $\chi^2(3)=266.64^a$, Log likelihood=140.12			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=209)							
Fixed							
Time	-0.02	0.02	-0.98	-0.02	0.02	-1.06	
EQ5D Index value (n-1 lag)	0.61	0.06	10.73[a]	0.58	0.06	9.59[a]	
RRS Brooding (n-1 lag)	-0.01	0.00	-2.18[c]	-0.01	0.00	-2.23[c]	
Age	0.00	0.00	-1.69	0.00	0.00	-1.47	
Sex	-0.04	0.02	-1.82	-0.04	0.02	-1.83	
IMD	0.00	0.00	-0.97	0.00	0.00	-1.13	
Q1 ESSI	0.01	0.00	3.82[a]	0.01	0.00	3.51[a]	$X^2(2)=5.19$
Q1 NYHA	-0.05	0.02	-2.81[b]	-0.06	0.02	-2.75[b]	
Days since index event	0.00	0.00	-0.08	0.00	0.00	-0.08	
Random							
Participant √ψ	0.23	9.96		0.00	0.00		
Participant √θ	0.11	1.66		0.12	0.01		
Time √ψ	0.10	3.40					
Overall model	Wald $\chi^2(9)=372.85$[a], Log likelihood=146.89			Wald $\chi^2(9)=312.46$[a], Log likelihood= 144.29			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Table 4.28: Multilevel (repeated measures) models of worry with EQ5D Index value

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=222)							
Fixed							
Time	-0.02	0.02	-1.33	-0.02	0.02	-1.38	
EQ5D Index value (n-1 lag)	0.73	0.05	14.95[a]	0.72	0.05	13.94[a]	
Total PSWQ (n-1 lag)	0.00	0.00	-2.07[c]	0.00	0.00	-2.07[c]	
Random							$X^2(1)=1.99$
Participant √ψ	0.30	-		0.00	0.00		
Participant √θ	0.10	0.01		0.13	0.01		
Time √ψ	0.12	0.01					
Overall model	Wald $\chi^2(3)=307.19$[a], Log likelihood=141.43			Wald $\chi^2(3)=269.97$[a], Log likelihood=140.43			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=209)							
Fixed							
Time	-0.02	0.02	-1.02	-0.02	0.02	-1.08	
EQ5D Index value (n-1 lag)	0.62	0.06	11.32[a]	0.59	0.06	10.00[a]	
Total PSWQ (n-1 lag)	0.00	0.00	-2.25[c]	0.00	0.00	-2.11[b]	
Age	0.00	0.00	-1.49	0.00	0.00	-1.24	
Sex	-0.03	0.02	-1.55	-0.04	0.02	-1.60	
IMD	0.00	0.00	-0.81	0.00	0.00	-0.94	
Q1 ESSI	0.01	0.00	3.62[a]	0.01	0.00	3.38[a]	$X^2(2)=5.45$
Q1 NYHA	-0.05	0.02	-2.64[b]	-0.05	0.02	-2.63[b]	
Days since index event	0.00	0.00	-0.36	0.00	0.00	-0.30	
Random							
Participant √ψ	0.44	1.43		0.00	0.00		
Participant √θ	0.03	1.82		0.12	0.01		
Time √ψ	0.18	0.54					
Overall model	Wald $\chi^2(9)=375.31$[a], Log likelihood=146.17			Wald $\chi^2(9)= 310.43$[a], Log likelihood=143.45			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

4.4.8.4.3 Predictors of EQ5D subscales

Both random coefficient and random intercept proportional-odds models for all EQ5D subscales failed to converge. Since failure to converge was common to the simple (i) and extended (ii and iii) models, a possible explanation is that random intercepts and slopes were not necessary for these models.

Since it was not possible to run multilevel (repeated measures) models with the EQ5D subscales as outcomes, an alternative approach in line with the multilevel (repeated measures) modelling method used for the other continuous outcome variables was sought. Therefore, ordered logistic regression analysis was performed for each EQ5D subscale using the cluster option (defining participants as clusters) to obtain robust standard errors due to the nested data structure. The predictor variables in each model consisted of: (1) a fixed lag variable (n-1) for RRS brooding or total PSWQ (in separate models) to investigate associations between predictors at one assessment time with outcomes at a subsequent assessment time, (2) a fixed lag variable (n-1) for the relevant EQ5D subscale (i.e. the current response was regressed on the previous response), and (3) the covariates age, sex, index of multiple deprivation, social support, severity of cardiac disease and days since index event.

Findings are summarised in Table 4.29. All overall models were significant, explaining from 23% to 48% of variance, and previous subscale responses predicted subsequent subscale responses in all models. Results of regression models with RRS brooding as the main predictor are presented in Appendix 37, and results of regression models with PSWQ as the main predictor are presented in Appendix 38.

Table 4.29: Summary of ordered logistic regression analyses with brooding and worry lag variables as predictors and EQ5D subscales as outcomes

Brooding models	EQ5D Mobility	EQ5D Self-care	EQ5D Usual activities	EQ5D Pain	EQ5D Anxiety/ depression
Age	✓		✓		
Sex					
IMD	✓				
Q1 ESSI	✓	✓	✓	✓	✓
Q1 NYHA	✓		✓	✓	✓
Days since index event					
EQ5D outcome (n-1 lag)	✓	✓	✓	✓	✓
RRS Brooding (n-1 lag)			✓	✓	p=0.089

Worry models	EQ5D Mobility	EQ5D Self-care	EQ5D Usual activities	EQ5D Pain	EQ5D Anxiety/ depression
Age	✓		✓		
Sex					
IMD	✓				
Q1 ESSI	p=0.074	✓	✓	✓	✓
Q1 NYHA	✓	p=0.070	✓	✓	✓
Days since index event					
EQ5D outcome (n-1 lag)	✓	✓	✓	✓	✓
Total PSWQ (n-1 lag)	✓		p=0.056	✓	✓

p≤0.05	p≤0.01	p≤0.001

Q1=baseline.

4.4.8.5 Predictors of cardiac disease-specific quality of life (SAQ)

The results of fully adjusted multilevel (repeated measures) models with SAQ subscales as outcomes are summarised in Table 4.30.

Simple random intercept models (model i) indicated that only trajectories of SAQ angina frequency varied significantly between participants. In extended models (models ii and iii) all SAQ subscales at the previous assessment time were significant predictors of responses on that SAQ subscale at the subsequent assessment time. Low social support, greater severity of cardiac disease and being male were identified as additional significant predictors of worse cardiac disease-related quality of life. After controlling for confounders there was a trend towards RRS brooding at the previous

assessment time significantly predicting SAQ disease perception (p=0.052) and SAQ angina frequency (p=0.077) at the subsequent assessment time.

The results of all multilevel (repeated measures) models related to SAQ physical limitations are provided in Appendix 39, SAQ angina frequency in Appendix 40, SAQ angina stability in Appendix 41, SAQ treatment satisfaction in Appendix 42 and SAQ disease perception in Appendix 43.

Table 4.30: Summary of multilevel (repeated measures) models with brooding and worry lag variables as predictors and SAQ subscales as outcomes

Brooding models	SAQ Physical limitations	SAQ Angina frequency	SAQ Angina stability	SAQ Treatment satisfaction	SAQ Disease perception
Age					
Sex*				✓	
IMD					
Q1 ESSI	✓	p=0.078	✓	✓	✓
Q1 NYHA	✓	✓			✓
Days since index event					
SAQ outcome (n-1 lag)	✓	✓	✓	✓	✓
RRS Brooding (n-1 lag)		p=0.077			p=0.052

Worry models	SAQ Physical limitations	SAQ Angina frequency	SAQ Angina stability	SAQ Treatment satisfaction	SAQ Disease perception
Age					
Sex*				✓	
IMD					
Q1 ESSI	✓	✓	✓	✓	✓
Q1 NYHA	✓	✓			
Days since index event					
SAQ outcome (n-1 lag)	✓	✓	✓	✓	✓
Total PSWQ (n-1 lag)					

p≤0.05	p≤0.01	p≤0.001

*Being male was a significant predictor of poorer treatment satisfaction.
Q1=baseline.

4.4.8.6 Impact of time from index event and time from baseline assessment

The number of days from index event was added as a covariate to all multilevel (repeated measures) models and results showed that it did not significantly predict any outcomes, meaning that differences in time from index event did not confound the prospective association of brooding and worry with outcomes related to depression and quality of life.

In addition, a sensitivity analysis was performed which involved adding the number of days from baseline to completion of 2 month and 6 month assessments as an additional covariate to all fully adjusted multilevel (repeated measures) models. Random intercept models were used for all outcomes since random coefficients models failed to converge where depression and anxiety were the outcome variables. The results showed that the number of days from baseline to both 2 and 6 month assessments did not predict any outcome variable, meaning that differences in time from baseline did not confound the prospective association of brooding and worry with outcomes related to depression and quality of life. Since the number of days from baseline was not a significant predictor of any outcome and it did not significantly alter the findings of any of the models, it was not included as a covariate in the final models. To allow comparison of the findings from models with and without number of days from baseline an example is provided in Appendix 44 (where brooding at the previous was the main predictor variable and depression at the subsequent assessment time was the outcome variable).

4.4.8.7 Evaluation of multilevel (repeated measures) model assumptions

Shapiro-Wilk tests of normality (of residuals) for all multilevel (repeated measures) models showed that level 1 and level 2 residuals were not normally distributed in any of the multilevel (repeated measures) models (results are summarised in Appendix 45). In addition, inspection of residuals versus fitted values plots indicated violation of the assumption of homoscedasticity for the majority of models (an example is provided in Appendix 46). Therefore, an attempt was made to re-estimate the models using a robust option (sandwich estimator) to adjust the standard errors. However, these models failed to converge and with this in mind the standard errors produced using standard maximum likelihood estimation for these models could be biased. However the multilevel (repeated measures) models were

exploratory in order to validate and extend the findings of the staged multivariable regression models presented previously. The results are consistent between the two approaches suggesting the multilevel (repeated measures) models are reliable.

4.4.8.8 Summary of findings of multilevel (repeated measures) models

Findings of unadjusted and adjusted multilevel (repeated measures) models that included lag-1 variables (n-1) to assess the impact of predictors at a previous assessment time (*t*) on outcomes at a subsequent assessment time (*t*+1) are summarised in Table 4.31.

Table 4.31: Summary of significant predictors of all outcomes based on unadjusted and adjusted multilevel (repeated measures) models

Outcome	Brooding (unadjusted)	Brooding (adjusted)	Worry (unadjusted)	Worry (adjusted)	Other predictors
PHQ Depression*	✓	p=0.065			Previous outcome, social support
BAI Anxiety*					Previous outcome, social support
EQ5D VAS	✓		✓	✓	Previous outcome, social support, severity of cardiac disease
EQ5D index	p=0.057	✓	✓	✓	Previous outcome, social support, severity of cardiac disease
EQ5D Mobility			✓	✓	Previous outcome, social support, severity of cardiac disease, age, index of multiple deprivation
EQ5D Self-care	p=0.060		p=0.059		Previous outcome, social support, age
EQ5D Usual activities	✓	✓	✓	p=0.056	Previous outcome, social support, severity of cardiac disease, age
EQ5D Pain	✓	✓	✓	✓	Previous outcome, social support, severity of cardiac disease
EQ5D Anxiety / depression	✓	p=0.089	✓	✓	Previous outcome, social support, severity of cardiac disease
SAQ Physical limitations					Previous outcome, social support, severity of cardiac disease
SAQ Angina frequency	✓	p=0.077			Previous outcome, social support, severity of cardiac disease
SAQ Angina stability			p=0.061		Previous outcome, social support
SAQ Treatment satisfaction	✓		p=0.062		Previous outcome, social support, sex
SAQ Disease perception	✓	p=0.052	✓		Previous outcome, social support, severity of cardiac disease

✓=significant predictor.

Green=significant predictor in brooding models only.

Red=significant predictor in worry models only.

*Significant between participant variation in trajectories of depression and anxiety.

4.5 Summary of findings

The main aim of this study was to explore in patients with recent ACS whether rumination and worry would prospectively predict depression, anxiety and worse health-related quality of life over 6 months following hospital admission.

A sample of 169 patients (mean age 67 years, 75% male) with ACS were recruited from secondary care cardiology services of a single hospital within 6 months of hospital admission for myocardial infarction or coronary revascularisation. Just over a quarter of the sample had a diagnosis of angina with the rest split approximately evenly between diagnoses of STEMI and NSTEMI.

Of the 169 participants who completed baseline assessments only 66% completed repeat assessments at 6 months, although non-completers did not differ from completers in any sample characteristics. Otherwise, the quantity of missing data at case and item level was within acceptable ranges (e.g.[358]).

At baseline 14% of the sample was depressed (PHQ≥10) and these participants were younger, more socially isolated, had a history of depression and worse socioeconomic status than the group without depression. Those who were depressed at baseline also reported greater functional limitations related to severity of cardiac disease compared to those without depression, although there was no difference between the groups in measures of severity extracted from medical records (left ventricular function, number of diseased coronary vessels, troponin level). A higher proportion of depressed participants failed to complete 6 month assessments compared to non-depressed participants.

There were no significant changes in mean brooding, worry, depression, anxiety or quality of life scores across the three assessment times (baseline, 2 months and 6 months).

There were small to medium sized correlations between baseline brooding and worry with worse 6 month depression, anxiety and some measures of quality of life. An exploratory analysis revealed that the prospective association of baseline brooding and 6 month depression was stronger in those who were depressed at baseline compared to those not depressed at baseline.

Staged multivariable regression models that controlled for the effects of important confounding variables (age, sex, socioeconomic status, history of depression, social support, severity of cardiac disease, baseline depression/anxiety/quality of life) showed that baseline brooding was a significant predictor of depression at 6 months, accounting for 2% of the variance. Baseline worry was a significant predictor of worse quality of life related to mobility problems at 6 months.

Baseline values of outcome variables were strong predictors of 6 month outcomes and low perceived availability of social support was a strong predictor of 6 month depression, anxiety and quality of life. Greater severity of cardiac disease was a consistent predictor of worse outcomes particularly in relation to measures of quality of life.

Associations of baseline brooding and worry with 2 month outcomes (and of 2 month brooding and worry with 6 month outcomes) were mostly consistent with associations observed between baseline brooding and worry with 6 month outcomes.

Longitudinal multilevel (repeated measures) models were used to validate and extend the findings of staged multivariable regression analyses by allowing for within-participant correlations due to repeated assessments (i.e. within-participant clustering). These models indicated that trajectories of depression and anxiety varied between participants over time suggesting that there may be subgroups of post-ACS patients particularly 'at risk' of worse outcomes.

Longitudinal models also showed that time since index event (i.e. number of days between hospitalisation and baseline assessment) and time between consecutive assessments were not significant predictors of outcomes, meaning that they did not confound the associations of brooding and worry with depression and other outcomes.

The association of brooding at the previous assessment time with depression at the next assessment time in multilevel (repeated measures) models was on the threshold of significance after controlling for confounding variables including social support. A sensitivity analysis in which social support was removed from the model showed that brooding was a significant predictor of depression.

Chapter 5 Cohort study results – Part II: Mediators of the association between brooding and worry with depression and quality of life

5.1 Chapter outline

The secondary aim of this observational prospective cohort study was to explore potential mechanisms by which perseverative negative thinking may impact on mood and worse physical health outcomes in people with coronary heart disease (CHD).

Several mechanisms have been suggested by which perseverative negative thinking may contribute to depression. These include reduced social support, impaired problem solving, reduced instrumental behaviours, and increased negative cognitive biases[120] (as detailed in section 1.2.4.5 of Chapter 1). Results from the previous chapter suggest that there is a prospective association between brooding and later depression, and between both brooding and worry with later quality of life, and so this chapter will focus on investigating whether reduced social support, impaired problem solving, reduced engagement in pleasant activities and increased negative cognitive biases may act as mediators for these associations.

Detailed methods related to the cohort study were presented in Chapter 3. This results chapter presents:

i. Hypotheses relating to the secondary aim of the study.
ii. A description of the statistical methods used.
iii. Results of mediation analyses.
iv. A brief summary of findings

Discussion of the methods and findings with reference to strengths, weaknesses, comparison with existing literature and implications for future research is combined with that relating to the previous results chapter (Chapter 4) and is presented in the general discussion chapter (Chapter 6).

5.2 Hypotheses

Four potentially complementary hypotheses of how rumination may impact upon subsequent depression were tested. The main hypotheses are that:

i. In patients with recent acute coronary syndrome (ACS), the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by low social support.

ii. In patients with recent ACS, the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by impaired problem solving.

iii. In patients with recent ACS, the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by reduced instrumental behaviours, as indexed by engagement in pleasant activities.

iv. In patients with recent ACS, the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by elevated negative cognitive biases, as indexed by negative self-relevant memory bias and negative interpretation bias.

The secondary hypotheses are that:

v. In patients with recent ACS, the impact of rumination and worry following the initial cardiac event upon worse quality of life at six month follow-up will be mediated by low social support.

vi. In patients with recent ACS, the impact of rumination and worry following the initial cardiac event upon worse quality of life at six month follow-up will be mediated by impaired problem solving.

vii. In patients with recent ACS, the impact of rumination and worry following the initial cardiac event upon worse quality of life at six month follow-up will be mediated by reduced instrumental behaviours, as indexed by engagement in pleasant activities.

viii. In patients with recent ACS, the impact of rumination and worry following the initial cardiac event upon worse quality of life at six month follow-up will be mediated by elevated negative cognitive biases, as indexed by negative self-relevant memory bias and negative interpretation bias.

A note on abbreviations

The measures used to assess the predictors, outcomes and mediator variables of interest were described fully in Chapter 3. Throughout this chapter the following abbreviations will be used: brooding ('RRS brooding'), worry ('PSWQ'), depression ('PHQ'), anxiety ('BAI'), general health-related quality of life ('EQ5D'), cardiac disease-specific quality of life ('SAQ'), social support ('ESSI'), problem solving ('SPSI'), pleasant activities ('PES'), socioeconomic status ('IMD').

5.3 Statistical analysis

5.3.1 Description of potential mediators at baseline

Potential mediator variables at baseline (ESSI social support, SPSI problem solving, PES pleasant events, negative cognitive biases) were summarised using descriptive statistics. Missing data were summarised and key characteristics (age, sex, depression) of cases with and without missing data were compared using Mann Whitney U or Chi-Square tests.

Spearman's rho or Kendall's Tau-b correlations, as appropriate, were used to explore bivariate associations among baseline sample characteristics (age, sex, years of education, employment status, relationship status, socioeconomic status, history of depression, smoking status, alcohol use, recreational drug use and exercise frequency) with potential mediator variables (ESSI, SPSI, PES, negative cognitive biases). For dichotomous variables related to sample characteristics, Mann-Whitney U tests were used instead to look at differences in mediator variables at different levels of the sample characteristics.

Spearman's rho or Kendall's Tau-b correlations were also used to explore bivariate associations among main predictors (RRS brooding and PSWQ) with potential mediator variables, among potential mediators with outcomes (PHQ, BAI, EQ5D, SAQ) at baseline, and among the potential mediator variables themselves.

5.3.2 Description of potential mediators at 2 months and 6 months

Similar to baseline assessments, the potential mediator variables at 2 months were summarised using descriptive statistics, and missing data was described. Key characteristics (age, sex, baseline PHQ) of cases with and without missing data at 2 months were compared using Mann Whitney U or Chi-Square tests.

Data pertaining to 6 month assessments were treated in the same way as data pertaining to 2 month assessments, as described above.

5.3.3 Changes in potential mediator variables over time

To investigate changes over time in each of the potential mediator variables a series of Friedman's tests with assessment time as the independent variable were used, combined with Wilcoxon's tests for post-hoc exploration of significant main effects.

5.3.4 Testing for mediation using multiple regression analyses

The role of social support, problem solving, engagement in pleasant activities and negative cognitive biases as potential mediators of the associations between (a) brooding with depression and (b) brooding and worry with quality of life were explored.

Mediation was tested using a series of regression analyses in an approach based on the evaluation of a set of causal steps as described by Baron & Kenny (1986)[359], combined with a bootstrap test of the mediated effect[360]. The premise of mediation analysis is that the total effect of the predictor variable on the outcome can be partitioned into a direct component which represents the effect the predictor independently exerts on the outcome, and an indirect component which represents the effect the predictor exerts on the outcome via a third, causal, variable (the mediated effect).

A series of three ordinary least squares regression analyses were conducted for each set of predictor, mediator and outcome variables (outcome regressed on predictor, proposed mediator regressed on predictor, and outcome regressed on both predictor and mediator in the same model) and the following conditions for mediation were evaluated (see Figure 5.1 for illustration):

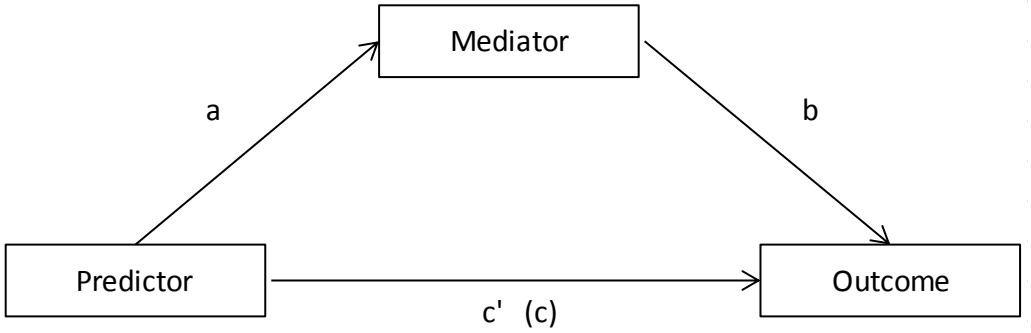
i. The predictor must significantly predict the outcome (the total, unadjusted, effect of predictor on outcome, *path c'*).

ii. The predictor must significantly predict the proposed mediator (the direct effect of predictor on mediator, *path a*).

iii. The proposed mediator must significantly predict the outcome in a model that also includes the predictor (*path b*, the direct effect of mediator on outcome).

iv. The regression coefficient of the predictor in a model that also includes the mediator (*path c*, the direct effect of predictor on outcome) must be smaller than the coefficient of the total effect (*path c'*).

Figure 5.1: Path diagram of mediation



c' = total effect of predictor on outcome.
a = direct effect of predictor on mediator.
b = direct effect of mediator on outcome.
c = direct effect of predictor on outcome.
a x b = indirect effect of predictor on outcome, via mediator.

According to the traditional Baron & Kenny (1986)[359] framework mediation is present if steps i to iv, above, are true. Full mediation is indicated if the predictor has no effect on the outcome after controlling for the mediator (i.e. there is no significant direct effect of the predictor on the outcome; *path c*), otherwise partial mediation is indicated. Ordinary regression coefficients and p values were considered acceptable tests of the total effect (*path c'*) and direct effects (*paths a*,*b* and *c*).

In line with more contemporary approaches the significance and magnitude of the indirect effect of the predictor on outcome via the proposed mediator (*path a* x *b*;

the mediated portion of the total effect) was also evaluated if the causal steps approach indicated findings consistent with mediation. The Sobel test recommended by Baron & Kenny (1986) for evaluating the significance of indirect effects has been criticized due to low power to detect effects[361, 362] and so the significance of the indirect effect was assessed using a bootstrap test with 5000 samples[360]. If bootstrapped bias corrected confidence intervals for the indirect effect did not cross zero the indirect effect was considered significant.

Since the current study was designed to investigate *prospective* associations of perseverative negative thinking (brooding and worry) with subsequent depression, anxiety and health-related quality of life, the regression models used for mediation analyses were constructed to test the temporal precedence of associations (that is, to investigate whether brooding and worry would prospectively predict the proposed mediators, while at the same time investigating whether the proposed mediators would prospectively predict outcomes). Consistent with the staged multivariable regression models presented in the preceding chapter, for mediation analyses the main predictor variables (RRS brooding or PSWQ) were taken from the baseline assessment, and the main outcomes (PHQ, EQ5D or SAQ) were taken from the 6 month assessment. The majority of proposed mediators (ESSI, SPSI, and PES) were taken from the 2 month assessment. It was intended that negative cognitive biases would also be taken from the 2 month assessment, however due to missing data at 2 months negative cognitive biases were taken from the baseline assessment instead. Mediation analyses were conducted only where a significant association was previously demonstrated (using staged multivariable regression analyses or multilevel (repeated measures) models) between the predictor and outcome after controlling for important confounding variables (see Chapter 4). Specifically, mediation of the following associations was investigated:

i. Baseline brooding with 6 month depression.
ii. Baseline brooding with 6 month health-related quality of life (EQ5D index value)[7].

[7]In order to limit the number of analyses significant associations between baseline brooding with EQ5D usual activities and EQ5D pain at 6 months were not explored with mediation analyses since these subscales contribute to EQ5D index value.

iii. Baseline brooding with 6 month cardiac disease-specific quality of life (SAQ disease perception).

iv. Baseline worry with 6 month health-related quality of life (EQ5D VAS, EQ5D index value)[8].

Due to limited data available at 2 month assessments for measures of negative cognitive biases, cross-sectional mediation analyses (predictors, proposed mediators and outcomes at baseline only) were conducted for negative cognitive biases as mediators. These analyses were exploratory since they were based on cross-sectional associations, although the findings could highlight factors of potential importance for future research.

Two sets of analyses were run for each set of predictor, mediator and outcome variables. First, unadjusted models were used to directly explore the associations of interest. Next, models including important covariates (consistent with the previous chapter: age, sex, socioeconomic status, history of depression[9], severity of cardiac disease and baseline values of the outcome variable) were conducted in order to control for confounding variables. Adjusted models were not conducted if results of the unadjusted model indicated no mediation.

Listwise deletion of cases was used for each set of regression analyses, to ensure that all steps of the mediation test were performed on the same subset of participants. Block entry method was used for all multiple regression analyses.

5.3.4.1 Multiple mediation models

The models outlined above considered the effect of each proposed mediator independently. Where multiple mediators of an association were identified, the models were extended to assess the combined effect of the mediators and to investigate the relative importance of each of the mediators.

The analyses proceeded in a similar manner to the single mediator approach. The regression models described above were extended so that in the third step direct

[8]Significant associations between baseline worry with EQ5D pain and EQ5D anxiety/depression at 6 months were not explored since these subscales contribute to EQ5D index value.
[9]Only where depression was the outcome variable.

effects from the mediator to the outcome (*path b*) were evaluated in a model that included the predictor and all proposed mediators, and in the fourth step the total effect (*path c'*) was compared to the direct effect (*path c*) of the predictor in a model that included all mediators. A bootstrapping method with 5000 samples and bias corrected confidence intervals was used to determine significance of the indirect effect.

5.3.5 Post-hoc analyses

In order to explore the findings in greater depth, a series of post-hoc analyses were conducted to investigate the associations of inflammation and negative cognitive biases with depression. A rationale and description of the analyses is presented with the results in Section 5.4.6.

5.4 Results

5.4.1 Baseline assessments

5.4.1.1 Description of potential mediators at baseline

Summary statistics for potential mediator variables (ESSI, SPSI, PES, negative cognitive biases) at baseline are summarised in Table 5.1.

5.4.1.2 Missing data at baseline

The number of missing cases for any of the questionnaire measures of potential mediator variables (ESSI, SPSI, PES) at baseline ranged from 0 to 5 (0% to 3.0% of cases, based on total n=169), and the total number of missing items for any multi-item variable at baseline ranged from 1 to 188 (0.1% to 5.6% of items).

The number of missing cases for task-based measures of potential mediator variables (negative cognitive biases) at baseline was 81 (47.9% of cases). Task-based measures were administered over the telephone just before or just after completion of the other self-report assessments. It was not possible to complete the tasks with a large number of participants because the participant was either unwilling or could not complete assessments over the phone for some practical reason (e.g. hard of hearing), or the participant did not answer the telephone after several attempts. Since negative

cognitive biases were not the primary outcome of the study participants were not excluded from the study if they were unwilling or unable to complete the tasks.

Missing data at case and subscale level for all potential mediator variables at baseline is summarised in Appendix 47.

For each potential mediator variable, there was no significant difference in characteristics (age, gender ratio, baseline PHQ) of respondents with missing data compared to those for whom data was available.

Table 5.1: Potential mediators at baseline

	N	Min	Max	Mean	SD	Median	IQR
Social support							
ESSI social support	169	7.00	30.00	25.50	5.75	28.00	6.00
Problem solving							
SPSI Positive problem orientation	168	0.00	20.00	11.44	4.04	12.00	5.00
SPSI Rational problem solving	168	0.00	20.00	9.52	4.15	9.00	5.00
SPSI Negative problem orientation	168	0.00	18.00	4.59	4.30	4.00	6.00
SPSI Impulsivity	168	0.00	16.00	4.59	3.37	4.00	5.00
SPSI Avoidance	168	0.00	16.00	4.67	3.55	4.00	5.00
SPSI Total score	168	4.80	18.80	13.42	2.66	13.80	3.40
Pleasant events							
PES Frequency	169	0.00	2.00	1.56	0.36	1.65	0.40
PES Pleasantness	164	0.20	2.00	1.65	0.30	1.70	0.35
PES Obtained pleasure	164	0.00	4.00	2.82	0.80	2.95	1.09
Memory bias							
Positive words endorsed	88	1.00	12.00	9.00	2.63	10.00	3.50
Negative words endorsed	88	0.00	10.00	1.01	1.99	0.00	1.00
Positive words recalled	88	0.00	8.00	2.95	1.96	2.50	3.00
Negative words recalled	88	0.00	8.00	2.31	1.85	2.00	2.00
Negative words recalled (%)	84	0.00	100.00	41.81	24.19	48.33	27.86
Endorsed positive words recalled	88	0.00	7.00	2.27	1.81	2.00	3.00
Endorsed negative words recalled	88	0.00	3.00	0.19	0.54	0.00	0.00
Endorsed negative words recalled (%)	75	0.00	100.00	7.00	18.79	0.00	0.00
Interpretation bias*							
Positive affective homophones (%)	88	40.00	100.00	66.72	13.09	68.33	17.78
Negative affective homophones (%)	88	12.50	100.00	49.80	18.39	50.00	25.00

*For positive and negative homophones the percentage of adjectives for which the affective meaning was accessed was calculated with reference to the percentage for which the neutral meaning was accessed. Therefore the variables for positive and negative homophones are independent.

5.4.1.3 Association of sample characteristics with potential mediators at baseline

There were no significant bivariate correlations of note between sample characteristics and any of the potential mediator variables at baseline. Correlations are presented in Appendix 48.

Results of difference tests showed that more negative words were endorsed as self-descriptive in the memory task in patients with elevated C-reactive protein at hospital admission. Other potential mediators varied according to sample characteristics in plausible ways. For example, those with a history of depression had lower obtained pleasure from pleasant activities and endorsed more negative words as self-descriptive. Perceived social support was higher in those with a spouse or partner compared to those without a partner. Significant findings are summarised fully in Appendix 49.

5.4.1.4 Association of potential mediators with predictors and outcomes at baseline

Correlations between each potential mediator variable with the main predictors and main outcome variables at baseline are presented in Table 5.2. The strongest associations were of brooding with SPSI subscales related to negative problem orientation and other negative aspects of problem solving (r=0.40 to r=0.62). There were similar associations of worry (r=0.29 to r=0.50), depression (r=0.30 to r=0.51), anxiety (r=0.32 to r=0.45) and more weakly overall health-related quality of life (r=0.20 to r=0.40) with negative aspects of problem solving.

There were small correlations between ESSI social support with depression and anxiety (r=0.37 to r=0.38), and more weakly between ESSI with the predictors brooding and worry, and with outcomes related to overall health-related quality of life (EQ5D index value, in particular) and cardiac disease-specific quality of life.

Brooding, depression, anxiety, overall health-related quality of life (EQ5D index value) and disease-specific quality of life related to poor treatment satisfaction and disease perception were weakly but significantly correlated with reduced frequency and pleasantness of pleasant activities (r=0.22 to r=0.36). In addition, quality of life measures related to reduced mobility and physical limitations were weakly associated with reduced frequency of pleasant events.

Finally, there was a small but significant correlation between more negative words endorsed in the memory task with greater brooding (r=0.32), and between a

higher proportion of negative endorsed words recalled with greater brooding, worry and depression (r=0.31 to r=0.41).

5.4.1.5 Associations among proposed mediators at baseline

A matrix of bivariate correlations among the proposed mediator variables at baseline is presented in Appendix 50. The strongest correlations were between subscales within each measure (e.g. correlations among SPSI subscales related to negative aspects of problem solving r=0.33 to r=0.56, correlations among PES subscales r=0.62 to r=0.89). There were also small correlations between low social support and lack of engagement in pleasant activities (r=0.36 to r=0.39), and a constellation of weak correlations between a number of variables indicating a general tendency towards negativity (high number of negative words endorsed as self-descriptive, high negative problem orientation, and low pleasantness ratings of enjoyable activities).

Table 5.2: Correlations between potential mediators with predictors and outcome variables at baseline

	ESSI social support	SPSI Positive problem orientation	SPSI Rational problem solving	SPSI Negative problem orientation	SPSI Impulsivity	SPSI Avoidance	SPSI Total	PES Frequency	PES Pleasantness
Predictors									
Total PSWQ	-0.26[a]	-0.18[c]	-0.03	0.50[a]	0.29[a]	0.26[a]	-0.34[a]	-0.13	-0.13
RRS brooding	-0.27[a]	-0.27[a]	-0.11	0.62[a]	0.40[a]	0.45[a]	-0.53[a]	-0.24[b]	-0.24[b]
Outcomes									
Total PHQ	-0.38[a]	-0.31[a]	-0.22[b]	0.49[a]	0.30[a]	0.38[a]	-0.51[a]	-0.30[a]	-0.34[a]
Total BAI	-0.37[a]	-0.20[b]	-0.18[c]	0.44[a]	0.35[a]	0.32[a]	-0.45[a]	-0.34[a]	-0.32[a]
EQ5D VAS	0.26[a]	0.18[c]	0.12	-0.22[b]	-0.25[b]	-0.20[b]	0.30[a]	0.24[b]	0.15[c]
EQ5D Index value	0.30[a]	0.22[b]	0.17[c]	-0.31[a]	-0.31[a]	-0.24[b]	0.40[a]	0.36[a]	0.28[a]
EQ5D Mobility	-0.13[c]	-0.18[b]	-0.15[c]	0.20[b]	0.27[a]	0.18[b]	-0.28[a]	-0.28[a]	-0.20[b]
EQ5D Self-care	-0.15[c]	-0.09	-0.07	0.19[b]	0.28[a]	0.10	-0.24[a]	-0.12[a]	0.00[b]
EQ5D Usual activities	-0.21[a]	-0.13[c]	-0.08	0.19[b]	0.23[a]	0.09	-0.23[a]	-0.23[a]	-0.16[b]
EQ5D Pain	-0.16[c]	-0.03	-0.09	0.15[c]	0.24[a]	0.14[c]	-0.22[a]	-0.20[a]	-0.18[b]
EQ5D Anxiety / depression	-0.28[a]	-0.21[b]	-0.10	0.41[a]	0.20[b]	0.29[a]	-0.34[a]	-0.22[a]	-0.25[a]
SAQ Physical limitations	0.27[a]	0.15[c]	0.03	-0.18[c]	-0.24[b]	-0.10	0.25[b]	0.39[a]	0.18[c]
SAQ Angina frequency	0.31[a]	0.12	-0.04	-0.21[b]	-0.12	-0.12	0.17[c]	0.25[a]	0.26[b]
SAQ Angina stability	0.19[c]	0.05	-0.05	-0.01	-0.08	-0.09	0.08	0.16[c]	0.15
SAQ Treatment satisfaction	0.30[a]	0.15	0.13	-0.13	-0.15[c]	-0.05	0.21[b]	0.26[a]	0.28[a]
SAQ Disease perception	0.40[a]	0.14	-0.01	-0.30[a]	-0.25[b]	-0.13	0.27[a]	0.28[a]	0.27[a]

Table continued on following page…

	PES Obtained pleasure	Negative words endorsed	Negative words recalled (%)	Endorsed negative words recalled (%)	Positive affective (%)	Negative affective (%)
Predictors						
Total PSWQ	-0.14	0.20	-0.15	0.31[b]	0.01	0.01
RRS brooding	-0.22[b]	0.32[b]	0.00	0.41[a]	-0.02	0.16
Outcomes						
Total PHQ	-0.32[a]	0.22[c]	0.20	0.38[a]	-0.19	0.22[c]
Total BAI	-0.33[a]	0.10	0.14	0.11	-0.08	0.11
EQ5D VAS	0.21[b]	-0.13	-0.17	-0.23[c]	0.17	-0.10
EQ5D Index value	0.35[a]	-0.16	-0.11	0.03	0.03	-0.17
EQ5D Mobility	-0.25[a]	0.18[c]	0.11	-0.03	-0.03	0.09
EQ5D Self-care	-0.07[a]	-0.04	0.07	-0.02	-0.02	-0.01
EQ5D Usual activities	-0.21[a]	0.02	0.05	-0.06	-0.04	0.15
EQ5D Pain	-0.21[a]	0.06	0.03	-0.06	-0.02	0.09
EQ5D Anxiety / depression	-0.25[a]	0.21[c]	0.04	0.33[b]	-0.11	0.09
SAQ Physical limitations	0.30[a]	-0.07	-0.12	0.09	0.06	-0.22
SAQ Angina frequency	0.25[b]	0.02	-0.14	0.05	0.05	-0.05
SAQ Angina stability	0.16[c]	0.06	0.03	-0.07	0.01	0.13
SAQ Treatment satisfaction	0.34[a]	0.05	0.05	-0.02	0.04	-0.10
SAQ Disease perception	0.29[a]	0.04[c]	-0.18	0.05	-0.08	-0.14

[a]$p<0.001$ [b]$p\leq0.01$ [c]$p\leq0.05$.

5.4.2 2 month assessments

5.4.2.1 Description of mediators at 2 months

Summary statistics for potential mediator variables (ESSI, SPSI, PES, negative cognitive biases) at 2 months are summarised in Table 5.3.

5.4.2.2 Missing data at 2 months

The number of missing cases for any of the questionnaire measures (ESSI, SPSI, PES) of potential mediator variables at baseline ranged from 2 to 4 (1.6% to 3.2% of cases, based on total n=125), and the total number of missing items for any multi-item variable at baseline ranged from 12 to 78 (1.9% to 3.1% of items).

The number of missing cases for task-based measures of potential mediator variables (negative cognitive biases) at baseline ranged from 90 to 91 (72.0% to 72.8% of cases). There was a large amount of missing data since many participants were unwilling/unable to complete the assessments over the telephone, or could not be reached by telephone after several attempts.

Missing data at case and subscale level for all potential mediator variables at 2 months is summarised in Appendix 51.

For each potential mediator variable, there was no significant difference in characteristics (age, gender ratio, 2 month PHQ) of respondents with missing data compared to those for whom data was available.

Table 5.3: Potential mediators at 2 months

	N	Min	Max	Mean	SD	Median	IQR
Social support							
ESSI social support	123	6.00	30.00	25.11	6.26	28.00	8.00
Problem solving							
SPSI Positive problem orientation	121	0.00	20.00	11.51	3.76	12.00	5.00
SPSI Rational problem solving	121	0.00	20.00	10.04	4.23	10.00	6.00
SPSI Negative problem orientation	121	0.00	19.00	3.98	4.10	3.00	5.00
SPSI Impulsivity	121	0.00	18.00	4.42	3.53	4.00	4.00
SPSI Avoidance	121	0.00	18.00	4.43	3.58	4.00	4.00
SPSI Total score	121	2.00	18.40	13.74	2.71	13.60	3.40
Pleasant events							
PES Frequency	123	0.00	2.00	1.58	0.31	1.65	0.44
PES Pleasantness	123	0.80	2.00	1.63	0.29	1.70	0.41
PES Obtained pleasure	123	0.00	4.00	2.80	0.79	2.90	1.05
Memory bias							
Positive words endorsed	35	5.00	12.00	9.29	2.31	10.00	5.00
Negative words endorsed	35	0.00	9.00	0.49	1.65	0.00	0.00
Positive words recalled	35	0.00	8.00	2.77	2.03	3.00	3.00
Negative words recalled	35	0.00	6.00	2.03	1.65	2.00	2.00
Negative words recalled (%)	35	0.00	100.00	36.54	23.67	40.00	16.67
Endorsed positive words recalled	35	0.00	7.00	2.11	1.83	2.00	2.00
Endorsed negative words recalled	35	0.00	0.00	0.00	0.00	0.00	0.00
Endorsed negative words recalled (%)	28	0.00	0.00	0.00	0.00	0.00	0.00
Interpretation bias							
Positive affective homophones (%)	34	50.00	90.00	67.06	10.57	70.00	17.78
Negative affective homophones (%)	34	12.50	75.00	49.26	15.16	50.00	25.00

5.4.3 6 month assessments

5.4.3.1 Description of mediators at 6 months

Summary statistics for potential mediator variables (ESSI, SPSI, PES, negative cognitive biases) at 2 months are summarised in Table 5.4.

5.4.3.2 Missing data at 6 months

The number of missing cases for any of the questionnaire measures (ESSI, SPSI, PES) of potential mediator variables at baseline ranged from 0 to 3 (0% to 2.7% of cases, based on total n=111), and the total number of missing items for any multi-item variable at baseline ranged from 0 to 85 (0% to 3.8% of items).

The number of missing cases for task-based measures of potential mediator variables (negative cognitive biases) at baseline was 97 (87.4% of cases). There was a large amount of missing data since many participants were unwilling/unable to complete the assessments over the telephone, or could not be reached by telephone after several attempts.

Missing data at case and subscale level for all potential mediator variables at 6 months is summarised in Appendix 52.

For each potential mediator variable characteristics (age, gender ratio, 6 month PHQ) of respondents with missing data were compared to those for whom data was available. Cases with missing SPSI subscales were older than cases for whom data was available (82 years vs. 68 years; z=-1.99, p=0.0463), and cases with missing negative cognitive bias tasks were older than cases for whom data was available (68 years vs. 66 years; z=2.02, p=0.0430).

Table 5.4: Potential mediators at 6 months

	N	Min	Max	Mean	SD	Median	IQR
Social support							
ESSI social support	111	3.00	30.00	25.05	6.81	28.00	7.00
Problem solving							
SPSI Positive problem orientation	109	0.00	20.00	11.84	4.05	11.04	5.00
SPSI Rational problem solving	109	1.00	20.00	9.85	4.56	10.00	7.00
SPSI Negative problem orientation	109	0.00	18.00	3.42	3.61	3.00	5.00
SPSI Impulsivity	109	0.00	15.00	4.34	3.41	4.00	6.00
SPSI Avoidance	109	0.00	18.00	4.16	3.31	4.00	4.00
SPSI Total score	109	2.40	19.20	13.95	2.63	13.80	3.00
Pleasant events							
PES Frequency	109	0.00	2.00	1.58	0.36	1.65	0.40
PES Pleasantness	108	0.30	2.00	1.63	0.34	1.74	0.41
PES Obtained pleasure	108	0.00	4.00	2.84	0.83	3.05	1.15
Memory bias							
Positive words endorsed	14	6.00	12.00	9.71	1.94	10.00	3.00
Negative words endorsed	14	0.00	2.00	0.21	0.58	0.00	0.00
Positive words recalled	14	1.00	6.00	3.36	1.78	4.00	3.00
Negative words recalled	14	0.00	5.00	2.71	1.64	3.00	2.00
Negative words recalled (%)	14	0.00	80.00	41.88	23.16	44.16	22.22
Endorsed positive words recalled	14	0.00	6.00	2.86	1.88	3.00	3.00
Endorsed negative words recalled	14	0.00	0.00	0.00	0.00	0.00	0.00
Endorsed negative words recalled (%)	13	0.00	0.00	0.00	0.00	0.00	0.00
Interpretation bias							
Positive affective homophones (%)	14	30.00	80.00	66.19	13.89	70.00	20.00
Negative affective homophones (%)	14	12.50	75.00	51.28	19.05	50.00	25.00

5.4.4 Changes over time in potential mediators

There were no significant changes in mean values of any potential mediators related to social support, pleasant events or negative cognitive biases, indicating that these measures were stable over time. The negative problem orientation subscale of the SPSI problem solving measure was significantly lower at 6 months compared to baseline (F=6.95, p=0.0310, z=2.68, p=0.0073) and 2 months (F=6.95, p=0.0310, z=2.15, p=0.0319), indicating an improvement in problem orientation at the 6 month assessment.

5.4.5 Testing mediation using regression analyses

5.4.5.1 Mediators of the association of brooding with depression

A summary of the findings of each series of regression analyses and bootstrap tests conducted to investigate potential mediators of the association between baseline brooding and 6 month depression[10] is presented in Table 5.5.

In the first step, Table 5.5 shows that in simple regression models unadjusted for confounding variables, baseline brooding was a significant direct predictor of 6 month depression[11] (*path c'* was significant).

In the second step, where Table 5.5 shows that *path a* was significant, baseline brooding predicted the relevant proposed mediator. Baseline brooding was a significant predictor of low perceived availability of social support at 2 months, all SPSI problem solving subscales at 2 months (indicating poorer problem solving), low frequency of engaging in pleasant activities, low pleasantness ratings of pleasant activities at 2 months, low obtained pleasure from engaging in pleasant activities at 2 months, more negative adjectives endorsed in the memory task at baseline and a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline.

In the third step, where Table 5.5 shows that *path b* was significant the proposed mediator predicted depression. Low perceived availability of social support at 2 months, greater negative problem orientation at 2 months, low pleasantness

[10]Association of baseline brooding and baseline depression for negative cognitive biases.
[11]Baseline brooding was a significant predictor of baseline depression for analyses involving negative cognitive biases.

ratings of pleasant activities at 2 months, and low obtained pleasure from engaging in pleasant activities at 2 months significantly predicted depression at 6 months. More negative adjectives endorsed in the memory task at baseline and a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline both significantly predicted depression at baseline.

In the fourth step, the regression coefficient of the total effect was larger than the regression coefficient of the direct effect (where significant effects of *paths c'*, *b* and *a* had already been demonstrated in the previous steps) consistent with the presence of mediation (according to the causal steps approach), as follows:

i. Baseline brooding was associated with 6 month depression via low perceived availability of social support. The direct effect of baseline brooding was still a significant predictor of 6 month depression after controlling for 2 month social support, consistent with partial mediation. In line with these findings a bootstrap test of the indirect effect was also significant, and the proportion of the total effect mediated by social support was 10.5%. These findings are illustrated in Figure 5.2.

ii. Baseline brooding was associated with 6 month depression via greater negative problem orientation. The direct effect of baseline brooding was still a significant predictor of 6 month depression after controlling for 2 month negative problem orientation, consistent with partial mediation. In line with these findings, a bootstrap test of the indirect effect was significant, and the proportion of the total effect mediated by negative problem orientation was 40.2%. These findings are illustrated in Figure 5.3.

iii. Baseline brooding was associated with 6 month depression via low pleasantness ratings of pleasant activities at 2 months and via low obtained pleasure from engaging in pleasant activities at 2 months. In both cases the direct effect of baseline brooding was still a significant predictor of 6 month depression after controlling for these aspects of pleasant activities, consistent with partial mediation. In line with these findings bootstrap tests of the indirect effects were significant, and the proportion of the total effect mediated by pleasantness ratings and obtained pleasure was 9.5%

and 9.3%, respectively. These findings are illustrated in Figure 5.4 (pleasantness ratings) and Figure 5.5 (obtained pleasure).

iv. In exploratory analyses, baseline brooding was associated with baseline depression via a greater proportion of negative over positive endorsed words recalled at baseline. The direct effect of baseline brooding was still a significant predictor of baseline depression after controlling for the proportion of negative over positive endorsed words recalled at baseline, consistent with partial mediation. In contrast to the findings of the causal steps approach, a bootstrap test of the indirect effect was not significant suggesting there was no mediation by proportion of negative over positive endorsed words. These findings are illustrated in Figure 5.6.

Table 5.5 also summarises the results of multiple regression analyses that controlled for confounders (age, sex, socioeconomic status, history of depression, severity of cardiac disease and baseline depression) in instances where the simple models found evidence of mediation. After adjusting for confounders there was no evidence that 2 month social support, negative problem orientation, pleasantness ratings of pleasant activities or obtained pleasure from engaging in pleasant activities mediated the association of baseline brooding with 6 month depression. In addition there was no evidence that the effect of baseline brooding on depression at the same time was mediated by the proportion of negative over positive endorsed words recalled.

Results of all unadjusted and adjusted regression analyses and bootstrap tests are presented in Appendix 53.

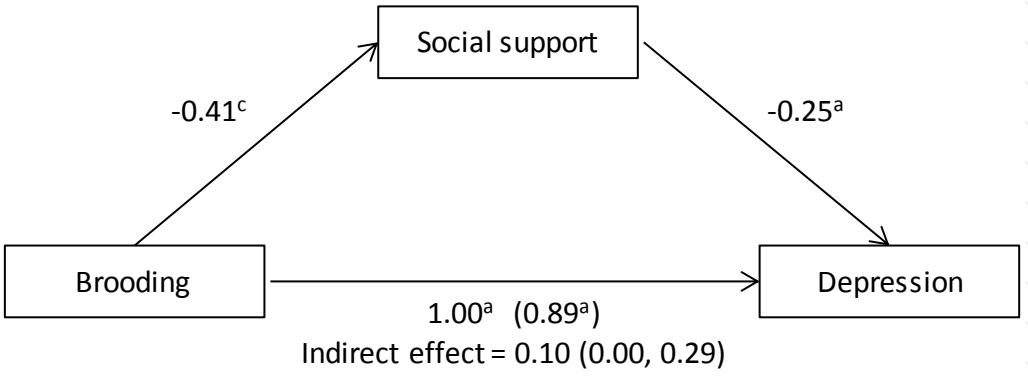
Table 5.5: Summary of mediation analyses for the association of brooding with depression

Proposed mediator	Adjusted	Step 1 Path c'	Step 2 Path a	Step 3 Path b	Step 4 c' > c	Direct effect	Indirect effect	Mediation
ESSI social support	No	✓	✓	✓	✓	✓	✓	Partial
SPSI Positive problem orientation	No	✓	✓	✗	✓	-	-	
SPSI Rational problem solving	No	✓	p=0.064	✗	✓	-	-	
SPSI Negative problem orientation	No	✓	✓	✓	✓	✓	✓	Partial
SPSI Impulsivity	No	✓	✓	✗	✓	-	-	
SPSI Avoidance	No	✓	✓	✗	✓	-	-	
SPSI Total score	No	✓	✓	✗	✓	-	-	
PES Frequency	No	✓	✓	✗	✓	-	-	
PES Pleasantness	No	✓	✓	✓	✓	✓	✓	Partial
PES Obtained pleasure	No	✓	✓	✓	✓	✓	✓	Partial
Negative words endorsed	No	✓	✓	✗	✓	-	-	
Negative words recalled	No	✓	✗	✗	✓	-	-	
Proportion negative endorsed words recalled	No	✓	✓	✓	✓	✓	✗	~Partial
Positive affective homophones (%)	No	✓	✗	✗	✓	-	-	
Negative affective homophones (%)	No	✓	✗	✗	✓	-	-	
ESSI social support	Yes	✓	✗	✓	✗	-	-	
SPSI Negative problem orientation	Yes	✓	✓	✗	✓	-	-	
PES Pleasantness	Yes	✓	✗	✗	✓	-	-	
PES Obtained pleasure	Yes	✓	✗	✗	✓	-	-	
Proportion negative endorsed words recalled	Yes	✓	✓	✗	✓	-	-	

✓= significant ✗=not significant.

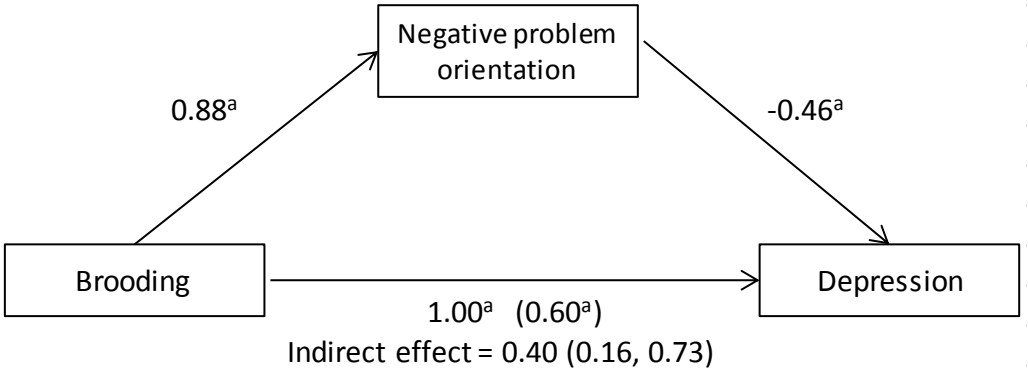
~Findings of causal steps and indirect effect approaches inconsistent.

Figure 5.2: Social support mediates the effect of brooding on depression (unadjusted model)



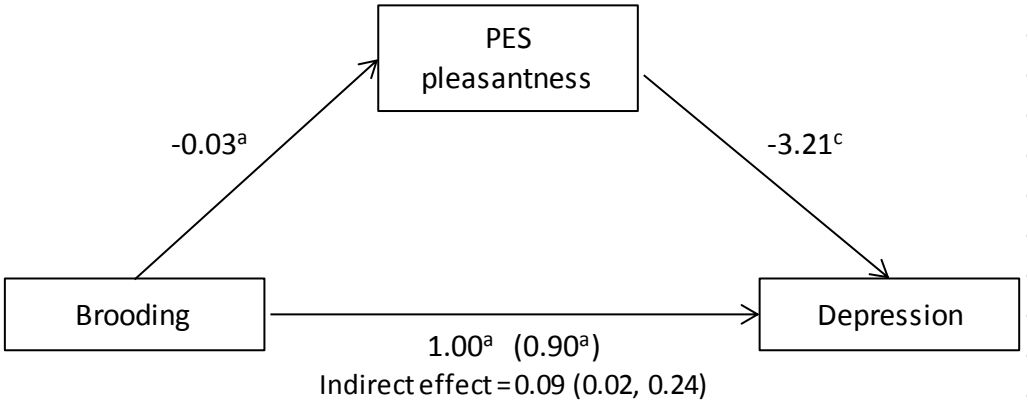
[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

Figure 5.3: Negative problem orientation mediates the effect of brooding on depression (unadjusted model)



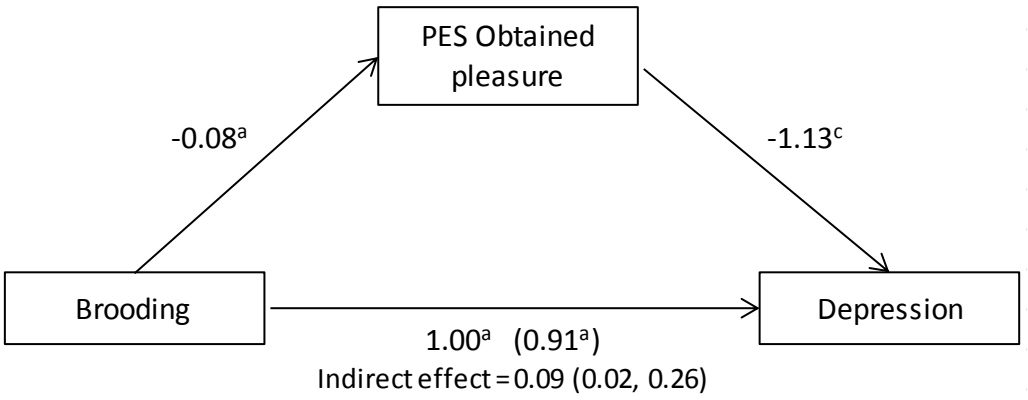
[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

Figure 5.4: Pleasantness ratings mediate the effect of brooding on depression (unadjusted model)



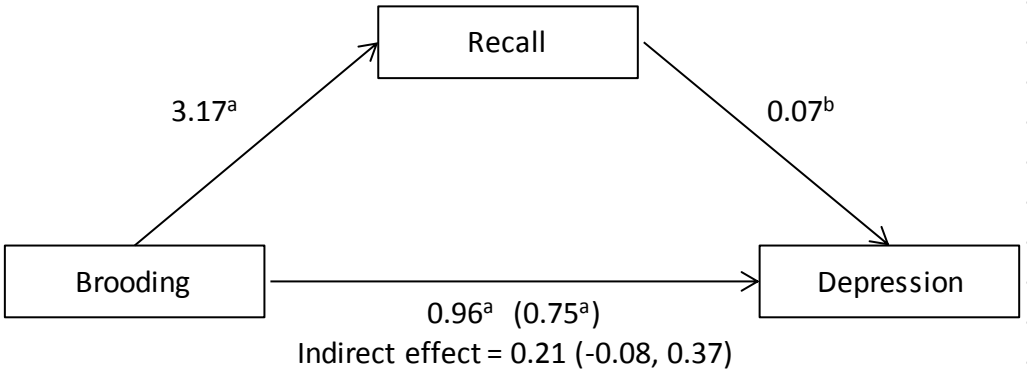
[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

Figure 5.5: Obtained pleasure ratings mediate the effect of brooding on depression (unadjusted model)



[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

Figure 5.6: Proportion of negative endorsed words recalled mediates the effect of brooding on depression (unadjusted model)



[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

5.4.5.1.1 Multiple mediation

An unadjusted multiple mediation model was used to investigate the combined effects of social support, problem solving, and engagement in pleasant activities as mediators of the association between baseline brooding with 6 month depression.

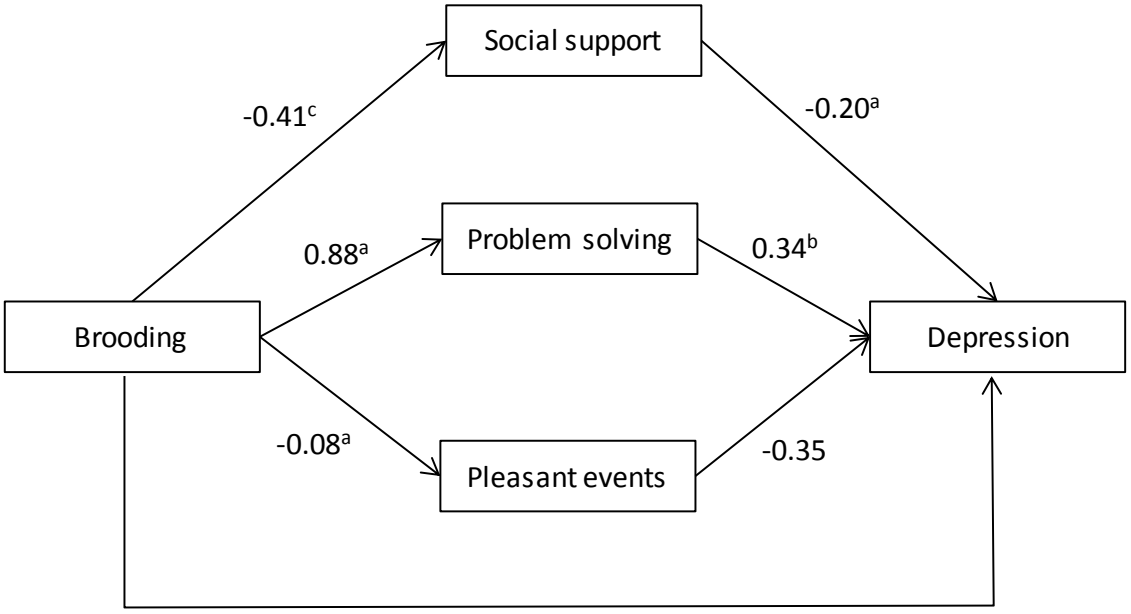
The SPSI negative problem orientation subscale was chosen to represent problem solving since the single mediator models suggested this was the only SPSI subscale that might mediate the association of brooding with depression. Two PES subscales related to engagement in pleasant activities were identified as potential mediators of the association between brooding with depression. The PES obtained pleasure subscale was chosen to represent engagement in pleasant activities because it indexed both frequency and pleasantness aspects of engagement in pleasant activities and was therefore considered the broadest measure.

The results are shown in Figure 5.7. Steps 1 and 2 were unchanged from the individual models: baseline brooding significantly predicted each of the mediators at 2 months and depression at 6 months. In step 3, significant predictors of 6 month depression (*path b*) were low perceived availability of social support at 2 months and greater negative problem orientation at 2 months. Obtained pleasure from engagement in pleasant events at 2 months was not a significant predictor of

depression at 6 months. In the fourth step, the regression coefficient of the total effect was larger than the regression coefficient of the direct effect (where significant effects of *paths c'*, *b* and *a* had already been demonstrated in the previous steps). The direct effect of baseline brooding remained a significant predictor of 6 month depression after controlling for all three proposed mediators at 2 months, consistent with partial mediation. In line with these findings, a bootstrap test of the indirect effect was also significant, and the proportion of the total effect mediated by the combination of social support and problem solving was 40.3%.

In the combined model, the regression coefficient representing the direct association (*path b*) of problem solving with depression was larger than the coefficient representing the direct association of social support with depression. In addition, the proportion of the total effect accounted for by problem solving in the single mediator model was not improved by the addition of social support and engagement in pleasant activities as further mediators.

Figure 5.7: Multiple mediation model of the association of baseline brooding with 6 month depression (unadjusted model)



[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
Paths annotated with unstandardised regression coefficients.

5.4.5.2 Mediators of the association between brooding and health-related quality of life

A summary of the findings of each series of regression analyses and bootstrap tests conducted to investigate potential mediators of the association between baseline brooding and 6 month health-related quality of life (EQ5D index value)[12] is presented in Table 5.6.

In the first step, in simple regression models, baseline brooding was a significant direct predictor of 6 month EQ5D index value[13] (indicating poorer overall quality of life), i.e. *path c'* was significant.

In the second step, significant *path a* models showed that baseline brooding was a significant predictor of low perceived availability of social support at 2 months, all SPSI problem solving subscales at 2 months (indicating poorer problem solving), low frequency of engaging in pleasant activities at 2 months, low pleasantness ratings of pleasant activities at 2 months and low obtained pleasure from engaging in pleasant activities at 2 months. Baseline brooding was also a significant predictor of more negative adjectives endorsed in the memory task at baseline and a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline.

In the third step, significant *path b* models showed that low perceived availability of social support at 2 months, low frequency of engaging in pleasant activities at 2 months, low pleasantness ratings of pleasant activities at 2 months and low obtained pleasure from engaging in pleasant activities at 2 months significantly predicted EQ5D index value at 6 months.

In the fourth step, there was no evidence of mediation using the causal steps approach i.e. where significant effects of *paths c'*, *b* and *a* had already been demonstrated in the previous steps, the regression coefficient of the total effect was not larger than the regression coefficient of the direct effect. Results of all regression analyses and bootstrap tests are presented in Appendix 54.

[12]Association of baseline brooding and baseline EQ5D index for negative cognitive biases.
[13]Baseline brooding was a significant predictor of baseline EQ5D index value for analyses involving negative cognitive biases.

Table 5.6: Summary of mediation analyses for the association of brooding with EQ5D index value

Proposed mediator	Adjusted	Step 1 Path c'	Step 2 Path a	Step 3 Path b	Step 4 c' > c	Direct effect	Indirect effect	Mediation
ESSI social support	No	✓	✓	✓	✗	-	-	
SPSI Positive problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Rational problem solving	No	✓	p=0.064	✗	✓	-	-	
SPSI Negative problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Impulsivity	No	✓	✓	p=0.081	✗	-	-	
SPSI Avoidance	No	✓	✓	✗	✗	-	-	
SPSI Total score	No	✓	✓	✗	✗	-	-	
PES Frequency	No	✓	✓	✓	✗	-	-	
PES Pleasantness	No	✓	✓	✓	✗	-	-	
PES Obtained pleasure	No	✓	✓	✓	✗	-	-	
Negative words endorsed	No	✓	✓	✗	✗	-	-	
Negative words recalled	No	✓	✗	✗	✗	-	-	
Proportion negative endorsed words recalled	No	✓	✓	✗	✓	-	-	
Positive affective homophones (%)	No	✓	✗	✗	✓	-	-	
Negative affective homophones (%)	No	✓	✗	✗	✗	-	-	

✓= significant ✗=not significant.

5.4.5.3 Mediators of the association between brooding with cardiac disease-specific quality of life

A summary of the findings of each series of regression analyses and bootstrap tests conducted to investigate potential mediators of the association between baseline brooding and 6 month cardiac disease-related quality of life[14] (SAQ disease perception) are presented in Table 5.7.

In the first step, simple regression models showed that baseline brooding was a significant direct predictor of worse SAQ disease perception at 6 months (i.e. *path c'* was significant).

In the second step, significant *path a* models showed that baseline brooding was a significant predictor of the proposed mediators: low perceived availability of social support at 2 months, poor problem solving (all SPSI subscales with the exception of rational problem solving) at 2 months, low engagement in pleasant activities at 2 months (all PES subscales), more negative adjectives endorsed in the memory task at baseline and a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline.

In the third step, significant *path b* models showed that low perceived availability of social support at 2 months, greater negative problem orientation at 2 months and all PES subscales related to engagement in pleasant activities at 2 months predicted worse SAQ disease perception at 6 months. In addition, a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline predicted worse SAQ disease perception at baseline (p=0.054).

In the fourth step, there were no significant effects consistent with mediation of the association between baseline brooding and 6 month SAQ disease perception according to the causal steps approach (i.e. where significant effects of *paths c'*, *b* and *a* had already been demonstrated in the previous steps, the regression coefficient of the total effect was not larger than the regression coefficient of the direct effect.) Results of all regression analyses and bootstrap tests are presented in Appendix 55.

[14]Association of baseline brooding and baseline cardiac disease-related quality of life for negative cognitive biases.

Table 5.7: Summary of mediation analyses for the association of brooding with SAQ disease perception

Proposed mediator	Adjusted	Step 1 Path c'	Step 2 Path a	Step 3 Path b	Step 4 c' > c	Direct effect	Indirect effect	Mediation
ESSI social support	No	✓	✓	✓	✗	-	-	
SPSI Positive problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Rational problem solving	No	✓	✗	✗	✗	-	-	
SPSI Negative problem orientation	No	✓	✓	✓	✗	-	-	
SPSI Impulsivity	No	✓	✓	✗	✗	-	-	
SPSI Avoidance	No	✓	✓	✗	✗	-	-	
SPSI Total score	No	✓	✓	✗	✗	-	-	
PES Frequency	No	✓	✓	✓	✗	-	-	
PES Pleasantness	No	✓	✓	✓	✗	-	-	
PES Obtained pleasure	No	✓	✓	✓	✗	-	-	
Negative words endorsed	No	✓	✓	✗	✓	-	-	
Negative words recalled	No	✓	✗	✗	✗	-	-	
Proportion negative endorsed words recalled	No	✓	✓	p=0.054	✓	-	-	
Positive affective homophones (%)	No	✓	✗	✗	✗	-	-	
Negative affective homophones (%)	No	✓	✗	✗	✗	-	-	

✓= significant ✗=not significant.

5.4.5.4 Mediators of the association between worry and overall health-related quality of life

A summary of the findings of each series of regression analyses and bootstrap tests conducted to investigate potential mediators of the association between baseline worry and 6 month health-related quality of life[15] are presented in Table 5.8 (EQ5D VAS) and Table 5.9 (EQ5D index value).

In the first steps, simple regression models showed that baseline worry was a significant direct predictor of worse EQ5D VAS and worse EQ5D index value at 6 months (i.e. *path c'* was significant).

In the second steps, significant *path a* models showed that baseline worry was a significant predictor of poor problem solving (all SPSI subscales with the exception of impulsivity) at 2 months, more negative adjectives endorsed in the memory task at baseline and a greater proportion of negative over positive endorsed adjectives recalled in the memory task at baseline.

In the third steps, significant *path b* models showed that the proposed mediators predicted outcomes as follows: low perceived availability of social support at 2 months predicted worse EQ5D VAS and EQ5D index value at 6 months; and all PES subscales related to low engagement in pleasant activities at 2 months predicted worse EQ5D VAS and EQ5D index value at 6 months.

In the fourth step, there were no significant effects consistent with mediation of the association between baseline worry and 6 month EQ5D VAS or EQ5D index value (i.e. where significant effects of *paths c'*, *b* and *a* had already been demonstrated in the previous steps, the regression coefficient of the total effect was not larger than the regression coefficient of the direct effect.) Results of all regression analyses and bootstrap tests are presented in Appendix 56 (EQ5D VAS) and Appendix 57 (EQ5D index value).

[15]Association of baseline worry and baseline health-related quality of life for negative cognitive biases.

Table 5.8: Summary of mediation analyses for the association of worry with EQ5D VAS

Proposed mediator	Adjusted	Step 1 Path c'	Step 2 Path a	Step 3 Path b	Step 4 c' > c	Direct effect	Indirect effect	Mediation
ESSI social support	No	✓	✗	✓	✗	-	-	
SPSI Positive problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Rational problem solving	No	✓	✓	✗	✓	-	-	
SPSI Negative problem orientation	No	✓	✓	p=0.059	✗	-	-	
SPSI Impulsivity	No	✓	✗	✗	✗	-	-	
SPSI Avoidance	No	✓	✓	✗	✗	-	-	
SPSI Total score	No	✓	✓	✗	✗	-	-	
PES Frequency	No	✓	✗	✓	✗	-	-	
PES Pleasantness	No	✓	p=0.054	✓	✗	-	-	
PES Obtained pleasure	No	✓	✗	✓	✗	-	-	
Negative words endorsed	No	✓	✓	✗	✗	-	-	
Negative words recalled	No	✓	✗	p=0.064	✓	-	-	
Proportion negative endorsed words recalled	No	✓	✓	✗	✗	-	-	
Positive affective homophones (%)	No	✓	✗	✗	✗	-	-	
Negative affective homophones (%)	No	✓	✗	✗	✓	-	-	

✓= significant ✗=not significant.

Table 5.9: Summary of mediation analyses for the association of worry with EQ5D index value

Proposed mediator	Adjusted	Step 1 Path c'	Step 2 Path a	Step 3 Path b	Step 4 c' > c	Direct effect	Indirect effect	Mediation
ESSI social support	No	✓	✗	✓	✗	-	-	
SPSI Positive problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Rational problem solving	No	✓	✓	✗	✓	-	-	
SPSI Negative problem orientation	No	✓	✓	✗	✗	-	-	
SPSI Impulsivity	No	✓	✗	p=0.058	✗	-	-	
SPSI Avoidance	No	✓	✓	✗	✓	-	-	
SPSI Total score	No	✓	✓	✗	✗	-	-	
PES Frequency	No	✓	✗	✓	✗	-	-	
PES Pleasantness	No	✓	p=0.054	✓	✗	-	-	
PES Obtained pleasure	No	✓	✗	✓	✗	-	-	
Negative words endorsed	No	✓	✓	p=0.058	✗	-	-	
Negative words recalled	No	✓	✗	✗	✓	-	-	
Proportion negative endorsed words recalled	No	✓	✓	✗	✗	-	-	
Positive affective homophones (%)	No	✓	✗	✗	✗	-	-	
Negative affective homophones (%)	No	✓	✗	✗	✓	-	-	

✓= significant ✗=not significant.

5.4.6 Results of post-hoc analyses

An interesting finding of this study was that negative cognitive biases (specifically the number of negative adjectives endorsed in the memory task at baseline) were greater in patients who had raised C-reactive protein (CRP) at hospital admission. Negative biases in the memory task were, in turn, found to be associated with concurrent depression.

Increased inflammatory markers have been associated with worse outcomes in CHD patients[304, 305], and previous studies have shown that depression is associated with increases in inflammatory markers such as CRP (e.g.[363, 364]) including in people with CHD[310]. Negative cognitive biases, such as selective memory for negative material, are also hypothesised to be causally associated with depression[215, 365].

Taken together this could reflect simply that worse severity of cardiac disease predicts depression. Alternatively, and more interestingly, it raises the possibility that inflammation may contribute to depression via negative biases in cognitive processing (or vice versa), and could explain why people with chronic physical illnesses characterised by elevated inflammation (such as CHD) are at greater risk of depression. The design of the present study does not allow these competing hypotheses to be formally tested. Nevertheless, a preliminary analysis was conducted to investigate which interpretation, if any, the findings would lend support to.

First, to investigate whether higher levels of CRP during hospital admission were associated with depression a simple logistic regression model was conducted with CRP as the predictor variable and baseline depression as the outcome. To investigate whether higher levels of CRP during hospital admission were associated with worse severity of cardiac disease a bivariate correlation (Kendall's Tau-b) between CRP and severity of cardiac disease (assessed using a summary measure of left ventricular function) was used. Second, to investigate whether inflammation remained a significant predictor of depression after controlling for the severity of cardiac disease, a multiple regression model was used with CRP as the predictor variable, baseline depression as the outcome and severity of cardiac disease entered as a covariate.

Next, to confirm that CRP was a significant predictor of number of negative adjectives endorsed, a simple logistic regression models was conducted with CRP as

the predictor and number of negative adjectives endorsed as the outcome variable. Since number of negative adjectives endorsed had previously been found to be associated with depression, the simple regression model was extended to control for baseline depression.

The results showed there was a trend for raised CRP during hospital admission to be associated with baseline depression (B=-1.09, z=-1.91, p=0.057), and there was a small significant bivariate correlation between raised CRP and worse severity of cardiac disease during hospitalisation (r=0.32, p=0.0028). Together these findings suggest inflammation is associated both with depression and with worse severity of cardiac disease. There was a trend for raised CRP during hospitalisation to be significantly associated with baseline depression (B=-1.16, z=1.77, p<0.077) suggesting that inflammation is associated with depression independently of severity of cardiac disease i.e. the association of inflammation with depression is not explained entirely by severity of cardiac disease. Finally, higher CRP during hospitalisation was associated with a greater number of negative adjectives endorsed at baseline (B=1.24, t=2.01, p-0.044), and after controlling for baseline depression there was a trend for raised CRP during hospitalisation to be associated with a greater number of negative adjectives endorsed at baseline (B=1.13, t=1.76, p=0.078). These findings tentatively suggest that inflammation is associated with negative cognitive biases independently of depression.

5.5 Summary of main findings

The secondary aim of the observational prospective cohort study presented in this thesis was to explore, in patients with recent ACS, potential mechanisms by which perseverative negative thinking may impact on mood and poor physical health outcomes over 6 months following hospital admission. Reduced social support, impaired problem solving, reduced motivation to perform positive instrumental behaviours and increased negative cognitive biases were proposed as possible mechanisms.

Unadjusted mediation analyses that considered each of the proposed mediators individually suggested that the association of baseline brooding with 6 month depression was partially mediated by (1) low perceived availability of social support, (2) poor problem solving related to negative problem orientation, and (3)

lower pleasantness ratings of pleasant activities and lack of 'obtained pleasure' from engagement in pleasant activities at 2 months. In addition, unadjusted preliminary analyses suggested that negative biases in memory partially mediated the cross-sectional association of brooding with depression.

An unadjusted multiple mediation model was used to investigate the combined effects of social support, problem solving and engagement in pleasant activities as mediators of the association between baseline brooding with 6 month depression. This model suggested that poor problem solving was the strongest mediating variable.

After adjusting for the effects of confounding variables (age, sex, socioeconomic status, history of depression, severity of cardiac disease and baseline values of the outcome variable) there was no longer any evidence to suggest that social support, problem solving, instrumental behaviours or negative cognitive biases mediated the association of baseline brooding with 6 month depression[16].

Finally, there was no evidence to suggest that social support, problem solving, instrumental behaviours or negative cognitive biases mediated the associations of brooding or worry with either general health-related quality of life or cardiac disease-specific quality of life.

[16]Baseline depression in the models including negative cognitive biases.

Chapter 6 Discussion

6.1 Chapter outline

The broad aim of this thesis was to investigate the association between perseverative negative thinking with depression, anxiety and worse quality of life in people with coronary heart disease (CHD).

First, a systematic review was conducted in order to identify, synthesise and evaluate existing empirical evidence of the prospective association of perseverative negative thinking with depression, anxiety and emotional distress in people with long term conditions (LTCs).

Second, an observational prospective cohort study was conducted to: (a) investigate whether rumination and worry would prospectively predict depression, anxiety and worse health-related quality of life following hospital admission in people with CHD, and (b) explore potential mechanisms by which perseverative negative thinking may impact on mood and worse physical health outcomes following hospital admission.

This chapter includes:

i. A brief re-statement of the background and aims of the thesis.
ii. A summary of findings of each of the empirical studies reported in this thesis.
iii. A discussion of the methods and findings with reference to strengths, limitations and comparison with existing literature.
iv. Consideration of the implications of this research and suggestions for future research.

A discussion specific to the systematic review was presented with the methods and findings of the review in Chapter 2 and the main conclusion of that chapter will be re-iterated here. A brief summary of findings was presented in Chapters 4 and 5, and discussion related to the observational prospective cohort study presented in those chapters is combined here.

6.2 Background and aims

Depression is common in people with LTCs including CHD and is associated with worse physical outcomes. The nature of the causal association between depression and CHD is not fully understood, and the mechanism underpinning the association between depression and poor medical outcomes remains unclear.

The effectiveness of antidepressant drugs and psychological interventions for depression appear to be limited in people with CHD. Furthermore trials have failed to demonstrate convincingly that improving depression also improves physical health outcomes, meaning proof that depression causes poor physical health outcomes among people with CHD is currently lacking.

Better understanding the factors that contribute to the development of depression in people with CHD and the mechanisms underpinning the association of depression with worse physical health outcomes could (a) help predict which patients are at increased risk of developing depression and, as a consequence, are at increased risk of adverse medical outcomes, (b) facilitate personalisation of treatment based on risk of developing depression, and (c) inform the development of novel interventions that could target the identified mechanistic processes which might improve both physical and mental health outcomes.

Perseverative negative thinking could predict depression and reduced quality of life in people with CHD. Perseverative negative thinking describes a number of cognitive processes, such as rumination and worry, in which individuals engage in repetitive, prolonged and recurrent negative thoughts about themselves, their symptoms or their problems and concerns. Perseverative negative thinking has been strongly associated with the onset and maintenance of depression in healthy and psychiatric populations, and also predicts adverse medical outcomes, such as poor cardiovascular health, impaired wound healing and immune dysfunction.

Perseverative negative thinking could therefore be helpful in better understanding depression in people with LTCs including CHD, and could provide a potential target for interventions aimed at improving both psychological and physical health outcomes. Most previous prospective research investigating the association of perseverative negative thinking with depression has focused on physically healthy populations, however. Therefore, the nature of the association, and the mechanisms

by which perseverative negative thinking may impact on both mood and physical health outcomes in people with CHD are unclear.

This thesis concerns perseverative negative thinking as a cognitive process that may contribute to or maintain depression in the context of chronic physical illness (in particular CHD), and seeks to (a) clarify the association of perseverative negative thinking with depression, anxiety and health-related quality of life, and (b) explore factors that may mediate the association of perseverative negative thinking with subsequent depression, anxiety and health-related quality of life.

The aims of this thesis were to:

i. Identify, synthesise and evaluate existing empirical evidence of the prospective association of perseverative negative thinking with depression, anxiety and emotional distress in people with LTCs.
ii. Investigate whether rumination and worry would prospectively predict depression, anxiety and worse health-related quality of life following hospital admission in people with CHD.
iii. Explore potential mechanisms by which perseverative negative thinking may impact on mood and worse physical health outcomes following hospital admission.

The following main hypotheses were tested:

i. In patients with recent acute coronary syndrome (ACS), rumination and worry following hospitalisation will predict depression at six month follow-up, after controlling for other confounding variables including baseline levels of depression.
ii. In patients with recent ACS, the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by four potentially complementary mechanistic factors (low social support, impaired problem solving, reduced instrumental behaviours, elevated negative cognitive biases[17]).

[17]The association of baseline rumination and baseline depression in the case of negative cognitive biases.

6.3 Summary of findings

6.3.1 Systematic review

Four electronic databases were searched for studies in adults with any LTC that included a standardised measure of perseverative negative thinking and a standardised measure of depression, anxiety or emotional distress, and which presented prospective associations.

From the 30 studies identified the majority of uncontrolled studies found an association between measures of perseverative negative thinking and subsequent depression, anxiety or emotional distress (bivariate correlations ranged from r=0.23 to r=0.73). Studies that controlled for the effects of covariates, including depression at baseline, using multivariable analysis showed more mixed results, though the majority of studies still supported a significant association, with effects being small in magnitude. These studies fall short of proving causation, and findings were limited mainly to the association of rumination and/or catastrophizing with subsequent depression. Results varied according to LTC, and study quality was limited in many cases by failure to adequately control for potential confounding variables and by attrition.

6.3.2 Observational prospective cohort study: Part I

The main aim of this study was to explore in patients with recent ACS whether rumination and worry would prospectively predict depression, anxiety and worse health-related quality of life over 6 months following hospital admission.

A sample of 169 ACS patients recruited within 6 months of hospital admission completed self-report assessments at baseline, and again at 2 month and 6 month follow-ups. The 14% of participants with depression were younger, more socially isolated, had a history of depression, worse socioeconomic status and reported greater severity of cardiac disease than those without depression.

After controlling for the effects of key covariates baseline brooding was a significant predictor of depression at 6 months, accounting for 2% of the variance in depression. Baseline brooding did not predict 2 month depression however. In addition, baseline worry was a significant predictor of worse quality of life related to mobility problems at 6 months. Other strong predictors of worse 6 month outcomes

were baseline values of the relevant outcome variable, social support and greater severity of cardiac disease.

Longitudinal multilevel (repeated measures) models were used to validate and extend the findings and indicated that trajectories of depression and anxiety varied between participants over time. Longitudinal models also showed that the association of brooding at the previous assessment time with depression at the next assessment time was on the threshold of significance after controlling for confounding variables including social support. A sensitivity analysis in which social support was removed from the model showed that brooding was a significant predictor of depression. The results of multilevel (repeated measures) models also indicated that both brooding and worry at the previous assessment time predicted worse subsequent health-related quality of life.

With regards to the specific hypotheses tested, the main hypothesis that, in patients with recent ACS, rumination and worry following hospitalisation will predict depression at six month follow-up was partially supported, since brooding, but not worry, appeared to be a significant prospective predictor of subsequent depression. It was not clear from the findings whether the prospective association of brooding with depression was direct, or whether the association was confounded by the effect low of social support.

The secondary hypothesis that, in patients with recent ACS, rumination and worry following hospitalisation will predict anxiety and quality of life at six month follow-up was also partially supported since both brooding and worry were significant prospective predictors of subsequent quality of life, but not of anxiety.

6.3.3 Observational prospective cohort study: Part II

The secondary aim of the study was to investigate, in patients with recent ACS, whether low social support, impaired problem solving, reduced instrumental behaviours or elevated negative cognitive biases mediate the association of perseverative negative thinking with depression and worse physical health outcomes over 6 months following hospital admission.

Individual mediation models showed that the association of baseline brooding with 6 month depression was partially mediated by low perceived availability of social

support, poor problem solving, and reduced instrumental behaviours at 2 months. Negative cognitive biases partially mediated the cross-sectional association of baseline brooding and depression. In a combined mediation model poor problem solving (specifically greater negative problem orientation) at 2 months was the strongest mediator of the association between baseline brooding and 6 month depression.

After adjusting for the effects of important confounding variables there was no longer any evidence to suggest that social support, problem solving, instrumental behaviours or negative cognitive biases mediated the association of baseline brooding with 6 month depression[18], although all proposed mediators remained strong predictors of depression.

With regards to the specific hypotheses tested, the main hypotheses that, in patients with recent ACS, the impact of rumination following the initial cardiac event upon depression at six month follow-up will be mediated by (1) low social support, (2) impaired problem solving, (3) reduced instrumental behaviours, and (4) elevated negative cognitive biases[18] were partially supported, since the findings were consistent with partial mediation but only in models unadjusted for confounding variables.

The secondary hypotheses that, in patients with recent ACS, the impact of rumination following the initial cardiac event upon quality of life at six month follow-up will be mediated by (1) low social support, (2) impaired problem solving, (3) reduced instrumental behaviours, and (4) elevated negative cognitive biases[18] were not supported.

6.4 Strengths and limitations

There were several main strengths of the observational cohort study presented in this thesis.

First, important variables that might confound the association of brooding or worry with depression, anxiety and quality of life were controlled. As identified in the systematic review presented in Chapter 2 previous studies failed to adequately control for potential confounding variables and could therefore have overestimated the effect

[18]The association of baseline brooding and baseline depression in the case of negative cognitive biases.

size of associations. Covariates were selected on the basis of previous literature that demonstrated an association with depression or anxiety.

Second, to clarify whether perseverative negative thinking was prospectively associated not only with depression but also with worse physical health outcomes in people with CHD, health-related quality of life was included as an additional outcome measure. Furthermore due to the high comorbidity of depression and anxiety, anxiety was also assessed in order to gain a more complete understanding of factors that may predict depression in CHD.

Third, while previous studies in people with LTCs have tended to focus on a single aspect of perseverative negative thinking both rumination and worry were included as predictor variables in this study, in order to investigate the association of a broader range of perseverative negative thinking with depression and other outcomes.

Fourth, self-report measures of (1) rumination and depression, and (2) worry and anxiety were selected carefully to minimise artefactual associations. The Ruminative Responses Scale was previously decomposed into brooding and reflection subscales in order to eliminate 'depression contaminated' items[315]. The brooding subscale was therefore chosen for use in the current study to avoid a spurious association. Similarly, the Beck Anxiety Inventory was selected for use in this study due to its relative lack of items addressing cognitive aspects of anxiety including worry.

Fifth, previous studies have not addressed mechanisms that could explain why perseverative negative thinking is associated with depression in people with CHD. Previous research suggests that low social support, poor problem solving, reduced instrumental behaviours and negative cognitive biases may explain the association of rumination with depression[120], and these factors were explored in the current study.

There were also several limitations of the observational prospective cohort study presented in this thesis, and these are addressed below in turn.

6.4.1 Poor uptake, attrition and missing data

Of the 397 individuals invited to participate only 44% completed at least baseline assessments. The age and gender ratio of the sample that took part was comparable to that of a group of individuals identified within the same setting who

were invited to participate but ultimately chose not to, and was also consistent with UK CHD prevalence statistics[3]. This suggests that the sample who participated in this study were crudely representative of the broader ACS population, although it is unknown whether the group who chose not to participate varied systematically from those who participated on other key variables such as depression scores.

There was a high level of attrition over the course of the study; only 66% of participants who completed baseline assessments also completed assessments at 6 months. Similar studies in CHD populations identified by the systematic review presented in Chapter 2 reported retention rates of between 67% to 85% [182, 183, 251, 270]. Two of these studies used postal follow-ups and achieved 82% and 79% retention rates at 3 months and 1 year follow-up, respectively. Sample characteristics of completers compared to non-completers at 6 months were similar, and It is unclear why retention was comparatively poor in this study (although 3 of the 4 other studies had only one follow-up assessment, and therefore arguably imposed a smaller burden on participants). The poor retention rate at 6 month follow-up means that there could have been a reduction in power to detect associations, and a risk of sample bias which could limit generalisability of findings.

Attrition can limit the generalisability of results where there are systematic differences between dropouts and completers (for example, participants with poorer physical health or depression may be more likely to drop out), meaning that the sample of completers does not accurately represent the whole patient population. Therefore, conclusions regarding prevalence of population characteristics (such as depression, for example) may not be accurate, and it is unclear whether the nature of any associations of interest may differ in dropouts compared to completers. Some studies suggest that non-participation in health surveys leads to underestimates of the prevalence of mental disorders although estimates of the associations between exposures and outcomes remain unbiased[366-368]. It is possible that attrition may have similar implications for findings.

Baseline characteristics of participants who completed 6 month assessments for this study were compared with those of dropouts, to assess whether there were systematic differences between the two groups at baseline. The groups were broadly similar in terms of sociodemographic, lifestyle and disease variables. Mean depression

scores did not differ, although a greater proportion of dropouts were depressed (PHQ≥10) at baseline compared with completers at baseline. Cross-sectional associations of perseverative negative thinking with depression, anxiety and quality of life at baseline did not differ between completers and dropouts. However, exploratory analyses tentatively suggested that the prospective association of baseline brooding with 6 month depression was strongest in participants with elevated depressive symptoms at baseline, which is consistent with previous research. It is possible therefore that the estimates of prospective associations in this study may be conservative as a result of attrition.

The number of cases with missing data for any of the main predictors or outcome variables (due to participants failing to complete specific assessments or items, or providing ambiguous responses) ranged from 0% to 9%. The quantity of missing data at case and item level was within acceptable ranges[358] and sample characteristics of participants with and without missing data were similar, indicating that missing data was unlikely to have biased the findings.

6.4.2 Timing of assessments

The timing of assessments was selected based on reports of elevated prevalence of depression in the 12 months post-MI[289-292] (participants for this study were recruited within 6 months of their hospital admission in order that follow-up assessments could be completed within the first year post-ACS). However, it is unclear (1) how the temporal relationship between depression and CHD evolves[33, 288], and (2) how the time course of rumination and worry following CHD may unfold. For example, rumination could be expected to be higher immediately post-MI due to the experience of a sudden life-threatening event (consistent with a study that reported a positive correlation between severity of negative life events and rumination[284]), or alternatively rumination might increase later in the process of recovery after patients have had time to reflect on the implications of their illness, particularly if it interferes with their usual lifestyle and attainment of other goals as control theory approaches to rumination suggest[115, 119].

Therefore the timings of assessments were largely arbitrary, and it is possible that the optimal timings of effects may have been missed, meaning the results

presented here could represent an underestimate of associations (although the systematic review presented in Chapter 2 suggested that follow-ups between 1 to 12 months after baseline assessments would be optimal to detect associations).

In addition, due to recruitment of patients from both inpatient and outpatient settings there was a degree of variability between participants in time from index event (defined here as the admission date of the most recent hospitalisation for ACS prior to completion of baseline assessments), and due to delays in returning the questionnaire packs (or in some cases owing to early completion) there was also some variability between participants in the timing of 2 month and 6 month assessments. Uneven spacing between assessment times makes interpretation of lag variables and other prospective analyses using assessment time as a factor more complicated, particularly if the associations of interest are not stable over time. One implication is that the ability to make recommendations about the most useful time to deliver potential interventions is limited.

To explore the effect of the actual timings of the assessments, time from index event and time from baseline were entered as covariates and results showed that they did not significantly predict any outcome variable, meaning that time since index event and time between assessments did not impact on the associations between brooding and worry with depression, anxiety or quality of life.

6.4.3 Data quality and violation of statistical assumptions

Regression diagnostics indicated that the assumptions of normally distributed residuals and of homoscedasticity were violated in the majority of staged multivariable regression models, and all multilevel (repeated measures) models violated the assumption of normally distributed residuals. Transforming the data was not effective, and robust methods to estimate standard errors were either not available or failed to converge. Therefore it is possible that standard errors and significance values could be biased. However, multivariable regression is relatively robust to violations of normality and homoscedasticity (e.g. [357]) and such violations are common with clinical indicators such as depression and anxiety scales, particularly in non-clinical samples. In similar published studies with ACS samples[182, 183] the evaluation of model assumptions were not reported although findings were consistent with those reported

here. Additionally, the results of regression analyses and multilevel (repeated measures) models reported here corresponded with each other, and the findings were consistent at different assessment times suggesting they are reliable.

A small number of outliers were identified for the majority of variables but upon inspection these were within expected ranges for the relevant assessments, and so were retained. Regression diagnostics indicated that outliers did not pose a risk of bias.

6.4.4 Self-report assessments of physical health outcomes

Physical health outcomes were assessed using self-report measures in this study. Mortality and morbidity were considered outcomes of interest and objective outcomes related to mortality and morbidity (such as monitoring hospital records for deaths and recurrences) would have been desirable. However, due to the relatively small sample size and the relatively short follow-up period few such events were anticipated. Therefore physical health outcomes were assessed using two quality of life instruments: the EuroQol-5D measure of general health-related quality of life (EQ5D) and the Seattle Angina Questionnaire (SAQ) to measure cardiac disease-specific quality of life.

Quality of life measures of health status are important tools that can complement more traditional objective measures of outcome such as morbidity and mortality, by providing information about the patients experience of health problems and treatments related to symptoms, physical function and other domains such as social functioning[285, 287]. However while these measures are widely used and many have well established psychometric properties, a key disadvantage is that subjective reports of physical health are not independent of mental health i.e. responses could be influenced by current mood state. For example, quality of life measures and depression measures correlate in patients with CHD[48, 369]. Therefore, although health-related quality of life is an important outcome in its own right, the results of this study do not allow inferences to be made about the association of perseverative negative thinking with objective physical health outcomes such as recurrence or mortality.

6.5 Interpretation of findings

The main findings of this thesis are interpreted to mean that brooding appears to prospectively predict depression in people with recent ACS, possibly via impaired problem solving (specifically, high negative problem orientation). Additionally, brooding and worry both appear to prospectively predict some aspects of quality of life, although mechanisms to explain this association were not identified.

The findings fall short of proving causation, and it remains possible that the apparent prospective association between brooding and depression is confounded, for example by poor social support.

6.6 Comparison with existing literature

6.6.1 Brooding and worry

The psychometric properties and performance of the Ruminative Responses Scale (RRS) brooding subscale and the Penn State Worry Questionnaire (PSWQ) have been well established particularly in young healthy and clinically anxious/depressed samples (e.g. [133, 140, 164, 315, 316, 370, 371]), however they have not been well characterised in people with ACS. The mean RRS brooding score in this study was consistent with that reported in a similar previous study with ACS patients[183], and the average PSWQ score in this study was similar to mean scores reported in previous studies that included participants with anxiety[316], cancer[264], a combination of long term conditions including CHD[178] and a healthy sample of older adults with a mean age similar to the sample included here[372]. Therefore, levels of brooding and worry in this study were as expected based on a limited amount of previous research.

Questionnaire assessments generally provide a 'snapshot' of the construct of interest at a single moment in time. However, emotional and cognitive processes can fluctuate over time and therefore questionnaire assessments cannot capture subtle temporal changes unless the assessments are repeated very frequently (e.g. ecological momentary assessment). However, rumination and worry are usually conceptualized as trait measures of repetitive thought. That is, the extent to which individuals *characteristically* engage in ruminative or worrisome thinking. As such the Ruminative Responses Scale (RRS) and the Penn State Worry Questionnaire (PSWQ), ask respondents to rate whether they 'generally' or 'typically' ruminate or worry.

Assessments of trait measures ought to be highly positively correlated at different occasions, and in previous studies test-retest correlations have been reported in community and clinical samples of r=0.59 to r=0.62 for RRS[152, 373] and r=0.92 to r=0.93 for PSWQ[133], suggesting these measures are stable over time. Consistent with this, in the current study there were large and highly significant correlations of brooding (r=0.76 to r=0.81) and worry (r=0.72 to r=0.77) across baseline and follow-up assessments, as would be expected of trait measures. Therefore, since rumination and worry appear to be stable over time, it is unlikely that the use of one-off questionnaire assessments of these constructs would have affected (weakened) the observed associations.

6.6.2 Depression, anxiety and quality of life

Mean depression (PHQ), anxiety (BAI), general health-related quality of life (EQ5D) and cardiac disease-specific quality of life (SAQ) scores indicated that overall the sample included in this study was not experiencing significant problems with depression, anxiety or poor quality of life at any of the assessment occasions. Participants in this study were less depressed and cardiac disease-specific quality of life was better than expected compared to previous studies.

6.6.2.1 Low proportion of participants with depression

Mean PHQ scores at baseline in this study (mean=4.3) were similar to a previous study of primary care CHD patients without previously identified depression (mean=4.5)[374] and a study of depression base rates in CHD inpatients and outpatients (mean=5.5)[375]. However, the proportion of participants with depression was low (14% at baseline falling to 10% at 2 month and 6 month assessments) compared to estimates of approximately 20% prevalence of depression in the first 12 months post-MI in other studies[71, 376, 377]. It is not immediately obvious why this is the case. Sample characteristics related to age, gender social support and left ventricular function as a measure of severity of cardiac disease did not appear different in this study from those seen in other similar cohorts. One possibility that might explain the low proportion of depression is that the participants in this study had relatively stable CHD by the time they completed baseline assessments (the mean time from index event was 111 days), as lower prevalence has been reported in some

other studies that recruited patients with stable disease rather than immediately after an acute event e.g.[378].

The implication of limited representativeness of the sample with regards to prevalence of depression is that the findings may not be applicable to a clinically depressed or anxious sample of ACS patients. Indeed, Denton et al.[183] found among a sample of ACS patients that the effects of rumination immediately post-MI on depression 3 months later differed according to depression status at baseline. Specifically, they found a direct effect of rumination on depression in those who were depressed at baseline, whereas rumination in those who were not depressed at baseline led to depression only indirectly (by amplifying the impact of other psychosocial vulnerabilities). In this study an exploratory sensitivity analysis supported this, showing that baseline brooding was more strongly correlated with 6 month depression in participants who were depressed compared to those who were not depressed, although these findings were based on a very small sample of depressed participants who remained in the study at 6 months.

6.6.2.2 Secondary outcome measures: anxiety and quality of life

Mean BAI scores (mean=8.7) in this study indicated little anxiety, consistent with previous studies in a sample of female CHD patients <65 years (mean=10.1)[46], and a sample of patients with coronary slow flow (mean=13.0)[379]. The proportion of participants in this study with at least moderate anxiety (BAI ≥19; 16%) was approximately consistent with UK prevalence estimates of anxiety disorders[380], and prevalence estimates of anxiety in CHD patients[381, 382].

General health-related quality of life (EQ5D index values and EQ5D visual analogue scale; means at baseline 0.78 and 72.9, respectively) in this study was comparable to UK population norms for an equivalent age group (index value norm=0.79, VAS norm=77.3)[383], and was also similar to that found in previous studies in MI patients (e.g. [332, 334, 335]) and a large multicentre study of CHD patients[384].

Cardiac disease-specific quality of life (SAQ subscale scores) in this study appeared to be elevated (i.e. better) compared to other studies of patients with coronary artery disease and ACS [336, 385, 386]. This could be an artefact of the

relatively few studies available for comparison since many studies chose to present SAQ scores collapsed into frequencies (e.g. [387, 388]). Alternatively, since cardiac disease-specific quality of life and depression correlate (e.g.[48, 389]) it is possible that elevated SAQ scores are related to the low levels of depression observed in this study. Depression was correlated with most SAQ subscales at baseline which would support this interpretation.

6.6.3 Stability of outcome variables over time

There was little change in mean scores over assessment times for any of the outcome variables. PHQ, BAI, EQ5D and SAQ are all state measures of mood or quality of life over the preceding days/weeks which would be expected to fluctuate. Since there was little variation over time, it could be argued that responses at one assessment time would be strong predictors of the same outcome at the next assessment time, leaving little variance to be explained by other predictors. This could have led to underestimates of the importance of other predictor variables, such as rumination and worry.

Interestingly, while mean values of the outcomes in the sample overall remained stable over time, multilevel (repeated measures) models showed that there was significant between-participant variation in trajectories of depression and anxiety over the course of the study. This raises the possibility that by identifying different trajectories of depression and anxiety it may be possible to reveal subgroups of post-ACS patients and characterise which patients might be particularly at risk of worse outcomes. Understanding how depression evolves over time post-ACS could also provide important information about the optimal timing of interventions.

Two approaches have been used previously in CHD patients; profiles of depression have been created by categorising patients using pre-defined clinical cut-off scores at different assessment times(e.g.[390]), or in a more data-driven approach trajectories have been identified using latent class analysis (e.g.[376, 391, 392]). None of these studies have investigated how perseverative negative thinking may vary across subgroups with different trajectories, although one study in a sample of ACS patients[376] investigated whether other psychosocial vulnerabilities for depression

(including stressful life events, engagement in pleasant events, cognitive distortions and 'Type D' disposition) differentiated the trajectories.

Due to the small sample size and low number of participants depressed at baseline it was not possible to explore the characteristics of subgroups with different trajectories in this study and how these might relate to worse outcomes.

6.6.4 Prospective associations of brooding with depression

In this study staged multivariable regression models that controlled for the effects of important confounding variables showed that baseline brooding was a significant predictor of depression at 6 months. Four previous studies investigating the prospective association of perseverative negative thinking (specifically rumination and catastrophizing) with depression and health related quality of life in patients with CHD were identified in the systematic review presented in Chapter 2[182, 183, 251, 270]. Consistent with the current study, 3 of the 4 previous studies found a significant association between baseline rumination with depression at between 3 to 12 months follow-up. The study which did not find an association[270] had a very low sample size at follow-up (n=17).

In the current study, baseline RRS brooding accounted for 2% of variance in 6 month depression. Effect sizes in the other studies with positive findings were similar. Denton et al. (2012) found that RRS brooding independently accounted for 1.2% of variance in 3 month depression after controlling for other confounding variables, and Baker (2014) reported that brooding independently accounted for 4% variance in depression (although in multivariable analyses they failed to control for socioeconomic status and history of depression which could explain the marginally larger effect size). Finally, Garnefski et al. (2010) did not present their findings in a way that allowed direct comparison as they combined rumination and catastrophizing into a single variable for multivariable analyses. They did however present a bivariate correlation of r=0.45 between baseline rumination with 1 year depression which is consistent with the current study (r=0.47 between baseline RRS brooding and 6 month depression).

The association of rumination with depression in people with ACS is consistent with the response styles theory[118, 120, 121] and with a large body of empirical work that supports an association in other populations (for reviews see e.g. [113, 168-170]).

6.6.4.1 Overlap of brooding and social support

Low perceived availability of social support was a strong predictor of depression in the staged multivariable regression models presented in Chapter 4. This is consistent with research that shows CHD patients with depression report lower levels of social support than those without depression e.g.[71, 192, 393]. The findings of this study suggested that the effects of social support and brooding could be partially overlapping. In a fully adjusted multilevel (repeated measures) model that controlled for social support brooding was a marginally significant predictor of subsequent depression. When social support was removed from the model the association of brooding with subsequent depression became significant. This suggests that brooding is an independent predictor of depression, despite probable shared variance with low social support.

Previous research shows that rumination is associated with less emotional support and more social friction[120], and that high ruminators create conflict and disturbances in their interpersonal relationships[200]. The association of rumination and social support and their shared association with depression, means that brooding could prove useful as an intervention target since it may be more amenable to change than social support. For example, in a systematic review and meta-regression to identify effective components of psychosocial interventions for depression in CHD patients Dickens et al. (2013) found that interventions to increase social support failed to improve depression[99]. In a large randomised controlled trial (the ENRICHD study) a CBT-based psychosocial intervention to increase social support resulted in only small improvements after 6 months in perceived social support and depression compared to treatment as usual, and the intervention did not improve outcomes related to recurrence or mortality[88].

Interestingly, interactive effects of social support and rumination on physiological outcomes have also been demonstrated in a previous study with healthy participants. Using an ecological momentary assessment technique combined with ambulatory monitoring of heart rate variability (HRV) Gerteis & Schwerdtfeger (2016) found that the impact of rumination on HRV differed according to availability of social support. Specifically rumination attenuated HRV when social support was low, and

increased HRV when social support was good, suggesting low availability of social support exacerbates the dysfunctional physiological consequences of rumination[394].

6.6.4.2 Impact of covariates

Simple regression models showed that brooding was significantly associated with depression, anxiety, general health-related quality of life and cardiac disease specific quality of life. However, after adding other covariates to the models the only association that remained significant was of brooding with depression. Covariates were selected for inclusion in the models based on previous literature demonstrating an association with depression. However, evidence suggests that at least some of the covariates chosen (e.g. history of depression, socioeconomic status, social support) may also be associated with rumination[162, 197, 395]. Therefore, the effects of brooding in the fully controlled models presented in this thesis may have been underestimated due to shared variance with other confounding variables.

6.6.4.3 Delay between brooding and development of depression

In the current study associations between (a) baseline predictors and 2 month outcomes, and (b) 2 month predictors and 6 month outcomes, were similar to those observed between baseline predictors and 6 month outcomes. Most associations were stronger when assessments were temporally closer together, although the pattern of associations appeared to be relatively stable over time. There was one notable exception which was that while RRS brooding at baseline significantly predicted 6 month depression after controlling for other confounding variables including baseline depression, RRS brooding at baseline did not significantly predict depression at 2 months.

This could help to explain why the multilevel (repeated measures) model that investigated the association of brooding at the previous assessment time with depression at the next assessment time found only a marginally significant effect of brooding, since the overall effect was weakened by the lack of association between baseline and 2 month assessments.

Since most associations appeared to be stronger when the assessments were temporally closer together the lack of association between baseline brooding and 2 month, but not 6 month, depression seems puzzling. It might be that baseline

depression was a stronger predictor of depression at 2 months than at 6 months, and therefore accounted for more of the variance, leaving less for brooding to explain.

Alternatively, it could be argued the lack of association early on represents a delay between brooding and the subsequent development of depression. This is consistent with the predictions of the cognitive neuropsychological model of depression[215, 365]. The model proposes that alterations in monoamine function as a result of genetic and environmental factors are causally related to negative biases in emotional and social processing. Negative biases in turn are thought to propagate negative schemata that lead to the development of depressive symptoms due to repeated experience of negative cues over long periods of time. Thus, the effect of brooding on subsequent depressive symptoms could be expected to develop with some delay. This could lead to associations between brooding and subsequent depression being missed or underestimated if follow-ups are conducted too soon.

6.6.5 Prospective association of worry with depression

Contrary to expectation, worry did not prospectively predict depression in the current study, after controlling for other important confounding variables. There is cross-sectional evidence to suggest that worry is associated with elevated depression in a sample with mixed long term conditions including CHD[178]. However worry has traditionally been linked more closely with anxiety than depression[131, 158]. In the staged multivariable regression models presented in Chapter 4 worry predicted depression in models unadjusted for confounders, albeit more weakly than brooding predicted depression. It may be that the effect of worry was not large enough to survive correction for other strong predictors of outcome such as baseline depression and social support. Future work could clarify this (a) in samples with more variability in measures of worry and depression, and (b) by exploring subgroups with varying trajectories of depression.

6.6.6 Prospective associations of brooding and worry with anxiety

Neither brooding or worry prospectively predicted anxiety in the current study, which conflicts with previous work in healthy samples[152, 155, 167, 396] and cancer patients[264, 275], although there is no previous work in samples with CHD with which to make comparisons.

One possible explanation for the lack of association could be related to the measure of anxiety used in this study. In order to minimise any confounding caused by the overlap of worry and anxiety measures, the Beck Anxiety Inventory (BAI) was used. The BAI mainly consists of items related to somatic and autonomic rather than cognitive aspects of anxiety. It has been suggested that due to its focus on somatic symptoms the BAI may be more sensitive to panic disorder than to other types of anxiety, such as generalised anxiety disorder[397, 398], that may be more relevant in people with CHD. Therefore this study provided a very conservative test of the association between brooding and worry with subsequent anxiety, and associations may have been overlooked.

6.6.7 Prospective associations of brooding and worry with quality of life

In the current study, rumination and worry both prospectively predicted overall generic health-related quality of life. Worry also predicted problems with mobility and there were trends to suggest rumination predicted greater angina frequency and worse disease perceptions related to the cardiac problem. These findings are consistent with other work that has linked worry and rumination with health outcomes such as impaired wound healing[224], immune dysfunction[225], worse functional outcomes in rheumatoid arthritis and psoriasis[399, 400] and worse cardiac outcomes[228]. These findings also fit within the theoretical framework of the perseverative cognition hypothesis[229, 230, 233] which suggests that perseverative negative thinking such as rumination and worry adversely impacts on physiological and health outcomes by maintaining and prolonging physiological responses to stressors.

The systematic review presented in Chapter 2 identified 4 studies in patients with CHD. Only 1 of those studies explored the association of perseverative negative thinking with physical health, and found that rumination did not predict general health-related quality of life or cardiac disease-specific quality of life[251]. However, this study used a different measure of generic health-related quality of life (the Short Form-12 Health Survey), and relied on a composite total score for SAQ which is not recommended as it does not allow investigation of the independent effects of different facets of cardiac disease-related quality of life.

Since the quality of life measures used to assess physical outcomes in this study were subjective self-report measures it is not known whether brooding and worry will prospectively predict objective physical health outcomes such as recurrence of MI or mortality. Future cohort studies in larger samples with a longer follow-up period would be required to confirm this.

6.6.8 Mediators of the association between perseverative negative thinking and depression

As hypothesised the results presented in Chapter 5 identified low social support, impaired problem solving and reduced engagement in pleasant activities as strong prospective predictors of depression and worse health-related quality of life, and in preliminary analyses negative cognitive biases (specifically biases related to memory) were concurrently associated with depression and worse health-related quality of life.

Individual mediation models showed that the association of baseline brooding with 6 month depression was partially mediated by low social support, poor problem solving (specifically negative problem orientation) and lack of engagement in pleasant activities at 2 months. A combined model, in which the impact of all three mediators were evaluated together, revealed that the association of baseline brooding with 6 month depression was mediated by poor problem solving at 2 months.

Interestingly, problem solving (specifically negative problem orientation) improved significantly from baseline to 6 months. There were no significant changes in mean depression scores over time, although the mean values were consistent with improvement over time. These (tentative) improvements in depression could reflect improvements in problem solving in a proportion of individuals. These findings are consistent with studies in healthy participants that showed negative problem orientation was prospectively associated with depressive symptoms[202, 203].

The strong association of problem solving with depression in this study suggests that interventions to improve problem solving may provide effective targets for treating depression in people with CHD. If problem solving does indeed lie on the causal pathway between brooding and depression, as the findings of mediation

analyses suggest here, then problem solving could prove to be a more proximal target for intervention.

Problem solving therapy [401, 402] is an intervention that focuses on training constructive problem solving attitudes and skills. The components of training relate to a number of core processes (problem orientation, problem definition and formulation, generation of alternatives, decision making, and solution implementation) and can include psychoeducation, problem-solving exercises and motivational approaches. Problem solving therapy has been shown to improve depression in clinically depressed samples[403, 404] and is well accepted in this group[405], although in patients with CHD research is more sparse.

A randomised controlled trial of primary care patients with poorly controlled diabetes and/or CHD with comorbid depression was conducted to evaluate a collaborative care intervention that involved motivational coaching to improve problem solving[406]. The primary outcome measures in this study were disease control and depression. At 12 months patients in the intervention arm had significantly greater improvement in measures of disease control, depression, quality of life and treatment satisfaction. Since the intervention consisted of multiple components it is unclear to what extent problem solving was responsible for the improvements seen in depression and other outcomes in this study. Similarly, in a randomised controlled trial of enhanced care which included problem solving therapy for ACS patients with persistent depression, improvements in depression were observed after 6 months of treatment[407]. However, problem solving was an 'opt-in' component of the treatment, and it is unclear to what extent this component of the intervention was responsible for improvements in depression. A systematic review and meta-regression of randomised controlled trials of psychological interventions in patients with CHD found small significant effects of problem solving interventions on depression, but only in a subgroup of patients without depression[99].

Evidence that improving problem solving in CHD patients can also reliably improve depression and physical health outcomes is therefore currently lacking. To confirm that poor problem solving mediates the association of brooding with the development of depression, and that problem solving is a valuable target for intervention, future work should seek to demonstrate in people with CHD that (a) high

ruminators have deficits in problem solving, (b) altering rumination changes problem solving, and (c) problem solving training improves depression.

6.6.9 Association of inflammation, negative cognitive biases and depression

An interesting exploratory post-hoc investigation was prompted by the finding that inflammation during hospitalisation was associated with negative cognitive biases (specifically biases related to self-referential endorsement of negative adjectives). Inflammation was found to be associated with negative cognitive biases even after controlling for depression. Speculatively, this might suggest that the association of inflammation with depression is not entirely explained by greater severity of cardiac disease and that inflammation may contribute to depression via negative cognitive biases which could explain why people with chronic physical illnesses such as CHD are at greater risk of depression.

The mechanisms by which inflammation may contribute to depression are unclear. That inflammation may provoke negative cognitive biases and thereby cause depression would fit with the cognitive neuropsychological model of depression described previously, suggesting that changes in mood are a result of biases in emotional processing[215, 365]. This would also be consistent with the findings of a recent systematic review of experimental studies that induced acute inflammation in healthy participants and measured effects on cognition[408]. The results of the review were mixed and limited by methodological heterogeneity of the included studies, although the most consistent findings were of negative effects on measures of emotional and social processing (e.g. reduced ability to recall emotional faces and feelings of social disconnectedness).

Previous studies have provided mixed evidence of an association between inflammation and depressive symptoms in people with CHD however(e.g.[310, 409-411]), and it has been suggested that an association may be present only in a subgroup of post-ACS patients with new onset depression who are particularly at risk of worse cardiac outcomes[70, 310]. Furthermore, while studies have shown that cognitive bias modification has been successful in achieving change in cognitive biases themselves, the effects on mood and psychopathology are less clear, and effect sizes have typically been small e.g.[412, 413].

Thus while the suggestion that inflammation may contribute to depression via negative cognitive biases is supported by a relevant theoretical framework, previous research has not clearly demonstrated that inflammation is causally related to depression or negative cognitive biases in people with CHD, and the utility of modifying negative cognitive biases for the treatment of depression is unknown. Still, there is the intriguing possibility that reducing inflammation or altering negative cognitive biases could provide future targets for treatments to improve depression.

The findings presented here were based on marginally significant cross-sectional associations among a small number of participants, and other potential confounding variables were not controlled. In addition a dichotomous variable was used to represent inflammation (C-reactive protein categorised as 'inflammation present' and 'inflammation absent') which could mean that important fine-grained information about the magnitude of inflammation was lost. These findings should therefore be treated as preliminary, and future research should aim to clarify the mechanism of the association between inflammation and depression in people with CHD.

6.7 Implications

The findings presented in this thesis have a number of clinical implications. First, it supports the view that detecting and treating depression in CHD patients is essential. Studies suggest that, despite its high prevalence, depression in CHD patients is under-recognised by healthcare professionals in primary and secondary care settings[82, 414], and that when it is recognised it is frequently left untreated[415]. Detection and treatment of depression in CHD patients is especially important owing to the association of depression with increased morbidity, mortality[39, 41, 42] and increased healthcare costs[38] in this group. Brief screening instruments are recommended for case-finding in CHD patients[86]. The findings presented in this thesis are consistent with other research showing that rumination is prospectively associated with depression in people with CHD[183], and therefore in the future screening for rumination could prove a useful strategy for predicting which patients are at increased risk of becoming depressed. These patients could be monitored more closely for signs of depression at follow-up or preventative strategies could be

implemented to ward off the development of depression. Interventions such as rumination-focused cognitive behavioural therapy could be introduced for those at highest risk.

Second, understanding the risk factors for depression can also improve our understanding of the mechanism of the association between depression and CHD. Since depression appears both to predict CHD and to worsen outcomes after the onset of CHD, risk factors for depression may also help to identify individuals at risk of CHD[416]. Identification of such risk factors could inform screening and prevention recommendations for CHD.

Third, the findings presented here have highlighted some possible intervention targets for the development of evidence-based treatments that could improve depression and may also impact on physical outcomes in people with CHD. Rumination itself could be considered the most distal target for treatment in the context of the observational prospective cohort study presented here. Among existing treatment approaches behavioural activation, rumination-focused cognitive behavioural therapy (RFCBT) and mindfulness-based cognitive behavioural therapy (MCBT) all contain components that target rumination including (1) functional analysis and self-monitoring to find alternative strategies with which to replace rumination, and (2) shifting thinking style or mode of thinking to increase concrete, process-focused thinking styles and reduce abstract and judgemental thinking. Beneficial effects of these treatment approaches have been demonstrated in patients with depression (e.g. [237, 239-241]) although evidence of their efficacy in treating depression in CHD populations is currently lacking. The current study demonstrated a large degree of overlap in the prospective association of brooding and low social support with subsequent depression. Coupled with previous research showing limited success of interventions involving social support in improving depression in people with CHD, this could suggest that focusing on the development of interventions to reduce rumination, or combining social support interventions with components that reduce rumination, may prove an alternative and more effective strategy in this population.

Problem solving emerged as a particularly strong mediator of the prospective association between brooding and depression in the observational prospective cohort study presented in this thesis, and could therefore be considered a more proximal

target for treatment. Problem solving therapy has conferred small significant improvements in depression and physical outcomes in CHD patients, and although proof of a causal association needs to be established it would be reasonable to offer problem solving therapy as an intervention in people with CHD.

Finally, the results presented here support the suggestion that there are subgroups of ACS patients with different trajectories of depression, and it is possible that risk factors for depression, and the association of depression with physical outcomes, may vary among these groups. Personalised treatment approaches according to the features of depression may therefore be warranted to improve the efficacy of treatments for depression in CHD.

6.8 Future research

This section provides some recommendations for future work, first by considering ways in which the methodology of the observational prospective cohort study presented in this thesis may inform future research, and second by considering new directions that the findings of this thesis indicate could be valuable to pursue.

6.8.1 Suggestions based on methodological considerations

There were some methodological limitations of the observational prospective cohort study reported in this thesis that have implications for the design of future work.

First, due to a high level of attrition there is a risk of sample bias which means it is uncertain how well the findings of this study will generalise to other ACS populations, and power to detect effects could have been reduced. Due to the longitudinal design of the study some attrition was anticipated, and a number of strategies were employed to maximize retention: questionnaire assessments were provided in a visually appealing booklet format and pre-addressed freepost envelopes were provided to minimize participant perceptions of burden and to reduce inconvenience; a reminder phone call was made if the assessments were not returned after 2 weeks; assistance was offered with completion of questionnaires if necessary; scheduling of follow-up assessments was managed flexibly in order to work around participant availability; and participant records were kept updated with any changes of address or other contact information.

Previous systematic reviews and qualitative studies indicate that monetary incentives, multiple reminders via different media and a flexible approach to follow-up tailored to the specific cohort are the most successful retention strategies, and use of multiple strategies is recommended[417-421]. Retention strategies have been identified in a number of domains including aspects of the study design, conduct and personnel (e.g. [419, 422]) suggesting that embedding retention strategies into the very early design of a prospective cohort study is important. This could include community involvement in the study design (e.g. to minimize burden and to identify barriers to retention), fostering a study identity (e.g. by designing consistent patient-facing study materials including logos, and maintaining a study website), managing participant expectations (e.g. describing follow-up requirements adequately), maintaining engagement (e.g. regular brief contact/updates), planning contact and scheduling methods flexibly, and providing benefits and incentives if possible. Some of these strategies were not feasible within the scope of this project, although they should be considered in similar future cohort studies in order to minimize attrition.

Second, although a particular strength of the observational prospective cohort study presented in this thesis was that it controlled for the effect of several important confounding variables, in contrast to previous studies that failed to adequately control for appropriate confounding variables, the large number of covariates made for extremely stringent tests of the hypotheses. For example, baseline scores of the outcome variables were included as covariates and these were particularly strong predictors of outcomes at later assessment times, seemingly because the sample included in this study appeared to be particularly 'well' with little variability in depression, anxiety and quality of life over time. Since a large amount of variance was accounted for by baseline scores, small but significant effects of other variables could have been masked and effect sizes of brooding (and worry) could have been underestimated. Future research might select participants with elevated depression at baseline, as this would give more scope for depression scores to vary (both upward and downward), meaning baseline depression scores would account for less variance in follow-up depression and thereby allow other predictors with small but important effects to emerge.

Third, physical outcomes were assessed using self-report quality of life measures. The current study could be extended by the inclusion of more objective measures of physical outcomes such as death or recurrence in future studies. A larger sample and a longer follow-up period would be necessary to allow a meaningful frequency of such events to occur, although this would provide important information about the prospective association of brooding with cardiac outcomes that did not rely on self-report measures of physical function.

Fourth, history of depression was ascertained from inspecting medical records. Although this could be considered a more reliable method of identifying patients with significant depressive disorder than self-reports, it may lack sensitivity to identify less severe depressive episodes or transient mood disturbances. History of depression was used as a covariate in the observational prospective cohort study reported here. Although it was correlated with depression and quality of life at baseline, history of depression was not a significant predictor of any outcomes in regression or multilevel (repeated measures) models. History of depression is important because it is related to post-MI depression, at least in a subgroup of patients, and depression that precedes an MI could have different risk factors compared to depression that develops post-MI e.g.[416]. Future studies should collect information regarding history of depression from self-reports or from diagnostic clinical interviews (e.g.[423, 424]), which would provide information regarding previous episodes and duration of current episode if applicable. This would (a) confirm the sensitivity of identifying previous depression from medical records, and (b) allow the effects of previous depression on later depression to be controlled.

Fifth, due to time constraints follow-ups were limited to 6 months in the current study. A larger sample and longer follow-up period would be advantageous in understanding how the association of brooding with depression develops over the longer term (i.e. after 6 months) in people with ACS, particularly as the time course of the association between CHD and depression is unclear[33, 68].

6.8.2 Suggestions based on study findings

Considering the findings presented in this thesis in relation to existing literature suggests that these findings could be extended in a number of ways.

First, consistent with previous research[183] the findings of exploratory analyses presented in Chapter 4 suggested that in post-ACS patients the prospective association of brooding with depression may be strongest in people with elevated baseline depressive symptoms. Therefore, selecting participants on the basis of elevated depression scores (or selecting participants based on presence and absence of depression according to pre-defined criteria) would indicate in which ACS patients rumination is prospectively associated with depression.

Second, findings of multilevel (repeated measures) models presented in Chapter 4 suggested that trajectories of depression and anxiety varied significantly between participants. This suggests that it might be possible to identify subgroups of ACS patients based on different trajectories (e.g. never depressed, new onset depression, stable depression, remitted depression) and to characterise groups that might be particularly at risk of worse outcomes. Understanding how depression evolves over time post-ACS could also provide important information about the optimal timing of interventions. Previous research has begun to investigate how trajectories of depression and anxiety in ACS patients may relate to age, sex, severity of cardiac disease and psychosocial vulnerabilities to depression(e.g.[376, 390-392]) although to date no studies have investigated how perseverative negative thinking may vary across trajectories. Future work should assess perseverative negative thinking, depression, anxiety and physical outcomes in a large sample of ACS patients at multiple assessment times in order to provide enough observations for latent class analysis to identify different trajectories. This would also allow the associations of perseverative negative thinking with depression, anxiety and physical outcomes in groups with different trajectories to be compared.

Third, preliminary post-hoc analyses tentatively suggested that, at least cross-sectionally, the association of inflammation with depression may not be entirely explained by greater severity of cardiac disease and that inflammation may contribute to depression via negative cognitive biases. To support this hypothesis a cohort study could be used to observe prospective associations between levels of inflammation and negative cognitive biases post-CHD. In turn, the prospective association of negative cognitive biases with depression would also need to be established in the same sample, to test whether negative cognitive biases may mediate the association of

inflammation with subsequent depression. Theoretically, manipulating (reducing) inflammation and observing changes (improvements) in negative cognitive biases, or altering negative cognitive biases and observing changes in mood could provide an alternative experimental approach, although concerns regarding whether this would be feasible or ethical in a CHD population makes an observational study design preferable.

Fourth, poor problem solving emerged as a particularly strong mediator of the association between baseline brooding and 6 month depression, and could therefore be considered a target for treatment of depression in people with CHD. Psychological interventions for depression in people with CHD that involved problem solving have previously been linked with small significant improvements in depression and physical outcomes[99, 406]. However, these treatment effects remain to be confirmed in high quality studies such as randomised controlled trials, which would prove causation. Additionally, small cross-sectional and experimental studies could explore the nature of the prospective association between brooding and depression, and who may be likely to benefit from interventions to improve problem solving by investigating in people with CHD (a) whether high ruminators have deficits in problem solving, (b) if altering rumination changes problem solving, and (c) whether problem solving training improves mood.

6.9 Final conclusion

In conclusion, this thesis suggests that rumination is a significant independent predictor of depression, and that this association may be explained by deficits in problem solving ability. Whilst it is plausible that rumination causes depression by impairing problem solving, the findings presented here fall short of proving such a causal relationship and this hypothesis would need to be tested in a clinical trial.

Future longitudinal research would aim to replicate the findings in a larger representative sample of ACS patients with a longer follow-up period.

Rumination and problem solving may provide useful targets for the development of evidence-based interventions to improve depression among people with CHD. Future trials could be used to investigate the causal nature of the association of rumination and problem solving with depression in people with ACS.

List of appendices

Appendix 1: Systematic review search strategy

The same search strategy was used with alterations as appropriate for each database.

1 depression.ti,ab,sh.
2 depressive disorder.ti,ab,sh.
3 anxiety.ti,ab,sh.
4 anxiety disorder*.ti,ab. or anxiety disorders.sh.
5 stress, psychological.sh.
6 psychological distress.ti,ab.
7 emotional distress.ti,ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 perseverative.ti,ab. and cognition.ti,ab,sh.
10 (perseverative and cognitive and processes).ti,ab.
11 perseverative.ti,ab. and thinking.ti,ab,sh.
12 (perseverative and thought).ti,ab.
13 repetitive.ti,ab. and thinking.ti,ab,sh.
14 (repetitive and thought).ti,ab.
15 (worry* or worrie* or worrisome).ti,ab.
16 ruminat*.ti,ab.
17 response styles theory.ti,ab.
18 brooding.ti,ab.
19 preoccupation.ti,ab.
20 (self focus or self focused attention).ti,ab.
21 emotion regulation.ti,ab.
22 coping strateg*.ti,ab.
23 coping style.ti,ab.
24 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 longitudinal studies.sh. or longitudinal study.ti,ab.
26 prospective studies.sh. or prospective study.ti,ab.
27 followup studies.sh. or follow up.ti,ab.
28 baseline.ti,ab.
29 experience sampling.ti,ab.
30 time series.ti,ab.
31 induction*.ti,ab.
32 25 or 26 or 27 or 28 or 29 or 30 or 31
33 8 and 24 and 32

Appendix 2: Vote count of associations (multivariable findings only)

		Depression	Anxiety	Negative affect	Distress	Psychological functioning	Negative mood
Heart disease	Rumination	1 3 4 5					
	Catastrophizing	5					
	Rumination/catastrophizing	2					
Rheumatoid arthritis	Rumination	8[R]					
	Catastrophizing	6 7 9	9	7			
Cancer	Anxious preoccupation	13 16	13 16	13	12		
	Preoccupation with death	19 19[R]	19 19[R]				
	Catastrophizing	10					
	Rumination	10 14 15	14				
Infertility	Catastrophizing	20					
	Rumination	20					
	Rumination/catastrophizing	21	21				
Muscular dystrophy/Cerebral palsy	Catastrophizing					22[C]	
Pain-related conditions	Catastrophizing	25[CE] 26[C] 27 28 29 30	27 28 30				
	Rumination/catastrophizing						24

Red=No association Green=Association Black=Mixed evidence.
Numbers refer to study ID (see Tables 2.1, 2.2 and 2.3).
Empty cells represent no relevant results.
[R]=reverse relationship (i.e. T1 negative affect associated with T2 perseverative negative thinking).
[C]=change scores (i.e. change in perseverative negative thinking associated with change in negative affect).
[E]=association not in expected direction.

Appendix 3: Baseline questionnaire pack

UNIVERSITY OF EXETER

Royal Devon and Exeter NHS
NHS Foundation Trust

QUESTIONNAIRE PACK

STUDY TITLE: The role of perseverative negative thinking in predicting depression in people with coronary heart disease

You have been sent this questionnaire pack as you indicated you would be interested in taking part in our study.

You do not need to fill in the whole pack in one go but please write the date you started it here:

D	D	M	M	Y	Y	Y	Y

Feel free to have somebody help you fill in this pack but please make sure all the answers are your own. If you have any questions, or if you need help to complete the questionnaire pack, please contact the researcher.

There are no right or wrong answers, we are interested in what you think. If you make a mistake, put a single 'X' through the mistake and put your initials next to the mistake. Then fill in the correct answer. Please do not leave any items blank—if there is anything you are unsure about please contact the researcher.

Once you have finished please return this pack AND the consent form in the freepost envelope provided.

Thank you for your time.
Best wishes,
Leanne Trick

You can contact me on: (01392) 725947 or L.V.Trick@exeter.ac.uk

N.B. The 2 month and 6 month packs were almost identical to the baseline pack, although did not include sociodemographic questions and instead contained space to communicate additional information regarding health events since the last assessment and changes in personal circumstances.

About you

1. What is your date of birth? D D M M Y Y Y Y

2. What is your age? ____ years

3. What is your gender? Male ○ Female ○

4. What was the date you were admitted to hospital with your heart problem? D D M M Y Y Y Y

5. What was the date you left hospital? D D M M Y Y Y Y

6. What is your employment status?

Employed full time ○ | Employed part time ○ | Self-employed ○

Unemployed ○ | Retired ○ | Homemaker ○

Other (please specify) _____

7. What is your current (or most recent) occupation?

_____

8. How many years of education have you completed? ____ years

9. What is your current relationship status?

Single ○ | Married ○ | Co-habiting ○

Civil partnership ○ | Widowed ○ | Divorced/separated ○

Other (please specify) _____

10. Do you live alone? Yes ○ No ○

Your lifestyle

11. Are you a smoker? Yes ○ No ○ Quitting ○

12. How many cigarettes a day do you smoke?

10 or less ○ 11—20 ○

21—30 ○ 31 or more ○

13. How often do you have a drink containing alcohol?

Never ○ Monthly or less ○ 2 to 4 times a month ○

2 to 3 times a week ○ 4 or more times a week ○

14. How often do you use drugs *other* than those required for medical reasons?

Never ○ Monthly or less ○ 2 to 4 times a month ○

2 to 3 times a week ○ 4 or more times a week ○

15. How often do you exercise?

Never ○ Monthly or less ○ 2 to 4 times a month ○

2 to 3 times a week ○ 4 or more times a week ○

Your GP details

16. What is the name of your doctor? DR

17. What is the name / address of your doctors surgery?

18. What is your doctors telephone number?

Your physical activity

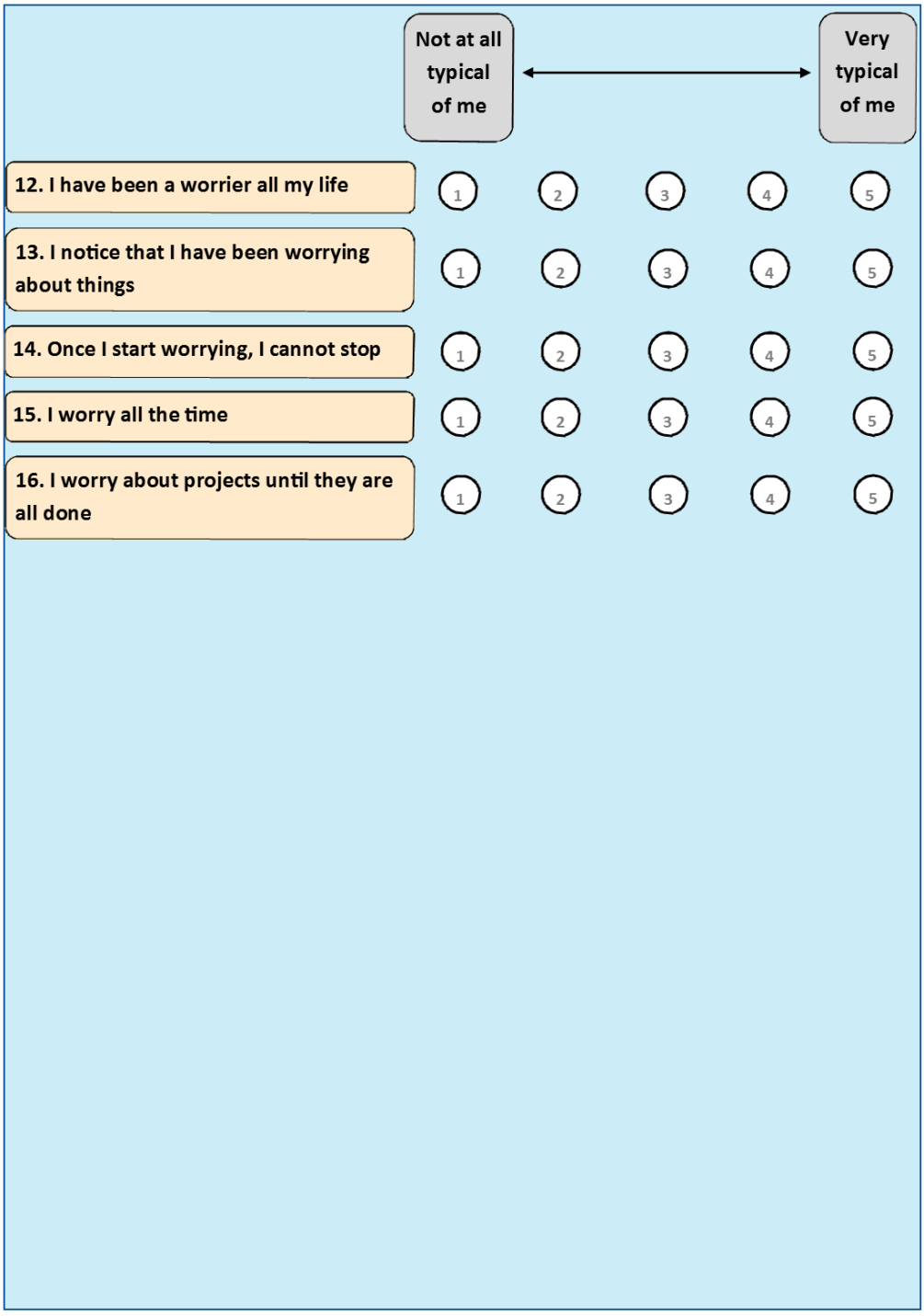
19. Thinking about your heart problem, please choose the one statement that best describes how well you are able to carry out your everyday physical activities

- No limitation of physical activity—ordinary physical activity does not cause undue fatigue, palpitations or shortness of breath ○
- Slight limitation of physical activity— comfortable at rest, but ordinary physical activity results in fatigue, palpitations or shortness of breath ○
- Moderate limitation of physical activity— comfortable at rest, but less than ordinary physical activity results in fatigue, palpitations or shortness of breath ○
- Severe limitation of physical activity— unable to carry out any physical activity without discomfort. Fatigue, palpitations or shortness of breath at rest, with increased discomfort if physical activity is undertaken ○

Penn State Worry Questionnaire

Please rate each of the following statements on a scale of 1 ("not at all typical of me") to 5 ("very typical of me"). Please tick <u>one</u> answer for each statement.

	Not at all typical of me				Very typical of me
1. If I do not have time to do everything, I do not worry about it	1	2	3	4	5
2. My worries overwhelm me	1	2	3	4	5
3. I do not tend to worry about things	1	2	3	4	5
4. Many situations make me worry	1	2	3	4	5
5. I know I should not worry about things, but I just cannot help it	1	2	3	4	5
6. When I am under pressure I worry a lot	1	2	3	4	5
7. I am always worrying about something	1	2	3	4	5
8. I find it easy to dismiss worrisome thoughts	1	2	3	4	5
9. As soon as I finish one task, I start to worry about everything else I have to do	1	2	3	4	5
10. I never worry about anything	1	2	3	4	5
11. When there is nothing more I can do about a concern, I do not worry about it any more	1	2	3	4	5


Not at all typical of me
Very typical of me
12. I have been a worrier all my life
1 2 3 4 5
13. I notice that I have been worrying about things
1 2 3 4 5
14. Once I start worrying, I cannot stop
1 2 3 4 5
15. I worry all the time
1 2 3 4 5
16. I worry about projects until they are all done
1 2 3 4 5

Ruminative Responses Scale

People think and do many different things when they feel depressed. Please read each of the items below and indicate whether you almost never, sometimes, often, or almost always think or do each one when you feel down, sad, or depressed. Please indicate what you *generally* do, not what you think you should do.

	Almost never	Some-times	Often	Almost always
1. Think about how alone you feel	1	2	3	4
2. Think "I won't be able to do my job if I don't snap out of this"	1	2	3	4
3. Think about your feelings of fatigue and achiness	1	2	3	4
4. Think about how hard it is to concentrate	1	2	3	4
5. Think "What am I doing to deserve this?"	1	2	3	4
6. Think about how passive and unmotivated you feel	1	2	3	4
7. Analyze recent events to try to understand why you are depressed	1	2	3	4
8. Think about how you don't seem to feel anything anymore	1	2	3	4
9. Think "Why can't I get going?"	1	2	3	4
10. Think "Why do I always react this way?"	1	2	3	4
11. Go away by yourself and think about why you feel this way	1	2	3	4

	Almost never	Some-times	Often	Almost always
12. Write down what you are thinking about and analyze it	1	2	3	4
13. Think about a recent situation, wishing it had gone better	1	2	3	4
14. Think "I won't be able to concentrate if I keep feeling this way"	1	2	3	4
15. Think "Why do I have problems other people don't have?"	1	2	3	4
16. Think "Why can't I handle things better?"	1	2	3	4
17. Think about how sad you feel	1	2	3	4
18. Think about all your shortcomings, failings, faults, mistakes	1	2	3	4
19. Think about how you don't feel up to doing anything	1	2	3	4
20. Analyze your personality to try to understand why you are depressed	1	2	3	4
21. Go someplace alone to think about your feelings	1	2	3	4
22. Think about how angry you are with yourself	1	2	3	4

Patient Health Questionnaire

Over the last two weeks how often have you been bothered by any of the following.

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Beck Anxiety Inventory

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Seattle Angina Questionnaire

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EuroQol Health Questionnaire

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Illness Perceptions Questionnaire

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ENRICHD Social Support Inventory

Please read the following questions and tick the response that most closely describes your current situation.

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. Is there someone available to you who you can count on to listen to you when you need to talk?	1	2	3	4	5
2. Is there someone available to give you good advice about a problem?	1	2	3	4	5
3. Is there someone available to you who shows you love and affection?	1	2	3	4	5
4. Is there someone available to help you with daily chores?	1	2	3	4	5
5. Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision)?	1	2	3	4	5
6. Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide?	1	2	3	4	5
7. Are you currently married or living with a partner?	Yes ○		No ○		

Social Problem Solving Inventory

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Pleasant Events Schedule

How often have these events happened in your life in the past month? Please answer this question by rating each item on the following scale:

0 = This has not happened in the past 30 days.

1 = This has happened a few times (1 to 6) in the past 30 days.

2 = This has happened often (7 or more) in the past 30 days.

	Not in the last 30 days	1—6 times	7 or more times
Reading stories, novels, plays or poems	0	1	2
Saying something clearly	0	1	2
Watching TV	0	1	2
Thinking about something good in the future	0	1	2
Laughing	0	1	2
Taking a shower (or bath)	0	1	2
Being with animals	0	1	2
Hearing jokes	0	1	2
Talking about my children or grandchildren	0	1	2
Seeing beautiful scenery	0	1	2
Eating good meals	0	1	2
Thinking about people I like	0	1	2

	Not in the last 30 days	1—6 times	7 or more times
Talking on the phone	0	1	2
Being with someone I love	0	1	2
Being with happy people	0	1	2
Smiling at people	0	1	2
Expressing my love to someone	0	1	2
Being complimented on something I have done well	0	1	2
Eating snacks	0	1	2
Being with my children	0	1	2

Now please go over the list once again. This time, the question is how pleasant, enjoyable or rewarding was each event over the past month. Please answer this question by rating each item on the following scale:

0 = This was not pleasant (use for neutral or unpleasant events).

1 = This was somewhat pleasant (use for mildly or moderately pleasant events).

2 = This was very pleasant (use for strongly or extremely pleasant events).

	Not pleasant	Somewhat pleasant	Very pleasant
Reading stories, novels, plays or poems	0	1	2
Saying something clearly	0	1	2
Watching TV	0	1	2
Thinking about something good in the future	0	1	2
Laughing	0	1	2
Taking a shower (or bath)	0	1	2
Being with animals	0	1	2
Hearing jokes	0	1	2
Talking about my children or grandchildren	0	1	2
Seeing beautiful scenery	0	1	2
Eating good meals	0	1	2
Thinking about people I like	0	1	2

	Not pleasant	Somewhat pleasant	Very pleasant
Talking on the phone	0	1	2
Being with someone I love	0	1	2
Being with happy people	0	1	2
Smiling at people	0	1	2
Expressing my love to someone	0	1	2
Being complimented on something I have done well	0	1	2
Eating snacks	0	1	2
Being with my children	0	1	2

Thank you!

You have reached the end of the pack

Please double check you have not missed any questions, and then return this pack in the freepost envelope provided.

Please make sure you also return the study consent form in the freepost envelope provided.

For more information or if you have any questions please contact Leanne Trick:

(01392) 725947

L.V.Trick@exeter.ac.uk

University of Exeter Medical School, St Lukes Campus, Heavitree Road, Exeter EX1 2LU

Appendix 4 Brief information sheet for participants

UNIVERSITY OF EXETER

Royal Devon and Exeter NHS
NHS Foundation Trust

Would you consider taking part in a research study for people with a heart condition?

Hello!
My name is Leanne and I am a researcher from the University of Exeter. I would be pleased if you would be prepared to talk to me briefly about this research.

What is this all about?
My study aims to understand how thoughts and feelings following a heart condition affects the way a person recovers and gets back to their normal life.

What am I asking for?
I would like to talk to you about my study to see if you are interested in taking part. Your participation would be completely voluntary and confidential, and whether or not you take part will not affect the treatment you receive.

Your participation in this study could lead to new treatments that help people recover better and more quickly after being in hospital with a heart condition.

What next?
Please fill in your name and telephone number and hand this form back to the person who gave it to you. I will then contact you at home in about a week's time.

Please enter your name and telephone number here (by giving us these details you are under no obligation to take part in the study):

NAME _____

PHONE NO. _____

Times you would prefer NOT to be contacted (circle): Mornings / Afternoons

Other (please state) _____

Who are we?
We are a team of researchers from the University of Exeter Medical School and the Royal Devon & Exeter Hospital cardiology department (Dr Gandhi). The main researcher is Leanne Trick who can be contacted on 01392 725947 or L.V.Trick@exeter.ac.uk.

Appendix 5: Participant information sheet

UNIVERSITY OF EXETER

Royal Devon and Exeter NHS
NHS Foundation Trust

The role of perseverative negative thinking in predicting depression in people with CHD: Prospective cohort study

Participant Information Sheet

We would like to invite you to take part in our research study. Before you decide it is important that you understand why the research is being done and what it would involve. Please read the following information carefully and ask if there is anything that is not clear. You may talk to others about the study if you wish.

What is the purpose of the study?
Some people who have recently had an admission to hospital with a heart problem (such as a heart attack or angina) may feel low in their mood, anxious and frightened for some time afterwards. Occasionally some people can even go on to develop depression after their heart problem, and this can last for months. These feelings could be important as they might affect the way someone recovers from their heart problem (e.g. how quickly they get back to their usual activities). We don't understand exactly what factors sometimes cause people to feel low, anxious or frightened, however.

The purpose of this research is to understand whether the extent to which people tend to repeatedly think about and dwell on frightening or unhappy thoughts (that is the extent to which they worry or ruminate) in the days following their heart problems might cause them to feel low, anxious or frightened. This research is important because it may lead to new treatments that help stop people feeling low, anxious or frightened and therefore help them get back to their normal selves as quickly as possible.

Why have I been chosen?
We are asking 250 people recently admitted with a heart problem (such as a heart attack or angina) to take part in this study.

Do I have to take part?
It is completely up to you whether or not you take part. You do not have to take part in the research, and if you decide not to participate this will not affect your treatment in any way.

What will happen to me if I take part?
You will be asked to complete the enclosed questionnaire pack when you join the study. The questionnaires ask about your recent feelings, health, activity levels, how you cope with problems, and the support you receive from friends and family. You can complete this pack at home and return it to us in your own time. You will be asked to complete the same questionnaire pack again 2 months later and 6 months later. It will take around 1 hour to complete each questionnaire pack. A researcher will telephone you to remind you about the study before each questionnaire pack is sent to you. You will also be asked to complete a short memory exercise and a spelling exercise over the telephone with a researcher at around the

same time you complete each questionnaire pack. These tasks will take approximately 5-10 minutes each, and we will agree a convenient time with you to do this.
If you take part we will also look at your medical records in order to collect information about your heart problem and any medication or treatments you may have been given.

60 people who take part in this study will be contacted by telephone after approximately 2 months to see if they would be willing to take part in an additional part of the study which would involve completing some computerized exercises. You will be given more information about this additional part of the study at the time you are contacted, and you will be free to choose whether or not to take part.

What do I have to do in order to take part?
Please fill in the enclosed 'participant consent form' and questionnaire pack and return them in the stamped addressed envelope provided. A researcher will telephone you before each questionnaire pack is sent out to remind you about the study. If you have any queries about the questionnaires, or would like help completing them, please contact the researcher.

What are the possible disadvantages and risks of taking part?
The questionnaires measure your feelings of lowness and anxiety. Sometimes when people are asked to think about their feelings it can remind them of unhappy events in the past which can cause them to feel upset temporarily. If any of the questions make you feel upset please let the researcher know. If you do feel upset you are free to withdraw from the study at any time. We can also provide information about support services available in Exeter. If you are worried about any thoughts or feelings you have which are triggered by completing the questionnaires please telephone the researcher using the contact details at the end of this letter.

What are the possible benefits of taking part?
It is hoped that the information gathered in this study will help to provide more information about the link between the ways people think in the days following admission to hospital with a heart problem and how they feel in their spirits. It is hoped that this will lead to better ways to support people after they have had a heart problem.

What would happen if we were concerned about your safety?
Some of the questionnaires may show you that you are experiencing severe problems with your mood, such as depression. If you are found to be very depressed, your safety will be our priority and we may talk to you about letting your GP know about your feelings so that he or she can offer you the best treatments available. Under these circumstances, a researcher may also want to talk to you more about how you are feeling and the support you may need. If we are still concerned about your safety after we have spoken to you, we will contact your GP if we think it is in your best interests.

Will my taking part in the study be kept confidential?
All information collected about you during the study will be stored securely at the University of Exeter, and will be treated in confidence. Personal data will not be kept once the study has ended – e.g. your name, date of birth, address etc. Data obtained from questionnaires may be stored for up to five years, though there will be no way in which you can be individually identified from the data we store.

What if I don't want to continue with the study anymore?
You are free to withdraw from the study at any time, without giving a reason. If you decide to withdraw from the study your treatment will not be affected in any way. If you decide to withdraw any questionnaires that you have already completed and information from your medical records will be kept, but any personal identifying information that you have provided (such as your name, date of birth, address etc) will be destroyed. We will not ask you to provide additional information after you tell us you wish to withdraw.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the main researcher (Leanne Trick, telephone: 01392 725947 or email: L.V.Trick@exeter.ac.uk).

What will happen to the results of the study?
The results will be written up and submitted for publication in an academic journal. The work may also be presented at academic conferences. None of your personal information will be revealed and you will not be identifiable in any written reports, or other presentations. If you wish to know the results of the study you can request this information from the researchers.

Who is organising and funding the research?
This research is being funded by the University of Exeter. The research is being carried out as part of a PhD being undertaken by the main researcher (Leanne Trick).

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the NRES Committee South West – Frenchay REC.

Contact for further information
Leanne Trick is the main researcher for this study. Please contact Leanne if you have any questions about this study: University of Exeter Medical School, St Lukes Campus, Heavitree Road, Exeter EX1 2LU (telephone: 01392 725947 or email: L.V.Trick@exeter.ac.uk).

The other researchers involved in this study are Professor Chris Dickens (University of Exeter Medical School, St Lukes Campus, Heavitree Road, Exeter EX1 2LU), Professor Ed Watkins (University of Exeter Mood Disorders Centre, School of Psychology, Perry Road, Exeter EX4 4QG) and Dr Manish Gandhi (Consultant Cardiologist, Royal Devon & Exeter NHS Foundation Trust, Cardiology Department, Gladstone Road, Exeter EX1 2ED).

Thank you for taking the time to read this information.
Please keep this information for your own records.

Appendix 6: Consent form

UNIVERSITY OF EXETER

Royal Devon and Exeter NHS
NHS Foundation Trust

The role of perseverative negative thinking in predicting depression in people with CHD: Prospective cohort study

Participant Consent Form

Please initial box

1. I confirm that I have read and understood the information sheet provided (Version 2 Dated 30/6/2014). ☐

2. I understand that my personal details will be kept securely and confidentially, and any information that is entered onto a computer will be password protected. My personal details will be stored separately from the data I provide (which will be stored anonymously) and none of my identifiable details will be used in the research write-up and/or publication. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason. ☐

4. I understand that participation in the study will not affect my cardiac treatment or any other treatment I receive in any way. ☐

5. I understand that if the researchers are worried about my health in any way they may want to discuss this with my GP. I understand they will discuss this with me in the first instance. ☐

6. I agree that the lead researcher may contact me in order to arrange for follow-up assessments and to send reminders. ☐

7. Hospital records will be accessed by the lead researcher in-order to gather relevant information used in the research. I understand the researcher will have an honorary contact with the Royal Devon and Exeter NHS Foundation Trust and this means there will be a record of any files they look at. I understand that my records will not be tampered with or changed in any way and that the researcher will look at my cardiac symptoms and history, and any medications or treatments. ☐

8. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Exeter, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐

9. I understand that the researchers may wish to contact me during my participation in the study, in order to invite me to participate in an additional part to the study. This would only happen once. **Please tick here if you are happy to be contacted for this purpose?** ☐ ☐

10. **I agree to take part in the study.**

Name: ..... **Date:** .....

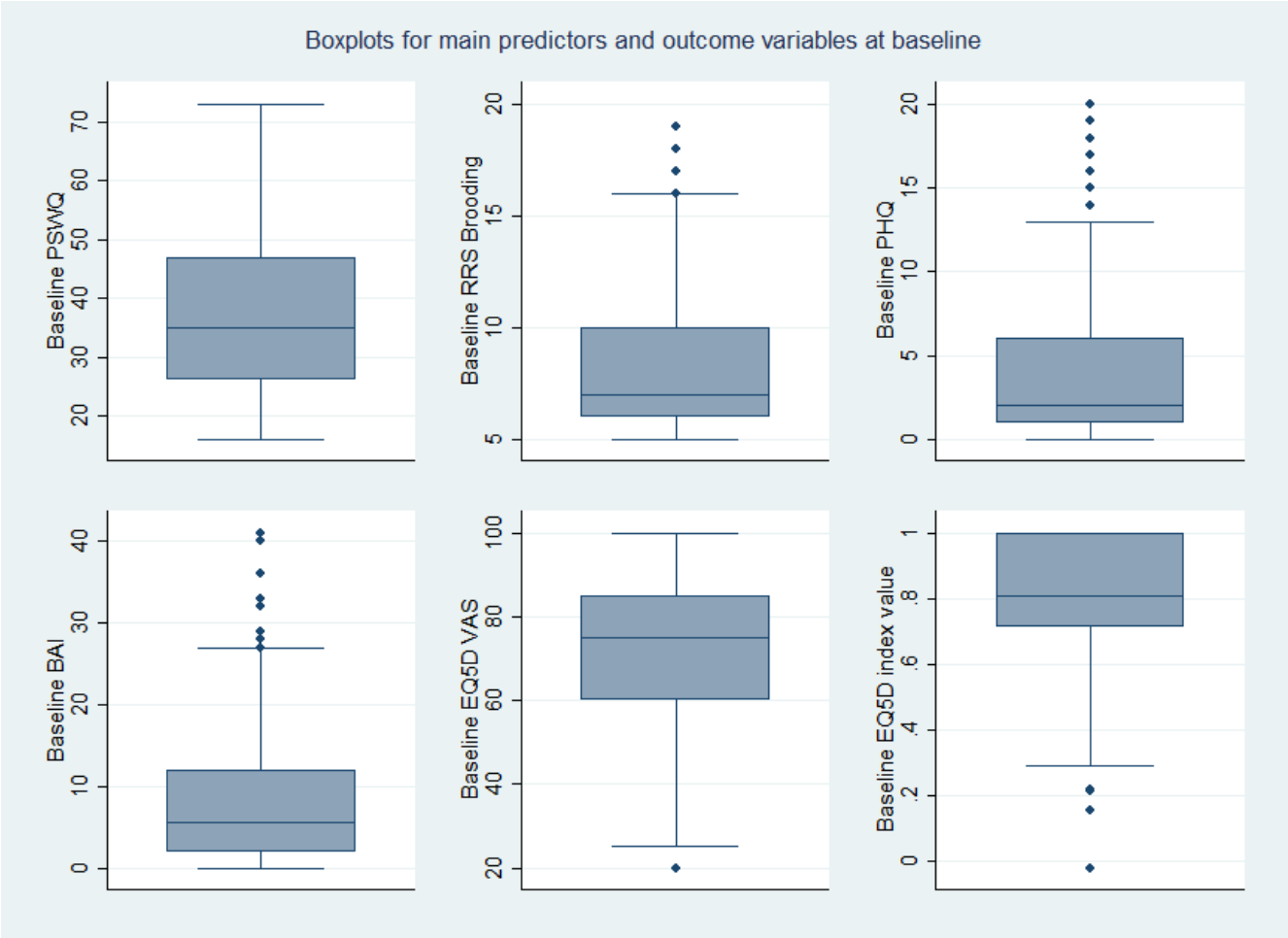
Signature: ..... **Phone:** .....

Address: .....

.....

Protocol Number: LTPhD_01
Participant Consent Form Version 2 Dated 30/6/2014 Page 1

Appendix 7: Example of boxplots for main predictors and main outcome variables



Appendix 8: Shapiro-Wilk tests of normality

A: Normality tests for all continuous variables at baseline

	N	W	p
Demographic variables			
Age	169	0.98	≤0.05
Years of education	152	0.98	≤0.05
Disease variables			
Time since index event	161	0.83	≤0.001
Troponin	116	0.54	≤0.001
Main predictors			
Total PSWQ	163	0.95	0.00003
RRS Brooding	162	0.89	≤0.001
Main outcomes			
Total PHQ	167	0.82	≤0.001
Total BAI	167	0.83	≤0.001
EQ5D VAS	167	0.95	≤0.001
EQ5D Index value	165	0.90	≤0.001
SAQ Physical limitations	162	0.94	≤0.001
SAQ Angina frequency	167	0.80	≤0.001
SAQ Angina stability	156	0.92	≤0.001
SAQ Treatment satisfaction	164	0.82	≤0.001
SAQ Disease perception	160	0.95	≤0.001
Covariates/mediators			
ENRICHD	169	0.83	≤0.001
SPSI Positive problem orientation	168	0.98	≤0.05
SPSI Rational problem solving	168	0.99	ns
SPSI Negative problem orientation	168	0.90	≤0.001
SPSI Impulsivity	168	0.95	≤0.001
SPSI Avoidance	168	0.95	≤0.001
SPSI Total score	168	0.97	≤0.001
PES Frequency	169	0.86	≤0.001
PES Pleasantness	164	0.88	≤0.001
PES Obtained pleasure	164	0.95	≤0.001
Negative words recalled (%)	84	0.97	≤0.05
Endorsed negative words recalled (%)	75	0.73	≤0.001
% Positive affective	88	0.99	ns
% Negative affective	88	0.99	ns

B: Normality tests for all continuous predictor and outcome variables at 2 months

	N	W	p
Main predictors			
Total PSWQ	124	0.94	≤0.001
RRS Brooding	124	0.85	≤0.001
Main outcomes			
Total PHQ	124	0.81	≤0.001
Total BAI	122	0.82	≤0.001
EQ5D VAS	124	0.90	≤0.001
EQ5D Index value	123	0.88	≤0.001
SAQ Physical limitations	120	0.91	≤0.001
SAQ Angina frequency	122	0.75	≤0.001
SAQ Angina stability	116	0.95	≤0.001
SAQ Treatment satisfaction	119	0.84	≤0.001
SAQ Disease perception	118	0.92	≤0.001
Covariates/mediators			
ENRICHD	123	0.82	≤0.001
SPSI Positive problem orientation	121	0.99	ns
SPSI Rational problem solving	121	0.99	ns
SPSI Negative problem orientation	121	0.88	≤0.001
SPSI Impulsivity	121	0.92	≤0.001
SPSI Avoidance	121	0.92	≤0.001
SPSI Total score	121	0.94	≤0.001
PES Frequency	123	0.88	≤0.001
PES Pleasantness	123	0.94	≤0.001
PES Obtained pleasure	123	0.95	≤0.001
Negative words recalled (%)	35	0.91	≤0.001
Endorsed negative words recalled (%)*	-	-	-
% Positive affective	34	0.97	ns
% Negative affective	34	0.99	ns

*Could not be calculated (no endorsed negative words recalled).

C: Normality tests for all continuous predictor and outcome variables at 6 months

	N	W	p
Main predictors			
Total PSWQ	110	0.93	≤0.001
RRS Brooding	108	0.87	≤0.001
Main outcomes			
Total PHQ	111	0.74	≤0.001
Total BAI	110	0.80	≤0.001
EQ5D VAS	110	0.88	≤0.001
EQ5D Index value	110	0.85	≤0.001
SAQ Physical limitations	107	0.88	≤0.001
SAQ Angina frequency	110	0.80	≤0.001
SAQ Angina stability	101	0.95	≤0.001
SAQ Treatment satisfaction	105	0.78	≤0.001
SAQ Disease perception	105	0.93	≤0.001
Covariates/mediators			
ENRICHD	111	0.78	≤0.001
SPSI Positive problem orientation	109	0.99	ns
SPSI Rational problem solving	109	0.99	ns
SPSI Negative problem orientation	109	0.88	≤0.001
SPSI Impulsivity	109	0.94	≤0.001
SPSI Avoidance	109	0.91	≤0.001
SPSI Total score	109	0.95	≤0.001
PES Frequency	109	0.81	≤0.001
PES Pleasantness	108	0.87	≤0.001
PES Obtained pleasure	108	0.92	≤0.001
Negative words recalled (%)	14	0.94	ns
Endorsed negative words recalled (%)*	-	-	-
% Positive affective	14	0.82	≤0.05
% Negative affective	14	0.97	ns

*Could not be calculated (no endorsed negative words recalled).

Appendix 9: Comparison of sample characteristics of depressed and non-depressed participants at baseline

		Depressed at baseline (N=24)			Not depressed at baseline (N=143)			Between group differences
		N	Mean	SD	N	Mean	SD	
Demographic variables								
Age (years)			57.88	13.56		68.08	10.54	$z=3.37^{a}$
Sex	Male / Female	16 / 8			114 / 29			$X^2(1)=2.03$
Years of education	Secondary / Higher	10 / 11			48 / 82			$X^2(1)=0.87$
Employment status	Employed / Not employed	13 / 11			52 / 91			$X^2(1)=2.74$
Relationship status	Relationship / No relationship	12 / 12			109 / 33			$X^2(1)=7.44^{b}$
Lives alone	Yes / No	11 / 13			31 / 111			$X^2(1)=6.26^{c}$
Index of multiple deprivation	Least deprived / Most deprived	7 / 17			74 / 63			$X^2(1)=5.04^{c}$
History of depression	Yes / No	7 / 17			9 / 134			$X^2(1)=12.41^{a}$
Smoking status	Smoker / Non-smoker	8 / 16			10 / 132			$X^2(1)=14.68^{a}$
Alcohol use	Infrequent / Regular	18 / 6			76 / 65			$X^2(1)=3.72^{p=0.054}$
Drug use	Infrequent / Regular	23 / 1			142 / 1			$X^2(1)=2.08$
Exercise	Infrequent / Regular	13 / 11			43 / 98			$X^2(1)=5.13^{c}$
ESSI social support			20.38	8.03		26.32	4.84	$z=3.82^{a}$

Table continues on following page…

		Depressed at baseline (N=24)			Not depressed at baseline (N=143)			Between group differences
		N	Mean	SD	N	Mean	SD	
Disease variables								
Diagnosis	Angina / STEMI / NSTEMI	5 / 10 / 8			42 / 52 / 49			$X^2(2)=0.68$
Days since index event			122.41	65.92		109.45	76.94	z=-1.55
Left ventricular function	None / Mild / Moderate / Severe	9 / 4 / 3 / 1			53 / 38 / 17 / 5			$X^2(3)=0.71$
NYHA functional classification	None / Mild / Moderate / Severe	4 / 8 / 10 / 2			74 / 49 / 15 / 3			$X^2(3)=21.22^c$
Number of diseased vessels			1.54	0.98		1.81	0.81	z=1.31
Comorbidity score	1 or less / 2 or more	15 / 9			105 / 38			$X^2(2)=1.21$
Troponin			1395.41	2462.33		869.47	1754.22	z=-0.86
C-reactive protein	Inflammation / No inflammation	9 / 5			28 / 49			$X^2(1)=3.83^c$
White cell count	Raised / Normal	8 / 14			41 / 98			$X^2(1)=0.42$

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 10: Comparison of main predictors and outcomes of depressed and non-depressed participants at baseline

	Depressed at baseline (N=24)		Not depressed at baseline (N=143)		
	Mean	SD	Mean	SD	Group differences
Main predictors					
RRS Brooding	12.54	3.40	7.33	2.22	z=-6.30[a]
Total PSWQ	52.31	12.45	35.09	12.25	z=-5.28[a]
Main outcomes					
Total PHQ	14.42	3.32	2.55	2.43	z=-7.90[a]
Total BAI	25.17	9.53	5.98	5.56	z=-6.84[a]
EQ5D VAS	56.88	17.70	75.47	16.10	z=4.52[a]
EQ5D Index value	0.51	0.19	0.83	0.14	z=6.60[a]
SAQ Physical limitations	56.44	25.26	77.31	22.37	z=3.38[a]
SAQ Angina frequency	78.18	17.36	90.62	16.62	z=3.80[a]
SAQ Angina stability	76.19	29.02	84.51	23.51	z=1.30
SAQ Treatment satisfaction	84.38	13.05	90.71	14.85	z=2.84[b]
SAQ Disease perception	49.05	25.78	73.90	23.39	z=4.02[a]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

EQ5D subscales omitted since these are exploratory analyses.

Appendix 11: Description of missing data at baseline (total N=169)

	N	% missing cases	% cases with missing items*			Total number of missing items*	% missing items*
			Total	Item/s substituted	Scale/subscale excluded		
Predictors							
Total PSWQ	163	3.55	8.28	4.73	3.55	50.00	1.85
RRS Brooding	162	4.14	4.14	n/a	4.14	18.00	1.78
Outcomes							
Total PHQ	167	1.18	2.96	1.78	1.18	17.00	1.26
Total BAI	167	1.18	2.96	1.78	1.18	34.00	0.91
EQ5D VAS	167	1.18	n/a	n/a	n/a	n/a	n/a
EQ5D Index value	165	2.37	n/a	n/a	n/a	n/a	n/a
EQ5D Mobility	167	1.18	n/a	n/a	n/a	n/a	n/a
EQ5D Self-care	167	1.18	n/a	n/a	n/a	n/a	n/a
EQ5D Usual activities	166	1.78	n/a	n/a	n/a	n/a	n/a
EQ5D Pain	167	1.18	n/a	n/a	n/a	n/a	n/a
EQ5D Anxiety / depression	166	1.78	n/a	n/a	n/a	n/a	n/a
SAQ Physical limitations	162	4.14	5.92	1.78	4.14	48.00	3.16
SAQ Angina frequency	167	1.18	1.78	0.59	1.18	5.00	1.48
SAQ Angina stability	156	7.69	n/a	n/a	n/a	n/a	n/a
SAQ Treatment satisfaction	164	2.96	7.10	4.14	2.96	29.00	4.29
SAQ Disease perception	160	5.33	7.10	1.78	5.33	26.00	5.13

*Does not apply to single item scales**.**

Appendix 12: Correlations between sample characteristics and main predictor variables at baseline

	PSWQ	RRS brooding
Demographic variables		
Age	-0.23[b]	-0.20[b]
Years of education	0.02	0.08
Index of multiple deprivation	-0.11	-0.13[c]
ESSI social support	-0.26[a]	-0.27[a]
Disease variables		
Time since index event	0.02	0.09
Left ventricular function	-0.18[c]	-0.10
NYHA classification	0.14[c]	0.15[c]
Number of diseased vessels	-0.03	-0.05
Comorbidity score	0.07	0.00
Troponin	-0.02	-0-06

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 13: Correlations between sample characteristics with main outcome variables at baseline

	Total PHQ	Total BAI	EQ5D VAS	EQ5D Index value	EQ5D Mobility	EQ5D Self-care	EQ5D Usual activities	EQ5D Pain	EQ5D Anxiety / depression
Demographic variables									
Age	-0.31[a]	-0.20[b]	0.07	0.08	0.15[c]	0.04	0.03	-0.15	-0.32[a]
Years of education	0.00	-0.05	-0.11	0.04	-0.12	-0.03	0.03	-0.10	0.06
Index of multiple deprivation	-0.13[c]	-0.15[b]	0.00	0.11	-0.11	-0.12	-0.09	-0.09	-0.20[b]
ESSI social support	-0.38[a]	-0.37[a]	0.26[a]	0.30[a]	-0.16[c]	-0.17[c]	-0.26[a]	-0.19[c]	-0.33[a]
Disease variables									
Time since index event	0.04	-0.07	0.03	0.13	-0.07	0.06	-0.19[c]	-0.16[c]	0.10
Left ventricular function	-0.10	-0.06	-0.04	-0.07	0.12	0.09	0.07	0.07	-0.07
NYHA classification	0.33[a]	0.39[a]	-0.38[b]	0.33[a]	0.51[a]	0.34[a]	0.53[a]	0.47[a]	0.22[a]
Number of diseased vessels	-0.11	-0.08	-0.02	-0.01	0.08	0.05	-0.01	0.04	-0.07
Comorbidity score	0.05	0.08	-0.19[c]	-0.21[b]	0.42[a]	0.28[a]	0.21[b]	0.09	-0.01
Troponin	-0.01	-0.09	0.08	0.06	0.05	0.05	-0.07	-0.07	-0.01

Table continues on following page...

	SAQ Physical limitations	SAQ Angina frequency	SAQ Angina stability	SAQ Treatment satisfaction	SAQ Disease perception
Demographic variables					
Age	-0.27[a]	0.10	0.14	0.15	0.23[b]
Years of education	0.18[c]	0.09	-0.07	0.10	0.09
Index of multiple deprivation	0.02	0.10	0.03	0.07	0.11
ESSI social support	0.27[a]	0.31[a]	0.19[c]	0.30[a]	0.40[a]
Disease variables					
Time since index event	0.14	0.25[b]	0.14	0.07	0.19[c]
Left ventricular function	-0.06	-0.02	-0.11	0.00	-0.05
NYHA classification	-0.51[a]	-0.51[a]	-0.36[a]	-0.18[b]	-0.20[b]
Number of diseased vessels	-0.05	0.05	-0.04	-0.03	-0.02
Comorbidity score	-0.25[a]	0.01	-0.07	-0.05	-0.04
Troponin	0.11	0.12	-0.17	0.17	0.05

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 14: Summary of differences in baseline outcomes according to sample characteristics

	z	Median	
Sex		Male	Female
SAQ Physical limitations	-2.62[b]	83.33	69.44
Employment status		Working	Not working
RRS Brooding	-2.97[b]	7.50	7.00
EQ5D Anxiety/depression	-2.87[b]	1.81*	1.39*
SAQ Angina stability	2.29[c]	77.87*	87.10*
SAQ Disease perception	2.80[b]	75.00	83.33
Relationship status		Partner	No partner
EQ5D Anxiety/depression	2.63[b]	1.00	1.50
SAQ Physical limitations	-2.94[b]	86.11	66.67
History of depression		Yes	No
PHQ	-2.93[b]	5.93	2.00
EQ5D VAS	2.06[c]	65.00	80.00
EQ5D Index value	2.82[b]	0.68	0.84
EQ5D Usual activities	2.28[c]	2.00	1.00
EQ5D Pain	3.37[a]	2.31*	1.66*
EQ5D Anxiety/depression	2.60[b]	2.00	1.00
SAQ Disease perception	2.06[c]	54.17	79.17
Smoking status		Smoker	Non-smoker
PHQ	2.43[c]	6.50	2.00
BAI	2.75[b]	13.50	5.00
EQ5D Pain	2.27[c]	1.68*	2.06*
EQ5D Anxiety/depression	2.65[b]	2.50	1.00
SAQ Angina frequency	2.31[c]	90.00	100.00
SAQ Treatment satisfaction	2.41[c]	84.38	100.00
Alcohol use		Frequent	Infrequent
EQ5D VAS	3.00[b]	80.00	75.00
EQ5D Index value	3.55[a]	0.85	0.77
EQ5D Mobility	3.32[a]	1.00	1.50
EQ5D Self-care	2.30[c]	1.08*	1.24*
EQ5D Usual activities	3.98[a]	1.00	2.00
EQ5D Pain	3.28[a]	1.00	2.00
SAQ Physical limitations	3.86[a]	91.67	69.44
Recreational drug use		Frequent	Infrequent
No significant differences			

Table continued on following page…

	z	Median	
Exercise frequency		Frequent	Infrequent
PHQ	2.78[b]	2.00	4.00
BAI	3.00[b]	5.00	8.50
EQ5D VAS	2.88[b]	80.00	70.00
EQ5D Index value	3.20[a]	0.84	0.75
EQ5D Mobility	2.98[b]	1.00	2.00
EQ5D Self-care	3.48[a]	1.07*	1.38*
EQ5D Usual activities	2.92[b]	1.00	2.00
EQ5D Pain	2.06[c]	1.62*	1.93*
SAQ Physical limitations	3.43[a]	86.11	61.11
SAQ Treatment satisfaction	2.59[b]	100.00	93.75
SAQ Disease perception	3.22[b]	83.33	58.33
Diagnosis type			
No significant differences			
C-reactive protein		Inflammation	No inflammation
SAQ Treatment satisfaction	-2.31[c]	100	87.5
White cell count		Raised	Normal
No significant differences			

[a]p<0.001, [b]p≤0.01, [c]p≤0.05.

*Medians identical, therefore means presented instead to illustrate direction of difference.

Appendix 15: Correlation matrix of main outcome variables at baseline

	1	2	3	4	5	6	7	8	9
1.Total PHQ	1								
2.Total BAI	0.71[a]	1							
3.EQ5D VAS	-0.47[a]	-0.55[a]	1						
4.EQ5D Index value	-0.54[a]	-0.64[a]	0.60[a]	1					
5.EQ5D Mobility	0.28[a]	0.37[a]	-0.36[a]	-0.61[a]	1				
6.EQ5D Self-care	0.23[a]	0.27[a]	-0.40[a]	-0.42[a]	0.42[a]	1			
7.EQ5D Usual activities	0.33[a]	0.41[a]	-0.43[a]	-0.70[a]	0.61[a]	0.47[a]	1		
8.EQ5D Pain	0.33[a]	0.41[a]	-0.38[a]	-0.73[a]	0.46[a]	0.37[a]	0.55[a]	1	
9.EQ5D Anxiety / depression	0.56[a]	0.48[a]	-0.35[a]	-0.45[a]	0.19[b]	0.18[c]	0.30[a]	0.30[a]	1
10.SAQ Physical limitations	-0.32[a]	-0.43[a]	0.55[a]	0.46[a]	-0.46[a]	-0.39[a]	-0.48[a]	-0.33[a]	-0.14[c]
11.SAQ Angina frequency	-0.33[a]	-0.50[a]	0.31[a]	0.21[b]	-0.28[a]	-0.19[b]	-0.36[a]	-0.50[a]	-0.29[a]
12.SAQ Angina stability	-0.14	-0.20[c]	0.21[b]	0.25[b]	-0.20[b]	-0.24[b]	-0.18[c]	-0.20[b]	-0.11
13.SAQ Treatment satisfaction	-0.36[a]	-0.50[a]	0.19[c]	0.22[b]	-0.16[c]	-0.20[b]	-0.23[a]	-0.24[a]	-0.34[a]
14.SAQ Disease perception	-0.51[a]	-0.59[a]	0.33[a]	0.32[a]	-0.27[a]	-0.27[a]	-0.38[a]	-0.41[a]	-0.42[a]

	10	11	12	13	14
10.SAQ Physical limitations	1				
11.SAQ Angina frequency	0.41[a]	1			
12.SAQ Angina stability	0.18[c]	0.38[a]	1		
13.SAQ Treatment satisfaction	0.31[a]	0.49[a]	0.25[b]	1	
14.SAQ Disease perception	0.51[a]	0.57[a]	0.23[b]	0.59[a]	1

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 16: Description of missing data at 2 months (total N=125)

	N	% missing cases	% cases with missing items*			Total number of missing items*	% missing items*
			Total	Item/s substituted	Scale/subscale excluded		
Predictors							
Total PSWQ	124	0.80	4.80	4.00	0.80	21.00	1.05
RRS Brooding	124	0.80	0.80	0.00	0.80	4.00	0.64
Outcomes							
Total PHQ	124	0.80	1.60	0.80	0.80	9.00	0.90
Total BAI	122	2.40	7.20	4.80	2.40	37.00	1.35
EQ5D VAS	124	0.80	n/a	n/a	n/a	n/a	n/a
EQ5D Index value	123	1.60	n/a	n/a	n/a	n/a	n/a
EQ5D Mobility	124	0.80	n/a	n/a	n/a	n/a	n/a
EQ5D Self-care	124	0.80	n/a	n/a	n/a	n/a	n/a
EQ5D Usual activities	124	0.80	n/a	n/a	n/a	n/a	n/a
EQ5D Pain	123	1.60	n/a	n/a	n/a	n/a	n/a
EQ5D Anxiety / depression	124	0.80	n/a	n/a	n/a	n/a	n/a
SAQ Physical limitations	120	4.00	6.40	2.40	4.00	45.00	4.00
SAQ Angina frequency	122	2.40	4.00	1.60	2.40	8.00	3.20
SAQ Angina stability	116	7.20	n/a	n/a	n/a	n/a	n/a
SAQ Treatment satisfaction	119	4.80	8.00	3.20	4.80	28.00	5.60
SAQ Disease perception	118	5.60	8.00	2.40	5.60	20.00	5.33

*Does not apply to single item scales**.**

Appendix 17: Description of missing data at 6 months (total N=111)

	N	% missing cases	% cases with missing items*			Total number of missing items*	% missing items*
			Total	Item/s substituted	Scale/subscale excluded		
Predictors							
Total PSWQ	110	0.90	5.41	4.50	0.90	19.00	1.07
RRS Brooding	108	2.70	2.70	0.00	2.70	2.00	0.36
Outcomes							
Total PHQ	111	0.00	0.00	0.00	0.00	0.00	0.00
Total BAI	110	0.90	4.50	3.60	0.90	12.00	0.49
EQ5D VAS	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Index value	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Mobility	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Self-care	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Usual activities	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Pain	110	0.90	n/a	n/a	n/a	n/a	n/a
EQ5D Anxiety / depression	110	0.90	n/a	n/a	n/a	n/a	n/a
SAQ Physical limitations	107	3.60	3.60	0.00	3.60	27	2.70
SAQ Angina frequency	110	0.90	1.80	0.90	0.90	3.00	1.35
SAQ Angina stability	101	9.01	n/a	n/a	n/a	n/a	n/a
SAQ Treatment satisfaction	105	5.41	9.91	4.50	5.41	27.00	6.08
SAQ Disease perception	105	5.41	6.31	0.90	5.41	15.00	4.50

*Does not apply to single item scales.

Appendix 18: Comparison of correlations between brooding and worry with main outcome measures at baseline for completers and non-completers

	RRS brooding				PSWQ			
	Completers		Non-completers		Completers		Non-completers	
	N	r	N	r	N	r	N	r
Total PHQ	108	0.54[a]	54	0.57[a]	109	0.51[a]	54	0.35[c]
Total BAI	108	0.52[a]	54	0.56[a]	108	0.46[a]	54	0.42[b]
EQ5D VAS	107	-0.23[c]	54	-0.42[c]	108	-0.30[b]	54	-0.29[c]
EQ5D Index value	106	-0.35[a]	54	-0.58[a]	107	-0.36[a]	53	-0.36[b]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 19: Ordered logistic regression of baseline brooding with 6 month EQ5D subscales (N=103)

	B	SE	z	Model fit	Pseudo R^2
EQ5D Mobility				LR $\chi^2(7)=64.76^a$	0.33
Age	0.05	0.03	1.66		
Sex	0.17	0.59	0.30		
IMD	0.29	0.12	2.53^b		
Q1 ESSI	-0.10	0.04	-2.43^c		
Q1 NYHA	1.26	0.61	2.08^c		
Q1 EQ5D Mobility	1.71	0.38	4.52^a		
Q1 RRS Brooding	-0.01	0.08	-0.15		
EQ5D Self-care				LR $\chi^2(7)=35.96^a$	0.48
Age	0.08	0.06	1.19		
Sex	2.07	1.39	1.48		
IMD	0.12	0.20	0.63		
Q1 ESSI	-0.15	0.08	-1.72		
Q1 NYHA	1.58	1.28	1.23		
Q1 EQ5D Self-care	3.45	1.01	3.43^a		
Q1 RRS Brooding	0.05	0.16	0.35		
EQ5D Usual activities				LR $\chi^2(7)=55.01^a$	0.29
Age	0.09	0.03	3.01^a		
Sex	1.09	0.63	1.74		
IMD	0.08	0.10	0.79		
Q1 ESSI	-0.14	0.04	-3.27^a		
Q1 NYHA	1.51	0.56	2.70^b		
Q1 EQ5D Usual activities	0.83	0.25	3.30^a		
Q1 RRS Brooding	0.08	0.08	1.04		
EQ5D Pain				LR $\chi^2(7)=35.47^a$	0.15
Age	0.03	0.02	1.26		
Sex	0.46	0.53	0.86		
IMD	0.07	0.09	0.73		
Q1 ESSI	-0.09	0.04	-2.52^b		
Q1 NYHA	0.65	0.49	1.34		
Q1 EQ5D Pain	0.98	0.33	3.01^b		
Q1 RRS Brooding	0.03	0.07	0.45		
EQ5D Anxiety/depression				LR $\chi^2(7)=59.11^a$	0.33
Age	0.00	0.03	0.02		
Sex	1.30	0.71	1.83		
IMD	0.06	0.11	0.52		
Q1 ESSI	-0.18	0.04	-4.26^a		
Q1 NYHA	1.20	0.58	2.07^c		
Q1 EQ5D Anxiety/depression	1.04	0.41	2.55^b		
Q1 RRS Brooding	0.08	0.10	0.82		

$^a p \leq 0.001$ $^b p \leq 0.01$ $^c \leq 0.05$.
Q1=baseline.

Appendix 20: Ordered logistic regression of baseline worry with 6 month EQ5D subscales (N=104)

	B	SE	z	Model fit	Pseudo R^2
EQ5D Mobility				LR $\chi^2(7)=67.92^a$	0.34
Age	0.07	0.03	2.44[b]		
Sex	0.27	0.60	0.45		
IMD	0.29	0.12	2.33[c]		
Q1 ESSI	-0.07	0.04	-1.80		
Q1 NYHA	1.30	0.62	2.10[b]		
Q1 EQ5D Mobility	1.78	0.38	4.64[a]		
Q1 PSWQ	0.04	0.02	2.20[c]		
EQ5D Self-care				LR $\chi^2(7)=35.53^a$	0.47
Age	0.08	0.07	1.12		
Sex	1.99	1.39	1.43		
IMD	0.13	0.21	0.61		
Q1 ESSI	-0.15	0.08	-1.86		
Q1 NYHA	1.44	1.25	1.15		
Q1 EQ5D Self-care	3.58	1.02	3.53[a]		
Q1 RRS PSWQ	0.00	0.04	0.11		
EQ5D Usual activities				LR $\chi^2(7)=51.59^a$	0.27
Age	0.08	0.03	2.73[b]		
Sex	0.90	0.62	1.46		
IMD	0.09	0.11	0.85		
Q1 ESSI	-0.13	0.04	-3.10[b]		
Q1 NYHA	1.27	0.56	2.26[c]		
Q1 EQ5D Usual activities	0.87	0.25	3.51[a]		
Q1 RRS PSWQ	0.02	0.02	1.31		
EQ5D Pain				LR $\chi^2(7)=32.94^a$	0.14
Age	0.03	0.02	1.12		
Sex	0.31	0.52	0.60		
IMD	0.09	0.09	0.93		
Q1 ESSI	-0.08	0.03	-2.25[c]		
Q1 NYHA	0.53	0.49	1.08		
Q1 EQ5D Pain	0.92	0.33	2.81[b]		
Q1 RRS PSWQ	0.02	0.02	1.07		
EQ5D Anxiety/depression				LR $\chi^2(7)=56.01^a$	0.31
Age	0.01	0.03	0.18		
Sex	1.07	0.69	1.55		
IMD	0.04	0.12	0.32		
Q1 ESSI	-0.16	0.04	-3.94[a]		
Q1 NYHA	1.02	0.57	1.80		
Q1 EQ5D Anxiety/depression	0.98	0.35	2.82[b]		
Q1 RRS PSWQ	0.03	0.02	1.56		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Appendix 21: Staged multivariable regression of baseline brooding with 6 month quality of life (SAQ subscales)

A: Staged multivariable regression of baseline brooding with 6 month SAQ Physical limitations (N=100)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,94)=11.13[a]	0.34	
Age	-0.26	-0.65	0.21	-3.02b			
Sex	0.05	2.99	4.87	0.61			
IMD	-0.11	-1.06	0.86	-1.23			
Q1 ESSI	0.22	0.86	0.34	2.55[c]			
Q1 NYHA	-0.42	-19.21	3.99	-4.81[a]			
Step 2					F(6,93)= 14.55[a]	0.45	0.11 (F(1,93)=20.25[a])
Age	-0.16	-0.39	0.20	-1.92			
Sex	0.06	3.43	4.44	0.77			
IMD	-0.08	-0.79	0.79	-1.01			
Q1 ESSI	0.18	0.69	0.31	2.23[c]			
Q1 NYHA	-0.22	-9.90	4.18	-2.37[c]			
Q1 SAQ Physical limitations	0.41	0.42	0.09	4.50[a]			
Step 3					F(7,92)=12.34[a]	0.45	0.00 (F(1,92)=0.02
Age	-0.16	-0.40	0.21	-1.87			
Sex	0.06	3.40	4.47	0.76			
IMD	-0.08	-0.80	0.79	-1.01			
Q1 ESSI	0.18	0.68	0.32	2.11[c]			
Q1 NYHA	-0.22	-9.93	4.21	-2.36[c]			
Q1 SAQ Physical limitations	0.41	0.42	0.09	4.39[a]			
Q1 RRS Brooding	-0.01	-0.09	0.61	-0.15			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

B: Staged multivariable regression of baseline brooding with 6 month SAQ Angina frequency (N=105)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,99)=5.28[a]	0.17	
Age	0.03	0.06	0.18	0.32			
Sex	-0.11	-4.85	4.09	-1.19			
IMD	0.04	0.28	0.72	0.38			
Q1 ESSI	0.23	0.66	0.28	2.35[c]			
Q1 NYHA	-0.35	-12.17	3.36	-3.63[a]			
Step 2					F(6,98)= 10.61[a]	0.36	0.18 (F(1,98)=29.59[a])
Age	-0.04	-0.08	0.16	-0.52			
Sex	-0.09	-3.92	3.60	-1.09			
IMD	0.01	0.11	0.63	0.17			
Q1 ESSI	0.11	0.33	0.25	1.29			
Q1 NYHA	-0.22	-7.62	3.07	-2.48[c]			
Q1 SAQ Angina frequency	0.48	0.52	0.10	5.44[a]			
Step 3					F(7,97)=9.01[a]	0.35	0.00 (F(1,97)=0.04)
Age	-0.05	-0.09	0.17	-0.55			
Sex	-0.09	-3.97	3.63	-1.09			
IMD	0.01	0.11	0.64	0.17			
Q1 ESSI	0.11	0.32	0.26	1.22			
Q1 NYHA	-0.22	-7.65	3.09	-2.47[c]			
Q1 SAQ Angina frequency	0.47	0.52	0.10	5.08[a]			
Q1 RRS Brooding	-0.02	-0.11	0.52	-0.21			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

C: Staged multivariable regression of baseline brooding with 6 month SAQ Angina stability (N=94)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,88)=3.03[b]	0.10	
Age	0.11	0.35	0.31	1.12			
Sex	-0.14	-10.12	7.61	-1.33			
IMD	-0.04	-0.44	1.28	-0.35			
Q1 ESSI	0.33	1.49	0.49	3.07[b]			
Q1 NYHA	-0.10	-5.77	5.93	-0.97			
Step 2					F(6,87)=2.87[b]	0.11	0.02 (F(1,87)=1.90)
Age	0.09	0.27	0.32	0.84			
Sex	-0.15	-10.59	7.58	-1.40			
IMD	-0.04	-0.48	1.27	-0.38			
Q1 ESSI	0.32	1.47	0.48	3.04[b]			
Q1 NYHA	-0.09	-5.02	5.93	-0.85			
Q1 SAQ Angina stability	0.14	0.16	0.11	1.38			
Step 3					F(7,86)=2.50[c]	0.10	0.00 (F(1,86)=0.37)
Age	0.10	0.31	0.33	0.95			
Sex	-0.14	-10.24	7.63	-1.34			
IMD	-0.03	-0.42	1.28	-0.33			
Q1 ESSI	0.34	1.54	0.50	3.08[b]			
Q1 NYHA	-0.09	-5.05	5.95	-0.85			
Q1 SAQ Angina stability	0.14	0.16	0.12	1.38			
Q1 RRS Brooding	0.07	0.58	0.96	0.61			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

D: Staged multivariable regression of baseline brooding with 6 month SAQ Treatment satisfaction (N=97)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,91)=3.28[b]	0.11	
Age	0.03	0.06	0.17	0.34			
Sex	-0.09	-3.42	4.08	-0.84			
IMD	-0.01	-0.03	0.68	-0.05			
Q1 ESSI	0.33	0.87	0.28	3.13[b]			
Q1 NYHA	-0.14	-4.40	3.18	-1.38			
Step 2					F(6,90)=4.09[a]	0.16	0.06 (F(1,90)=7.05[b])
Age	0.01	0.02	0.17	0.06			
Sex	-0.11	-4.45	3.97	-1.12			
IMD	-0.03	-0.20	0.66	-0.31			
Q1 ESSI	0.27	0.71	0.28	2.57[b]			
Q1 NYHA	-0.10	-3.18	3.12	-1.02			
Q1 SAQ Treatment satisfaction	0.27	0.31	0.12	2.65[b]			
Step 3					F(7,89)=3.48[b]	0.15	0.00 (F(1,89)=0.11)
Age	0.01	0.02	0.17	0.13			
Sex	-0.11	-4.38	3.99	-1.10			
IMD	-0.03	-0.20	0.66	-0.30			
Q1 ESSI	0.27	0.73	0.28	2.57[b]			
Q1 NYHA	-0.10	-3.17	3.13	-1.01			
Q1 SAQ Treatment satisfaction	0.28	0.32	0.12	2.66[b]			
Q1 RRS Brooding	0.03	0.17	0.51	0.33			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

E: Staged multivariable regression of baseline brooding with 6 month SAQ Disease perception (N=96)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,90)=9.39[a]	0.31	
Age	0.19	0.43	0.20	2.14[c]			
Sex	-0.03	-1.35	4.79	-0.28			
IMD	0.04	0.34	0.80	0.42			
Q1 ESSI	0.42	1.41	0.32	4.42[a]			
Q1 NYHA	-0.21	-8.77	3.81	-2.30[b]			
Step 2					F(6,89)=12.16[a]	0.41	0.11 (F(1,89)=17.43[a])
Age	0.14	0.31	0.19	1.69			
Sex	-0.03	-1.80	4.40	-0.41			
IMD	0.05	0.46	0.74	0.62			
Q1 ESSI	0.30	1.01	0.31	3.29[a]			
Q1 NYHA	-0.13	-5.52	3.59	-1.53			
Q1 SAQ Disease perception	0.37	0.31	0.08	4.17[a]			
Step 3					F(7,88)=10.34[a]	0.41	0.00 (F(1,88)=0.13)
Age	0.13	0.30	0.19	1.57			
Sex	-0.04	-1.90	4.43	-0.43			
IMD	0.05	0.44	0.74	0.59			
Q1 ESSI	0.29	1.00	0.31	3.17[b]			
Q1 NYHA	-0.13	-5.58	3.62	-1.54			
Q1 SAQ Disease perception	0.36	0.31	0.08	3.86[a]			
Q1 RRS Brooding	-0.03	-0.21	0.60	-0.36			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Appendix 22: Staged multivariable regression of baseline worry with 6 month quality of life (SAQ subscales)

A: Staged multivariable regression of baseline worry with 6 month SAQ Physical limitations (N=101)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,95)=10.07[a]	0.31	
Age	-0.26	-0.65	0.22	-2.89[b]			
Sex	0.07	4.15	4.94	0.84			
IMD	-0.09	-0.93	0.89	-1.05			
Q1 ESSI	0.21	0.80	0.34	2.39[c]			
Q1 NYHA	-0.40	-18.17	4.06	-4.48[a]			
Step 2					F(6,94)=15.08[a]	0.46	0.14 (F(1,94)=26.59[a])
Age	-0.17	-0.41	0.20	-2.04[c]			
Sex	0.07	4.02	4.38	0.92			
IMD	-0.04	-0.38	0.80	-0.48			
Q1 ESSI	0.15	0.56	0.30	1.86			
Q1 NYHA	-0.18	-8.31	4.08	-2.04[c]			
Q1 SAQ Physical limitations	0.46	0.49	0.10	5.16[a]			
Step 3					F(7,93)=13.74[a]	0.47	0.02 (F(1,93)=3.37)
Age	-0.21	-0.53	0.21	-2.53[b]			
Sex	0.07	4.01	4.33	0.93			
IMD	-0.03	-0.33	0.79	-0.42			
Q1 ESSI	0.13	0.47	0.30	1.56			
Q1 NYHA	-0.18	-8.23	4.03	-2.04[c]			
Q1 SAQ Physical limitations	0.45	0.48	0.09	5.06[a]			
Q1 PSWQ	-0.14	-0.23	0.13	-1.84			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

B: Staged multivariable regression of baseline worry with 6 month SAQ Angina frequency (N=106)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,100)=4.95[a]	0.16	
Age	0.03	0.05	0.19	0.29			
Sex	-0.10	-4.19	4.08	-1.03			
IMD	0.04	0.32	0.73	0.44			
Q1 ESSI	0.21	0.60	0.28	2.19[c]			
Q1 NYHA	-0.34	-11.75	3.37	-3.49[a]			
Step 2					F(6,99)=9.57[a]	0.33	0.17 (F(1,99)=26.40[a])
Age	-0.04	-0.08	0.17	-0.50			
Sex	-0.07	-3.14	3.65	-0.86			
IMD	0.01	0.11	0.66	0.17			
Q1 ESSI	0.08	0.24	0.26	0.94			
Q1 NYHA	-0.21	-7.48	3.12	-2.40[c]			
Q1 SAQ Angina frequency	0.47	0.50	0.10	5.14[a]			
Step 3					F(7,98)=8.20[a]	0.32	0.00 (F(1,98)=0.34)
Age	-0.06	-0.11	0.18	-0.64			
Sex	-0.08	-3.25	3.66	-0.89			
IMD	0.02	0.13	0.66	0.20			
Q1 ESSI	0.08	0.22	0.26	0.83			
Q1 NYHA	-0.21	-7.42	3.13	-2.37[c]			
Q1 SAQ Angina frequency	0.46	0.49	0.10	5.05[a]			
Q1 PSWQ	-0.05	-0.06	0.11	-0.58			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

C: Staged multivariable regression of baseline worry with 6 month SAQ Angina stability (N=94)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,88)=2.24	0.06	
Age	0.09	0.30	0.33	0.91			
Sex	-0.12	-8.73	7.73	-1.13			
IMD	-0.03	-0.40	1.33	-0.30			
Q1 ESSI	0.28	1.23	0.49	2.54[b]			
Q1 NYHA	-0.10	-5.83	6.10	-0.96			
Step 2					F(6,87)=2.16[c]	0.07	0.02 (F(1,87)=1.70)
Age	0.07	0.22	0.33	0.66			
Sex	-0.13	-9.17	7.71	-1.19			
IMD	-0.04	-0.46	1.32	-0.35			
Q1 ESSI	0.27	1.22	0.48	2.51[b]			
Q1 NYHA	-0.09	-5.05	6.10	-0.83			
Q1 SAQ Angina stability	0.13	0.15	0.12	1.30			
Step 3					F(7,86)=1.87	0.06	0.00 (F(1,86)=0.19)
Age	0.06	0.18	0.35	0.51			
Sex	-0.13	-9.43	7.76	-1.21			
IMD	-0.04	-0.45	1.33	-0.34			
Q1 ESSI	0.27	1.18	0.49	2.39[c]			
Q1 NYHA	-0.09	-4.95	6.14	-0.81			
Q1 SAQ Angina stability	0.13	0.15	0.12	1.30			
Q1 PSWQ	-0.05	-0.09	0.21	-0.44			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

D: Staged multivariable regression of baseline worry with 6 month SAQ Treatment satisfaction (N=97)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,91)=2.89[c]	0.09	
Age	0.02	0.04	0.18	0.23			
Sex	-0.08	-3.03	4.09	-0.74			
IMD	0.00	-0.01	0.69	-0.02			
Q1 ESSI	0.30	0.77	0.27	2.83[b]			
Q1 NYHA	-0.15	-4.51	3.23	-1.40			
Step 2					F(6,90)=3.62[b]	0.14	0.06 (F(1,90)=6.42[b])
Age	0.00	0.00	0.17	-0.01			
Sex	-0.10	-3.97	3.99	-0.99			
IMD	-0.03	-0.21	0.68	-0.30			
Q1 ESSI	0.24	0.61	0.27	2.25[c]			
Q1 NYHA	-0.11	-3.25	3.18	-1.02			
Q1 SAQ Treatment satisfaction	0.26	0.30	0.12	2.53[b]			
Step 3					F(7,89)=3.19[b]	0.14	0.01 (F(1,89)=0.69)
Age	-0.03	-0.05	0.18	-0.25			
Sex	-0.10	-4.15	4.01	-1.03			
IMD	-0.03	-0.18	0.68	-0.27			
Q1 ESSI	0.23	0.58	0.28	2.11[c]			
Q1 NYHA	-0.10	-3.08	3.19	-0.96			
Q1 SAQ Treatment satisfaction	0.26	0.30	0.12	2.54[b]			
Q1 PSWQ	-0.08	-0.09	0.11	-0.83			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

E: Staged multivariable regression of baseline worry with 6 month SAQ Disease perception (N=96)

	β	B	SE	t	Model fit	Adj R^2	Change in R^2
Step 1					F(5,90)=8.37[a]	0.30	
Age	0.19	0.44	0.21	2.09[c]			
Sex	-0.01	-0.48	4.86	-0.10			
IMD	0.02	0.22	0.83	0.26			
Q1 ESSI	0.39	1.28	0.32	4.02[a]			
Q1 NYHA	-0.21	-8.49	3.92	-2.17[c]			
Step 2					F(6,89)=11.00[a]	0.39	0.11 (F(1,89)=16.79[a])
Age	0.14	0.32	0.19	1.67			
Sex	-0.02	-0.93	4.48	-0.21			
IMD	0.04	0.33	0.77	0.43			
Q1 ESSI	0.27	0.89	0.31	2.87[b]			
Q1 NYHA	-0.13	-5.20	3.71	-1.40			
Q1 SAQ Disease perception	0.38	0.32	0.08	4.10[a]			
Step 3					F(7,88)=9.37[a]	0.38	0.00 (F(1,88)=0.20)
Age	0.13	0.30	0.20	1.47			
Sex	-0.02	-1.05	4.51	-0.23			
IMD	0.04	0.34	0.77	0.44			
Q1 ESSI	0.26	0.87	0.31	2.78[b]			
Q1 NYHA	-0.12	-5.16	3.72	-1.39			
Q1 SAQ Disease perception	0.37	0.31	0.08	3.99[a]			
Q1 PSWQ	-0.04	-0.06	0.13	-0.44			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Q1=baseline.

Appendix 23: Summary of regression assumptions for staged multivariable regression models

Model	Shapiro-Wilk test	Breusch-Pagan test*	Durbin-Watson test	VIF	
	W		d	Max	Mean
Baseline RRS brooding→6 month PHQ	0.93[a]	55.61[a]	0.52	2.57	1.45
Baseline RRS brooding →6 month BAI	0.96[b]	9.97[b]	0.64	2.52	1.45
Baseline RRS brooding →6 month EQ5D VAS	0.91[a]	1.36	0.69	1.41	1.23
Baseline RRS brooding →6 month EQ5D Index value	0.92[a]	7.78[b]	0.88	1.76	1.32
Baseline RRS brooding →6 month SAQ Physical limitations	0.96[b]	12.37[a]	0.51	1.81	1.35
Baseline RRS brooding →6 month SAQ Angina frequency	0.90[a]	27.88[a]	0.76	1.27	1.19
Baseline RRS brooding →6 month SAQ Angina stability	0.94[a]	1.30	0.55	1.20	1.13
Baseline RRS brooding →6 month SAQ Treatment satisfaction	0.82[a]	2.42	0.48	1.20	1.15
Baseline RRS brooding →6 month SAQ Disease perception	0.98	9.60[b]	0.87	1.50	1.25
Baseline PSWQ→6 month PHQ	0.92[a]	62.40[a]	0.62	1.89	1.30
Baseline PSWQ →6 month BAI	0.95[a]	11.37[a]	0.68	1.83	1.29
Baseline PSWQ →6 month EQ5D VAS	0.91[a]	1.70	0.71	1.32	1.21
Baseline PSWQ →6 month EQ5D Index value	0.93[a]	12.20[a]	0.96	1.53	1.25
Baseline PSWQ →6 month SAQ Physical limitations	0.96[b]	13.28[a]	0.55	1.70	1.31
Baseline PSWQ →6 month SAQ Angina frequency	0.90[a]	31.75[a]	0.80	1.27	1.19
Baseline PSWQ →6 month SAQ Angina stability	0.94[a]	1.91	0.64	1.18	1.14
Baseline PSWQ →6 month SAQ Treatment satisfaction	0.83[a]	2.94	0.51	1.19	1.15
Baseline PSWQ →6 month SAQ Disease perception	0.98	11.79[a]	0.95	1.43	1.23

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Non-significant Breusch-Pagan test (p>0.05) indicates assumption of homoscedasticity met.

Appendix 24: Summary of regression diagnostics for staged multivariable regression models

Model	Studentized residuals >2		Range of studentized residuals		Cook's distance	
	Cases	%	Min	Max	Min	Max
Baseline RRS brooding→6 month PHQ	6	5.66	-3.90	3.47	0.00	0.43
Baseline RRS brooding →6 month BAI	7	6.54	-2.24	4.05	0.00	0.15
Baseline RRS brooding →6 month EQ5D VAS	6	5.77	-4.25	2.07	0.00	0.19
Baseline RRS brooding →6 month EQ5D Index value	5	4.85	-5.16	1.94	0.00	0.16
Baseline RRS brooding →6 month SAQ Physical limitations	5	5.00	-4.47	2.57	0.00	0.14
Baseline RRS brooding →6 month SAQ Angina frequency	5	4.76	-4.02	2.09	0.00	0.38
Baseline RRS brooding →6 month SAQ Angina stability	1	1.06	-1.90	2.15	0.00	0.58
Baseline RRS brooding →6 month SAQ Treatment satisfaction	3	3.09	-6.33	1.60	0.00	0.28
Baseline RRS brooding →6 month SAQ Disease perception	3	3.13	-2.07	2.27	0.00	0.13
Baseline PSWQ→6 month PHQ	7	6.54	-3.66	3.92	0.00	0.37
Baseline PSWQ →6 month BAI	7	6.60	-2.05	4.16	0.00	0.15
Baseline PSWQ →6 month EQ5D VAS	6	5.71	-4.26	1.87	0.00	0.18
Baseline PSWQ →6 month EQ5D Index value	5	4.81	-4.87	2.61	0.00	0.25
Baseline PSWQ →6 month SAQ Physical limitations	5	4.95	-4.18	2.56	0.00	0.20
Baseline PSWQ →6 month SAQ Angina frequency	6	5.66	-4.07	2.08	0.00	0.31
Baseline PSWQ →6 month SAQ Angina stability	1	1.06	-1.97	2.05	0.00	0.06
Baseline PSWQ →6 month SAQ Treatment satisfaction	5	5.15	-6.24	1.63	0.00	0.17
Baseline PSWQ →6 month SAQ Disease perception	4	4.17	-2.11	2.15	0.00	0.06

Appendix 25: Correlations between baseline PSWQ and RRS Brooding with main outcomes at 2 months

	Baseline RRS brooding		Baseline PSWQ	
	N	r	N	r
Total PHQ	120	0.46[a]	121	0.41[a]
Total BAI	118	0.44[a]	119	0.36[a]
EQ5D VAS	120	-0.27[b]	121	-0.30[a]
EQ5D Index value	120	-0.34[a]	121	-0.35[a]
EQ5D Mobility	120	0.12	121	0.13
EQ5D Self-care	120	0.24[b]	121	0.16[c]
EQ5D Usual activities	120	0.20[b]	121	0.13
EQ5D Pain	120	0.22[b]	121	0.21[b]
EQ5D Anxiety / depression	120	0.43[a]	121	0.41[a]
SAQ Physical limitations	116	-0.11	117	-0.10
SAQ Angina frequency	118	-0.23[b]	119	-0.20[c]
SAQ Angina stability	112	-0.03	113	-0.18[p=0.0529]
SAQ Treatment satisfaction	115	-0.29[b]	116	-0.21[c]
SAQ Disease perception	114	-0.45[a]	115	-0.33[a]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 26: Staged multivariable regression of baseline brooding with 2 month outcomes

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 PHQ (N=119)					F(8,110)=24.70[a]	0.62	0.00 (F(1,108)=0.61)
Age	-0.01	-0.01	0.03	-0.22			
Sex	-0.19	-0.02	0.71	-0.26			
IMD	-0.02	-0.01	0.13	-0.15			
Q1 ESSI	-0.03	-0.03	0.05	-0.48			
Q1 NYHA	1.16	0.12	0.60	1.93[p=0.056]			
History of depression	0.53	0.03	1.00	0.53			
Q1 PHQ	0.70	0.68	0.10	7.28[a]			
Q1 RRS Brooding	0.10	0.07	0.13	0.78			
Q2 BAI (N=117)					F(8,108)=25.46[a]	0.63	0.00 (F(1,110)=3.53[p=0.063])
Age	-0.02	-0.02	0.06	-0.29			
Sex	-0.09	0.00	1.30	-0.07			
IMD	0.03	0.01	0.23	0.15			
Q1 ESSI	-0.28	-0.18	0.10	-2.75[b]			
Q1 NYHA	1.75	0.10	1.15	1.52			
History of depression	1.16	0.04	1.86	0.62			
Q1 BAI	0.53	0.55	0.09	6.14[a]			
Q1 RRS Brooding	0.43	0.15	0.23	1.88[p=0.063]			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 EQ5D VAS (N=118)					F(7,110)=13.82[a]	0.43	0.00 (F(1,110)=0.91)
Age	0.03	0.01	0.15	0.17			
Sex	-2.19	-0.05	3.50	-0.63			
IMD	0.62	0.07	0.63	0.98			
Q1 ESSI	0.42	0.13	0.25	1.63			
Q1 NYHA	0.39	0.01	3.06	0.13			
Q1 EQ5D VAS	0.68	0.61	0.09	7.31[a]			
Q1 RRS Brooding	-0.47	-0.08	0.49	-0.96			
Q2 EQ5D Index value (N=117)					F(7,109)=30.61[a]	0.64	0.01 (F(1,109)=2.70)
Age	0.00	-0.13	0.00	-2.22[c]			
Sex	-0.03	-0.07	0.03	-1.11			
IMD	0.00	0.02	0.00	0.35			
Q1 ESSI	0.01	0.21	0.00	3.40[a]			
Q1 NYHA	-0.06	-0.16	0.03	-2.45[c]			
Q1 EQ5D Index value	0.58	0.58	0.07	8.13[a]			
Q1 RRS Brooding	-0.01	-0.11	0.00	-1.64			
Q2 SAQ Physical limitations (N=113)					F(7,105)=22.09[a]	0.57	0.00 (F(1,105)=0.16)
Age	-0.21	-0.09	0.17	-1.22			
Sex	6.39	0.12	3.63	1.76			
IMD	-0.96	-0.09	0.66	-1.46			
Q1 ESSI	0.71	0.17	0.27	2.59[c]			
Q1 NYHA	-8.57	-0.19	3.67	-2.34[c]			
Q1 SAQ Physical limitations	0.47	0.51	0.08	5.81[a]			
Q1 RRS Brooding	-0.23	-0.03	0.56	-0.40			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 SAQ Angina frequency (N=116)					F(7,108)=6.99[a]	0.27	0.01 (F(1,108)=2.13)
Age	-0.02	-0.01	0.14	-0.16			
Sex	-1.25	-0.03	3.35	-0.37			
IMD	0.08	0.01	0.60	0.13			
Q1 ESSI	0.16	0.06	0.24	0.68			
Q1 NYHA	-5.19	-0.16	2.82	-1.84[p=0.068]			
Q1 SAQ Angina frequency	0.35	0.38	0.09	4.01[a]			
Q1 RRS Brooding	-0.69	-0.13	0.48	-1.46			
Q2 SAQ Angina stability (N=107)					F(7, 99)=2.07[p=0.0542]	0.07	0.00 (F(1,99)=0.04)
Age	0.10	0.04	0.25	0.41			
Sex	0.77	0.01	6.30	0.12			
IMD	-0.36	-0.03	1.11	-0.32			
Q1 ESSI	0.28	0.07	0.42	0.67			
Q1 NYHA	-5.67	-0.11	4.97	-1.14			
Q1 SAQ Angina stability	0.31	0.30	0.10	3.05[b]			
Q1 RRS Brooding	0.15	0.02	0.83	0.19			
Q2 SAQ Treatment satisfaction (N=110)					F(7,102)=8.99[a]	0.34	0.01 (F(1,102)= 2.07)
Age	0.06	0.04	0.11	0.53			
Sex	-4.99	-0.15	2.75	-1.82[p=0.072]			
IMD	-0.33	-0.06	0.47	-0.70			
Q1 ESSI	0.41	0.18	0.19	2.15[c]			
Q1 NYHA	-2.45	-0.09	2.17	-1.13			
Q1 SAQ Treatment satisfaction	0.44	0.46	0.08	5.34[a]			
Q1 RRS Brooding	-0.52	-0.12	0.36	-1.44			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 SAQ Disease perception (N=108)					$F(7, 100)=23.29^{a}$	0.59	0.01 ($F(1,100)=3.34^{p=0.071}$)
Age	-0.05	-0.02	0.15	-0.33			
Sex	-4.29	-0.08	3.58	-1.20			
IMD	-0.91	-0.09	0.62	-1.46			
Q1 ESSI	0.56	0.15	0.25	2.25^{c}			
Q1 NYHA	-3.13	-0.07	3.04	-1.03			
Q1 SAQ Disease perception	0.53	0.64	0.07	8.15^{a}			
Q1 RRS Brooding	-0.91	-0.13	0.50	$-1.83^{p=0.071}$			

$^{a}p\leq0.001$ $^{b}p\leq0.01$ $^{c}\leq0.05$.

*Change in R^2 attributable to addition of brooding in final step.

Final steps only reported (for brevity).

Q1=baseline, Q2=2 month.

Appendix 27: Staged multivariable regression of baseline worry with 2 month outcomes

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 PHQ (N=120)					F(8,111)=24.28[a]	0.61	0.00 (F(1,111)=0.11)
Age	-0.01	-0.02	0.03	-0.38			
Sex	-0.24	-0.02	0.71	-0.34			
IMD	0.00	0.00	0.13	-0.02			
Q1 ESSI	-0.02	-0.02	0.05	-0.29			
Q1 NYHA	1.03	0.11	0.60	1.72[p=0.088]			
History of depression	0.60	0.04	1.00	0.60			
Q1 PHQ	0.76	0.74	0.08	9.26[a]			
Q1 Total PSWQ	-0.01	-0.02	0.02	-0.33			
Q2 BAI (N=117)					F(8,108)=24.58[a]	0.62	0.00 (F(1,108)=0.48)
Age	-0.03	-0.04	0.06	-0.58			
Sex	-0.04	0.00	1.33	-0.03			
IMD	0.02	0.00	0.24	0.08			
Q1 ESSI	-0.29	-0.19	0.10	-2.88[b]			
Q1 NYHA	1.41	0.08	1.15	1.23			
History of depression	0.92	0.03	1.89	0.49			
Q1 BAI	0.61	0.63	0.08	8.05[a]			
Q1 Total PSWQ	0.03	0.05	0.04	0.69			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 EQ5D VAS (N=119)					F(7, 111)=14.28[a]	0.44	0.01 (F(1,111)=2.64)
Age	0.01	0.01	0.15	0.07			
Sex	-2.12	-0.04	3.45	-0.61			
IMD	0.62	0.07	0.63	0.99			
Q1 ESSI	0.36	0.11	0.24	1.49			
Q1 NYHA	0.24	0.01	3.01	0.08			
Q1 EQ5D VAS	0.67	0.60	0.09	7.45[a]			
Q1 Total PSWQ	-0.17	-0.12	0.10	-1.63			
Q2 EQ5D Index value (N=118)					F(7, 110)=30.18[a]	0.64	0.01 (F(1,110)=1.72)
Age	0.00	-0.12	0.00	-2.07[c]			
Sex	-0.02	-0.05	0.03	-0.88			
IMD	0.00	0.03	0.00	0.49			
Q1 ESSI	0.01	0.20	0.00	3.28[a]			
Q1 NYHA	-0.06	-0.15	0.03	-2.26[c]			
Q1 EQ5D Index value	0.61	0.61	0.07	8.88[a]			
Q1 Total PSWQ	0.00	-0.08	0.00	-1.31			
Q2 SAQ Physical limitations (N=114)					F(7, 106)=21.87[a]	0.56	0.00 (F(1,106)=0.93)
Age	-0.22	-0.09	0.16	-1.37[p=0.064]			
Sex	6.72	0.12	3.60	1.87			
IMD	-0.91	-0.09	0.66	-1.38			
Q1 ESSI	0.62	0.16	0.26	2.35[c]			
Q1 NYHA	-7.91	-0.18	3.56	-2.23[c]			
Q1 SAQ Physical limitations	0.49	0.51	0.08	6.35[a]			
Q1 Total PSWQ	-0.10	-0.06	0.11	-0.96			

Table continues on following page…

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 SAQ Angina frequency (N=117)					F(7, 109)=6.29[a]	0.24	0.00 (F(1, 109)=0.41)
Age	0.03	0.02	0.14	0.20			
Sex	-0.45	-0.01	3.37	-0.13			
IMD	0.02	0.00	0.61	0.03			
Q1 ESSI	0.16	0.06	0.24	0.67			
Q1 NYHA	-4.77	-0.15	2.84	-1.68			
Q1 SAQ Angina frequency	0.37	0.41	0.09	4.35[a]			
Q1 Total PSWQ	-0.06	-0.06	0.10	-0.64			
Q2 SAQ Angina stability (N=107)					F(7, 99)=2.68[c]	0.10	0.03 (F(1,99)=3.49[p=0.065])
Age	0.08	0.03	0.25	0.34			
Sex	1.29	0.02	6.14	0.21			
IMD	-0.72	-0.06	1.10	-0.66			
Q1 ESSI	0.07	0.02	0.40	0.17			
Q1 NYHA	-4.00	-0.08	4.89	-0.82			
Q1 SAQ Angina stability	0.30	0.29	0.10	2.99[b]			
Q1 Total PSWQ	-0.32	-0.18	0.17	-1.87[p=0.065]			
Q2 SAQ Treatment satisfaction (N=110)					F(7, 102)=7.87[a]	0.31	0.00 (F(1,102)=0.19)
Age	0.12	0.09	0.11	1.04			
Sex	-4.24	-0.13	2.81	-1.51			
IMD	-0.50	-0.09	0.49	-1.02			
Q1 ESSI	0.38	0.17	0.19	1.97			
Q1 NYHA	-2.01	-0.08	2.24	-0.89			
Q1 SAQ Treatment satisfaction	0.47	0.49	0.08	5.57			
Q1 Total PSWQ	-0.03	-0.04	0.08	-0.44			

Table continues on following page…

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q2 SAQ Disease perception(N=108)					$F(7, 100)=20.79^a$	0.56	0.01 (F(1,100)=1.96)
Age	-0.02	-0.01	0.16	-0.16			
Sex	-3.26	-0.06	3.70	-0.88			
IMD	-0.97	-0.10	0.65	-1.49			
Q1 ESSI	0.45	0.13	0.25	$1.76^{p=0.081}$			
Q1 NYHA	-2.36	-0.05	3.17	-0.74			
Q1 SAQ Disease perception	0.57	0.68	0.06	8.76^a			
Q1 Total PSWQ	-0.15	-0.09	0.11	-1.40			

$^a p \leq 0.001$ $^b p \leq 0.01$ $^c \leq 0.05$.

*Change in R^2 attributable to addition of brooding in final step.

Final steps only reported (for brevity).

Q1=baseline, Q2=2 month.

Appendix 28: Correlations between 2 month PSWQ and RRS Brooding with main outcomes at 6 months

	2 month RRS brooding		2 month PSWQ	
	N	r	N	r
Total PHQ	105	0.52[a]	105	0.47[a]
Total BAI	105	0.42[a]	104	0.42[a]
EQ5D VAS	104	-0.26[b]	104	-0.35[a]
EQ5D Index value	104	-0.31[b]	104	-0.41[a]
EQ5D Mobility	104	0.15	104	0.24[b]
EQ5D Self-care	104	0.23[b]	104	0.15
EQ5D Usual activities	104	0.23[b]	104	0.23[b]
EQ5D Pain	104	0.29[a]	104	0.32[a]
EQ5D Anxiety / depression	104	0.35[a]	104	0.41[a]
SAQ Physical limitations	101	-0.26[b]	101	-0.18
SAQ Angina frequency	104	-0.37[a]	104	-0.24[b]
SAQ Angina stability	95	-0.15	95	-0.16
SAQ Treatment satisfaction	99	-0.32[a]	99	-0.30[b]
SAQ Disease perception	99	-0.50[a]	99	-0.36[a]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05**.**

Appendix 29: Staged multivariable regression of 2 month brooding with 6 month outcomes

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 PHQ (N=104)					F(8,95)= 33.57[a]	0.72	0.00 (F(1,95)=4.54[c])
Age	-0.04	-0.07	0.03	-1.30			
Sex	0.59	0.05	0.64	0.93			
IMD	0.00	0.00	0.11	-0.04			
Q1 ESSI	-0.16	-0.22	0.05	-3.46[a]			
Q1 NYHA	0.24	0.03	0.54	0.45			
History of depression	-0.47	-0.03	0.95	-0.49			
Q2 PHQ	0.66	0.64	0.07	8.82[a]			
Q2 RRS Brooding	0.25	0.14	0.12	2.13[c]			
Q3 BAI (N=102)					F(8,93)=32.14[a]	0.71	0.00 (F(1,93)=0.02)
Age	-0.08	-0.08	0.06	-1.46			
Sex	1.04	0.05	1.15	0.91			
IMD	0.12	0.03	0.21	0.61			
Q1 ESSI	-0.27	-0.19	0.09	-2.88[b]			
Q1 NYHA	1.40	0.08	1.00	1.40			
History of depression	-0.89	-0.03	1.76	-0.51			
Q2 BAI	0.67	0.72	0.07	9.04[a]			
Q2 RRS Brooding	-0.03	-0.01	0.23	-0.15			

Table continues on following page…

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 EQ5D VAS (N=103)					F(7,95)=15.15[a]	0.49	0.01 (F(1,95)=2.41)
Age	-0.18	-0.08	0.16	-1.12			
Sex	-2.99	-0.07	3.41	-0.88			
IMD	-0.91	-0.11	0.60	-1.52			
Q1 ESSI	0.66	0.22	0.24	2.72[b]			
Q1 NYHA	-3.28	-0.09	2.86	-1.15			
Q2 EQ5D VAS	0.51	0.53	0.08	6.60[a]			
Q2 RRS Brooding	-0.90	-0.13	0.58	-1.55			
Q3 EQ5D Index value (N=103)					F(7,95)=16.15[a]	0.51	0.01 (F(1,95)=2.37)
Age	0.00	-0.04	0.00	-0.57			
Sex	-0.05	-0.12	0.04	-1.55			
IMD	-0.01	-0.10	0.01	-1.44			
Q1 ESSI	0.00	0.15	0.00	1.78[p=0.078]			
Q1 NYHA	-0.04	-0.10	0.03	-1.26			
Q2 EQ5D Index value	0.57	0.53	0.10	5.51[a]			
Q2 RRS Brooding	-0.01	-0.13	0.01	-1.54			
Q3 SAQ Physical limitations (N=97)					F(7,89)=18.35[a]	0.56	0.01 (F(1,89)=1.22)
Age	-0.18	-0.07	0.21	-0.84			
Sex	0.38	0.01	4.21	0.09			
IMD	-0.29	-0.03	0.75	-0.39			
Q1 ESSI	0.23	0.06	0.33	0.71			
Q1 NYHA	-7.67	-0.17	3.77	-2.04[c]			
Q2 SAQ Physical limitations	0.65	0.60	0.10	6.31[a]			
Q2 RRS Brooding	-0.76	-0.09	0.68	-1.10			

Table continues on following page…

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 SAQ Angina frequency (N=103)					F(7,95)=28.56[a]	0.65	0.00 (F(1,95)=0.56)
Age	0.09	0.04	0.13	0.69			
Sex	-2.03	-0.05	2.71	-0.75			
IMD	0.29	0.04	0.48	0.62			
Q1 ESSI	0.12	0.04	0.19	0.61			
Q1 NYHA	-3.83	-0.11	2.30	-1.67			
Q2 SAQ Angina frequency	0.87	0.74	0.08	10.82[a]			
Q2 RRS Brooding	-0.34	-0.05	0.45	-0.75			
Q3 SAQ Angina stability (N=91)					F(7,83)=5.27[a]	0.25	0.00 (F(1,83)=0.11)
Age	0.08	0.02	0.31	0.25			
Sex	-9.74	-0.13	7.19	-1.36			
IMD	-0.36	-0.03	1.22	-0.30			
Q1 ESSI	1.20	0.27	0.46	2.61[c]			
Q1 NYHA	-0.64	-0.01	5.68	-0.11			
Q2 SAQ Angina stability	0.50	0.45	0.11	4.69[a]			
Q2 RRS Brooding	-0.35	-0.03	1.05	-0.33			
Q3 SAQ Treatment satisfaction (N=98)					F(7,90)=10.13[a]	0.40	0.00 (F(1,90)=0.08)
Age	0.01	0.00	0.15	0.06			
Sex	-2.96	-0.08	3.30	-0.90			
IMD	-0.14	-0.02	0.56	-0.24			
Q1 ESSI	0.30	0.12	0.24	1.24			
Q1 NYHA	-0.58	-0.02	2.68	-0.22			
Q2 SAQ Treatment satisfaction	0.70	0.60	0.11	6.45[a]			
Q2 RRS Brooding	-0.14	-0.02	0.53	-0.27			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 SAQ Disease perception (N=97)					$F(7,89)=16.75^a$	0.53	0.01 ($F(1,89)=1.12$)
Age	0.32	0.13	0.18	$1.83^{p=0.071}$			
Sex	0.35	0.01	3.88	0.09			
IMD	0.72	0.08	0.67	1.08			
Q1 ESSI	0.48	0.14	0.28	1.69			
Q1 NYHA	-4.07	-0.10	3.23	-1.26			
Q2 SAQ Disease perception	0.55	0.54	0.09	5.93^a			
Q2 RRS Brooding	-0.70	-0.09	0.66	-1.05			

$^a p \leq 0.001$ $^b p \leq 0.01$ $^c \leq 0.05$.

*Change in R^2 attributable to addition of brooding in final step.

Final steps only reported (for brevity).

Q1=baseline, Q2=2 month, Q3=6 month.

Appendix 30: Staged multivariable regression of 2 month worry with 6 month outcomes

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 PHQ (N=103)					F(8,94)=31.68[a]	0.71	0.00 (F(1,94)=1.07)
Age	-0.04	-0.08	0.03	-1.44			
Sex	0.49	0.04	0.66	0.74			
IMD	-0.01	-0.01	0.11	-0.09			
Q1 ESSI	-0.17	-0.22	0.05	-3.50[a]			
Q1 NYHA	0.23	0.02	0.56	0.41			
History of depression	-0.57	-0.03	0.98	-0.58			
Q2 PHQ	0.69	0.67	0.08	8.65[a]			
Q2 Total PSWQ	0.03	0.07	0.02	1.03			
Q3 BAI (N=101)					F(8,92)=32.17	0.71	0.00 (F(1,92)=0.17)
Age	-0.07	-0.07	0.06	-1.28			
Sex	0.96	0.05	1.16	0.83			
IMD	0.11	0.03	0.21	0.52			
Q1 ESSI	-0.27	-0.19	0.09	-2.87[b]			
Q1 NYHA	1.32	0.08	1.01	1.31			
History of depression	-0.92	-0.03	1.75	-0.52			
Q2 BAI	0.65	0.70	0.07	9.26[a]			
Q2 Total PSWQ	0.02	0.03	0.04	0.41			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 EQ5D VAS (N=102)					F(7,94)=15.64[a]	0.50	0.02 (F(1,94)=4.98[c])
Age	-0.18	-0.08	0.16	-1.12			
Sex	-2.41	-0.05	3.37	-0.71			
IMD	-0.90	-0.11	0.59	-1.51			
Q1 ESSI	0.60	0.20	0.24	2.47[c]			
Q1 NYHA	-3.53	-0.09	2.86	-1.23			
Q2 EQ5D VAS	0.49	0.51	0.08	6.39[a]			
Q2 Total PSWQ	-0.24	-0.18	0.11	-2.23[c]			
Q3 EQ5D Index value (N=102)					F(7,94)=16.13[a]	0.51	0.01 (F(1,94)=2.82)
Age	0.00	-0.04	0.00	-0.48			
Sex	-0.05	-0.10	0.03	-1.41			
IMD	-0.01	-0.10	0.01	-1.41			
Q1 ESSI	0.00	0.14	0.00	1.68			
Q1 NYHA	-0.04	-0.11	0.03	-1.34			
Q2 EQ5D Index value	0.57	0.52	0.10	5.39[a]			
Q2 Total PSWQ	0.00	-0.14	0.00	-1.68			
Q3 SAQ Physical limitations (N=96)					F(7,88)=17.66[a]	0.55	0.00 (F(1,88)=0.04)
Age	-0.10	-0.04	0.21	-0.47			
Sex	0.28	0.00	4.27	0.07			
IMD	-0.31	-0.03	0.76	-0.41			
Q1 ESSI	0.28	0.07	0.33	0.85			
Q1 NYHA	-7.63	-0.17	3.85	-1.98[p=0.051]			
Q2 SAQ Physical limitations	0.68	0.61	0.10	6.49[a]			
Q2 Total PSWQ	-0.02	-0.01	0.13	-0.19			

Table continues on following page…

Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 SAQ Angina frequency (N=102)					F(7,94)=28.20[a]	0.65	0.00 F(1,94)=0.47)
Age	0.14	0.07	0.13	1.07			
Sex	-1.89	-0.04	2.72	-0.70			
IMD	0.27	0.04	0.48	0.57			
Q1 ESSI	0.17	0.06	0.19	0.90			
Q1 NYHA	-3.93	-0.11	2.34	-1.68			
Q2 SAQ Angina frequency	0.90	0.76	0.08	11.43[a]			
Q2 Total PSWQ	0.06	0.05	0.08	0.69			
Q3 SAQ Angina stability (N=90)					F(7,82)=5.59[a]	0.27	0.00 (F(1,82)=0.46)
Age	0.06	0.02	0.31	0.19			
Sex	-8.49	-0.12	7.09	-1.20			
IMD	-0.18	-0.01	1.22	-0.15			
Q1 ESSI	1.41	0.32	0.46	3.03[b]			
Q1 NYHA	1.01	0.02	5.73	0.18			
Q2 SAQ Angina stability	0.55	0.49	0.11	4.91[a]			
Q2 Total PSWQ	0.14	0.07	0.20	0.68			
Q3 SAQ Treatment satisfaction (N=97)					F(7,89)=10.12[a]	0.40	0.01 (F(1,89)=0.80)
Age	0.00	0.00	0.15	-0.01			
Sex	-2.99	-0.08	3.30	-0.91			
IMD	-0.14	-0.02	0.57	-0.25			
Q1 ESSI	0.26	0.10	0.24	1.07			
Q1 NYHA	-0.67	-0.02	2.71	-0.25			
Q2 SAQ Treatment satisfaction	0.69	0.58	0.11	6.43[a]			
Q2 Total PSWQ	-0.09	-0.08	0.10	-0.89			

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Model	β	B	SE	t	Model fit	Adj R^2	Change in R^2*
Q3 SAQ Disease perception (N=96)					F(7,88)=16.39	0.53	0.00 (F(1,88)=0.02)
Age	0.33	0.14	0.18	1.84[p=0.070]			
Sex	0.88	0.02	3.90	0.22			
IMD	0.81	0.09	0.67	1.21			
Q1 ESSI	0.53	0.16	0.29	1.85[p=0.068]			
Q1 NYHA	-3.35	-0.08	3.28	-1.02			
Q2 SAQ Disease perception	0.59	0.59	0.09	6.65[a]			
Q2 Total PSWQ	-0.02	-0.01	0.12	-0.14			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Change in R^2 attributable to addition of brooding in final step.

Final steps only reported (for brevity).

Q1=baseline, Q2=2 month, Q3=6 month.

Appendix 31: Results of variance components models

	N	β	√ψ	√θ	*LR χbar^2	ICC
PHQ	402	4.01	4.41	2.13	249.07[a]	0.81
BAI	399	8.29	7.87	4.10	232.42[a]	0.79
EQ5D VAS	401	73.65	14.48	11.20	130.07[a]	0.63
EQ5D Index value	398	0.79	0.17	0.11	161.85[a]	0.71
SAQ Physical limitations	389	75.81	19.77	13.17	155.07[a]	0.70
SAQ Angina frequency	399	89.21	13.25	10.89	117.51[a]	0.60
SAQ Angina stability	373	77.86	13.62	22.38	21.09[a]	0.27
SAQ Treatment satisfaction	388	89.65	10.71	10.09	73.66[a]	0.53
SAQ Disease perception	383	73.43	18.94	13.52	133.27[a]	0.66

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

ICC=intra-class correlation coefficient.

*LR χbar^2 all df=1.

Appendix 32: Results of simple multilevel (repeated measures) models for depression (model i) (N=229)

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Fixed							
Time	-0.13	0.44	-0.30	-0.13	0.37	-0.35	
Total PHQ (n-1 lag)	0.91	0.03	28.04[a]	0.82	0.04	20.09[a]	
Random							
Participant √ψ	11.11	661.53		0.00	0.00		$X^2(2)=19.77^a$
Participant √θ	1.42	397.29		2.80	0.13		
Time √ψ	4.36	259.31					
Overall model	Wald $\chi^2(2)=788.51^a$, Log likelihood=-550.97			Wald $\chi^2(2)=405.47^a$, Log likelihood=-560.85			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

Appendix 33: Random intercept models of the association between brooding and depression with and without social support as a covariate

	Random intercept model not including social support as a covariate			Random intercept model including social support as a covariate		
	β	SE	z	β	SE	z
Model iii (N=212)						
Fixed						
Time	0.03	0.38	0.08	-0.03	0.37	-0.07
Total PHQ (n-1 lag)	0.68	0.06	11.10[a]	0.64	0.06	10.35[a]
RRS Brooding (n-1 lag)	0.17	0.09	1.98[c]	0.15	0.09	1.77[p=0.076]
Age	-0.02	0.02	-1.03	-0.02	0.02	-0.76
Sex	0.08	0.52	0.16	0.35	0.52	0.67
IMD	0.00	0.09	0.01	0.01	0.09	0.13
Q1 ESSI				-0.11	0.04	-2.89[b]
Q1 NYHA	1.12	0.42	2.69[b]	0.84	0.42	2.01[c]
History of depression	0.73	0.69	1.05	0.36	0.69	0.52
Days since index event	0.00	0.00	0.63	0.00	0.00	0.44
Random						
Participant √ψ	0.00	0.00		0.00	0.00	
Participant √θ	2.74	0.13		2.69	0.13	
Time √ψ						
Overall model	Wald $\chi^2(9)=365.00^a$, Log likelihood=-514.37			Wald $\chi^2(10)=387.79^a$, Log likelihood=-510.27		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 34: Results of simple multilevel (repeated measures) models for anxiety (model i) (N=223)

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Fixed							
Time	-	-	-	0.11	0.69	0.17	
Total BAI (n-1 lag)	-	-	-	0.76	0.04	19.88[a]	
Random							-
Participant √ψ	-	-		0.00	0.00		
Participant √θ	-	-		5.11	0.24		
Time √ψ	-	-					
Overall model	Model failed to converge			Wald $\chi^2(2)=395.89^a$, Log likelihood=-680.36			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

Appendix 35: Results of simple multilevel (repeated measures) models for EQ5D VAS (model i) (N=228)

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Fixed							
Time	0.93	2.07	0.45	1.09	1.88	0.58	
EQ5D VAS (n-1 lag)	0.75	0.05	15.77[a]	0.68	0.05	13.11[a]	
Random							
Participant √ψ	36.56	139.93		0.00	0.00		$X^2(2)=3.32$
Participant √θ	11.96	32.85		14.14	0.66		
Time √ψ	14.49	54.32					
Overall model	Wald $\chi^2(2)=249.17$[a], Log likelihood=-925.80			Wald $\chi^2(2)=172.45$[a], Log likelihood=-927.46			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

Appendix 36: Results of simple multilevel (repeated measures) models for EQ5D Index value (model i) (N=225)

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Fixed							
Time	-0.02	0.02	-1.32	-0.02	0.02	-1.37	
EQ5D Index value (n-1 lag)	0.78	0.04	17.26[a]	0.76	0.05	16.27[a]	
Random							
Participant √ψ	0.26	2.27		0.00	0.00		$X^2(2)=2.07$
Participant √θ	0.11	0.41		0.13	0.01		
Time √ψ	0.11	0.83					
Overall model	Wald $\chi^2(2)=298.23$[a], Log likelihood=142.70			Wald $\chi^2(2)=264.70$[a], Log likelihood=141.66			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

Appendix 37: Ordered logistic regression (with cluster option) of brooding lag variable with EQ5D subscales (N=209)

	OR	Robust SE	z	Model fit (Wald test)	Pseudo R^2
EQ5D Mobility				$\chi^2(8)=105.55^a$	0.36
Age	1.05	0.02	2.86[b]		
Sex	1.48	0.78	0.75		
IMD	1.19	0.09	2.26[c]		
Q1 ESSI	0.95	0.02	-2.34[c]		
Q1 NYHA	3.40	1.24	3.34[a]		
Days since index event	1.00	0.00	-0.82		
EQ5D Mobility (n-1 lag)	5.90	1.76	5.94[a]		
RRS Brooding (n-1 lag)	1.07	0.07	1.05		
EQ5D Self-care				$\chi^2(8)=70.72^a$	0.48
Age	1.02	0.03	0.56		
Sex	4.07	3.82	1.50		
IMD	1.10	0.13	0.78		
Q1 ESSI	0.91	0.03	-2.81[b]		
Q1 NYHA	8.81	10.46	1.83		
Days since index event	1.00	0.00	-0.57		
EQ5D Self-care (n-1 lag)	14.35	8.27	4.62[a]		
RRS Brooding (n-1 lag)	1.14	0.12	1.27		
EQ5D Usual activities				$\chi^2(8)=108.19^a$	0.32
Age	1.07	0.02	3.42[a]		
Sex	2.23	1.06	1.68		
IMD	1.11	0.09	1.18		
Q1 ESSI	0.91	0.03	-3.16[b]		
Q1 NYHA	5.22	2.20	3.91[a]		
Days since index event	1.00	0.00	-1.86		
EQ5D Usual activities (n-1 lag)	2.72	0.76	3.59[a]		
RRS Brooding (n-1 lag)	1.18	0.08	2.38[c]		
EQ5D Pain				$\chi^2(8)=107.79^a$	0.24
Age	1.02	0.02	1.43		
Sex	1.62	0.68	1.15		
IMD	1.06	0.08	0.84		
Q1 ESSI	0.93	0.02	-3.16[b]		
Q1 NYHA	2.41	0.89	2.38[c]		
Days since index event	1.00	0.00	0.31		
EQ5D Pain (n-1 lag)	3.87	0.96	5.48[a]		
RRS Brooding (n-1 lag)	1.12	0.06	2.28[c]		

Table continues on following page…

	OR	Robust SE	z	Model fit (Wald test)	Pseudo R^2
EQ5D Anxiety/depression				$\chi^2(8)=72.52^a$	0.33
Age	0.99	0.02	-0.80		
Sex	1.67	0.74	1.14		
IMD	1.00	0.07	-0.06		
Q1 ESSI	0.90	0.03	-3.30^a		
Q1 NYHA	2.65	0.96	2.67^b		
Days since index event	1.00	0.00	0.41		
EQ5D Anxiety/depression (n-1 lag)	4.48	1.55	4.34^a		
RRS Brooding (n-1 lag)	1.12	0.07	$1.70^{p=0.089}$		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
OR=Odds ratio.
Q1=baseline.

Appendix 38: Ordered logistic regression (with cluster option) of worry lag variable with EQ5D subscales (N=209)

	OR	Robust SE	z	Model fit (Wald test)	Pseudo R^2
EQ5D Mobility				$\chi^2(8)=88.08^a$	0.36
Age	1.06	0.02	3.11[b]		
Sex	1.44	0.76	0.70		
IMD	1.17	0.09	2.13[c]		
Q1 ESSI	0.96	0.02	-1.79[p=0.074]		
Q1 NYHA	3.49	1.27	3.44[a]		
Days since index event	1.00	0.00	-0.81		
EQ5D Mobility (n-1 lag)	6.13	1.82	6.11[a]		
Total PSWQ (n-1 lag)	1.03	0.01	2.33[c]		
EQ5D Self-care				$\chi^2(8)=71.24^a$	0.47
Age	1.01	0.04	0.34		
Sex	3.99	3.67	1.50		
IMD	1.11	0.12	0.94		
Q1 ESSI	0.89	0.04	-2.78[b]		
Q1 NYHA	7.82	8.88	1.81[p=0.070]		
Days since index event	1.00	0.00	-0.35		
EQ5D Usual activities (n-1 lag)	17.34	9.57	5.17[a]		
Total PSWQ (n-1 lag)	1.01	0.02	0.47		
EQ5D Usual activities				$\chi^2(8)=86.50^a$	0.31
Age	1.06	0.02	2.96[b]		
Sex	1.98	0.93	1.46		
IMD	1.11	0.09	1.26		
Q1 ESSI	0.92	0.03	-2.63[b]		
Q1 NYHA	4.63	1.95	3.64[a]		
Days since index event	1.00	0.00	-1.38		
EQ5D Self-care (n-1 lag)	3.04	0.79	4.31[a]		
Total PSWQ (n-1 lag)	1.02	0.01	1.91[p=0.056]		
EQ5D Pain				$\chi^2(8)=100.45^a$	0.23
Age	1.02	0.02	1.19		
Sex	1.52	0.62	1.04		
IMD	1.05	0.08	0.60		
Q1 ESSI	0.93	0.02	-2.95[b]		
Q1 NYHA	2.53	0.92	2.55[b]		
Days since index event	1.00	0.00	0.52		
EQ5D Pain (n-1 lag)	3.77	0.86	5.80[a]		
Total PSWQ (n-1 lag)	1.02	0.01	2.35[b]		

Table continues on following page…

	OR	Robust SE	z	Model fit (Wald test)	Pseudo R^2
EQ5D Anxiety/depression				$\chi^2(8)=67.30^a$	0.34
Age	0.98	0.02	-0.99		
Sex	1.41	0.63	0.76		
IMD	0.97	0.06	-0.45		
Q1 ESSI	0.90	0.03	-3.34^a		
Q1 NYHA	2.65	0.95	2.72^b		
Days since index event	1.00	0.00	0.88		
EQ5D Anxiety/depression (n-1 lag)	3.84	1.23	4.18^a		
Total PSWQ (n-1 lag)	1.04	0.02	2.78^b		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.
OR=Odds ratio.
Q1=baseline.

Appendix 39: Results of multilevel (repeated measures) models with SAQ Physical limitations as the outcome variable

A: Simple multilevel (repeated measures) models for SAQ Physical limitations

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model i (N=217)							
Fixed							
Time	-3.63	2.33	-1.56	-3.47	2.21	-1.57	
SAQ Physical limitations (n-1 lag)	0.74	0.05	16.17[a]	0.71	0.05	14.88[a]	
Random							
Participant √ψ	31.05	178.33		0.00	0.00		$X^2(2)=1.04$
Participant √θ	14.67	28.95		16.07	0.77		
Time √ψ	12.42	68.56					
Overall model	Wald $\chi^2(2)=261.72$[a], Log likelihood=-909.99			Wald $\chi^2(2)=221.50$[a], Log likelihood=-910.51			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

B: Multilevel (repeated measures) models of brooding with SAQ Physical limitations

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=212)							
Fixed							
Time	-2.86	2.30	-1.25	-2.74	2.19	-1.25	
SAQ Physical limitations (n-1 lag)	0.75	0.05	15.74[a]	0.71	0.05	14.39[a]	
RRS Brooding (n-1 lag)	-0.21	0.38	-0.55	-0.24	0.40	-0.60	
Random							$X^2(2)=1.30$
Participant √ψ	31.34	136.94		0.00	0.00		
Participant √θ	14.34	22.95		15.70	0.76		
Time √ψ	12.00	55.04					
Overall model	Wald $\chi^2(3)=274.22^a$, Log likelihood= -883.97			Wald $\chi^2(3)=231.03^a$, Log likelihood=-884.62			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=199)							
Fixed							
Time	-2.17	2.21	-0.98	-2.15	2.15	-1.00	
SAQ Physical limitations (n-1 lag)	0.55	0.06	8.79[a]	0.53	0.06	8.36[a]	
RRS Brooding (n-1 lag)	-0.37	0.44	-0.83	-0.42	0.45	-0.93	
Age	-0.17	0.14	-1.27	-0.19	0.14	-1.34	
Sex	4.66	2.97	1.57	4.76	3.05	1.56	
IMD	-0.74	0.50	-1.49	-0.75	0.51	-1.47	
Q1 ESSI	0.52	0.21	2.41[c]	0.52	0.22	2.35[c]	$X^2(1)=0.17$
Q1 NYHA	-8.19	2.60	-3.15[b]	-8.67	2.66	-3.26[a]	
Days since index event	-0.01	0.01	-0.99	-0.01	0.01	-0.91	
Random							
Participant √ψ	27.97	1750.92		0.00	0.00		
Participant √θ	13.15	286.51		14.90	0.75		
Time √ψ	11.18	674.12					
Overall model	Wald $\chi^2(9)=291.18$[a], Log likelihood= -819.87			Wald $\chi^2(9)=273.32$[a], Log likelihood= -819.96			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subjects standard deviation.

Q1=baseline.

C: Multilevel (repeated measures) models of worry with SAQ Physical limitations

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=213)							
Fixed							
Time	-3.53	2.42	-1.46	-3.26	2.21	-1.47	
SAQ Physical limitations (n-1 lag)	0.78	0.05	16.70[a]	0.73	0.05	14.53[a]	
Total PSWQ (n-1 lag)	-0.07	0.07	-0.99	-0.07	0.08	-0.87	
Random							$X^2(2)=2.52$
Participant √ψ	-1.00	0.35		0.00	0.00		
Participant √θ	13.50	101.46		16.01	0.78		
Time √ψ	16.25	168.55					
Overall model	Wald $\chi^2(3)=295.49$[a], Log likelihood=-891.69			Wald $\chi^2(3)=224.19$[a], Log likelihood=-892.95			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=199)							
Fixed							
Time	-2.39	2.26	-1.06	-2.30	2.15	-1.07	
SAQ Physical limitations (n-1 lag)	0.59	0.06	9.80[a]	0.55	0.06	8.88[a]	
Total PSWQ (n-1 lag)	-0.07	0.08	-0.82	-0.06	0.08	-0.73	
Age	-0.15	0.13	-1.13	-0.16	0.14	-1.19	
Sex	4.63	2.88	1.61	4.81	3.05	1.58	
IMD	-0.64	0.49	-1.30	-0.68	0.52	-1.32	
Q1 ESSI	0.45	0.20	2.19[c]	0.47	0.22	2.19[c]	$X^2(1)=0.72$
Q1 NYHA	-7.43	2.51	-2.96[b]	-8.40	2.64	-3.18[a]	
Days since index event	-0.02	0.01	-1.23	-0.01	0.01	-1.05	
Random							
Participant √ψ	45.78	6.11		0.00	0.00		
Participant √θ	9.21	-		14.90	0.75		
Time √ψ	18.17	2.43					
Overall model	Wald $\chi^2(9)=307.93$[a], Log likelihood=-819.63			Wald $\chi^2(9)=268.83$[a], Log likelihood= -819.99			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 40: Results of multilevel (repeated measures) models with SAQ Angina frequency as the outcome variable

A: Simple multilevel (repeated measures) models for SAQ Angina frequency

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model i (N=226)							
Fixed							
Time	1.91	-1.46	0.15	1.65	-1.48	0.14	
SAQ Angina frequency (n-1 lag)	0.77	0.05	15.79[a]	0.55	0.06	10.04[a]	
Random							
Participant √ψ	43.55	522.36		5.97	4.07		$X^2(2)=10.12$[b]
Participant √θ	9.33	187.55		12.24	1.73		
Time √ψ	15.73	222.43					
Overall model	Wald $\chi^2(2)=250.02$[a], Log likelihood=-903.73			Wald $\chi^2(2)= 101.81$[a], Log likelihood=-908.79			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

B: Multilevel (repeated measures) models of brooding with SAQ Angina frequency

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=221)							
Fixed							
Time	-3.34	1.61	-2.07[c]	-3.15	1.33	-2.37[b]	
SAQ Angina frequency (n-1 lag)	0.64	0.06	11.03[a]	0.37	0.06	6.20[a]	
RRS Brooding (n-1 lag)	-0.71	0.33	-2.13[c]	-1.07	0.36	-2.96[b]	
Random							$X^2(2)=1.34$
Participant √ψ	25.12	174.25		9.20	2.15		
Participant √θ	10.47	32.18		9.60	1.20		
Time √ψ	8.16	82.49					
Overall model	Wald $\chi^2(3)=172.30$[a], Log likelihood=-871.43			Wald $\chi^2(3)=70.10$[a], Log likelihood=-872.104			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=209)							
Fixed							
Time	-2.89	1.29	-2.23[b]	-2.87	1.27	-2.25[c]	
SAQ Angina frequency (n-1 lag)	0.26	0.06	4.26[a]	0.25	0.06	3.97[a]	
RRS Brooding (n-1 lag)	-0.65	0.38	-1.73[p=0.083]	-0.67	0.38	-1.77[p=0.077]	
Age	0.02	0.12	0.14	0.02	0.13	0.15	
Sex	-5.05	3.05	-1.65	-5.09	3.10	-1.64	
IMD	0.20	0.50	0.39	0.21	0.51	0.41	
Q1 ESSI	0.35	0.20	1.76[p=0.078]	0.36	0.20	1.76[p=0.078]	$X^2(2)=0.01$
Q1 NYHA	-7.91	2.37	-3.34[a]	-8.04	2.40	-3.35[a]	
Days since index event	-0.02	0.01	-1.49	-0.02	0.01	-1.48	
Random							
Participant √ψ	13.62	99.37		9.23	1.99		
Participant √θ	8.69	12.10		8.94	1.11		
Time √ψ	3.75	55.42					
Overall model	Wald $\chi^2(9)=76.82$[a], Log likelihood=-815.17			Wald $\chi^2(9)=72.53$[a], Log likelihood=-815.18			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

C: Multilevel (repeated measures) models of worry with SAQ Angina frequency

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=222)							
Fixed							
Time	-3.22	1.49	-2.15[c]	-3.13	1.37	-2.28[c]	
SAQ Angina frequency (n-1 lag)	0.54	0.05	9.88[a]	0.43	0.06	7.69[a]	
Total PSWQ (n-1 lag)	-0.07	0.07	-1.00	-0.08	0.07	-1.11	
Random							$X^2(2)=0.74$
Participant √ψ	24.53	1741.30		8.83	2.06		
Participant √θ	9.32	352.63		10.01	1.15		
Time √ψ	8.33	789.35					
Overall model	Wald $\chi^2(3)=113.90$[a], Log likelihood=-878.99			Wald $\chi^2(3)=72.06$[a], Log likelihood=-879.36			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=209)							
Fixed							
Time				-2.92	1.27	-2.29[c]	
SAQ Angina frequency (n-1 lag)				0.26	0.06	4.30[a]	
Total PSWQ (n-1 lag)				0.02	0.07	0.21	
Age				0.08	0.13	0.61	
Sex				-4.87	3.13	-1.55	
IMD				0.16	0.52	0.30	
Q1 ESSI				0.43	0.21	2.07[c]	-
Q1 NYHA				-8.13	2.43	-3.34[a]	
Days since index event				-0.02	0.01	-1.57	
Random							
Participant √ψ				9.39	1.91		
Participant √θ				8.96	1.07		
Time √ψ							
Overall model	Model failed to converge			Wald $\chi^2(9)=66.58$[a], Log likelihood=-816.70			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 41: Results of multilevel (repeated measures) models with SAQ Angina stability as the outcome variable

A: Simple multilevel (repeated measures) models for SAQ Angina stability

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
model i (N=204)							
Fixed							
Time	-5.05	3.24	-1.56	-4.94	3.24	-1.52	
SAQ Angina stability (n-1 lag)	0.35	0.07	4.84[a]	0.37	0.07	5.11[a]	
Random							
Participant √ψ	44.92	2699.59		9.47	4.31		$X^2(2)=0.82$
Participant √θ	18.21	512.16		22.50	1.92		
Time √ψ	18.35	1016.66					
Overall model	Wald $\chi^2(2)=29.21$[a], Log likelihood=-939.80			Wald $\chi^2(2)=31.96$[a], Log likelihood=-940.21			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

B: Multilevel (repeated measures) models of brooding with SAQ Angina stability

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=200)							
Fixed							
Time	-5.17	3.33	-1.55	-5.10	3.33	-1.53	
SAQ Angina stability (n-1 lag)	0.36	0.07	4.93[a]	0.37	0.07	5.14[a]	
RRS Brooding (n-1 lag)	-0.54	0.62	-0.87	-0.57	0.62	-0.92	
Random							$X^2(2)=0.66$
Participant √ψ	36.39	2228.80		8.03	5.08		
Participant √θ	20.07	310.95		22.86	1.97		
Time √ψ	15.16	823.00					
Overall model	Wald $\chi^2(3)=32.52$[a], Log likelihood=-920.41			Wald $\chi^2(3)=34.95$[a], Log likelihood=-920.74			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=190)							
Fixed							
Time	-5.95	3.32	-1.79	-5.90	3.32	-1.78	
SAQ Angina stability (n-1 lag)	0.33	0.08	4.32[a]	0.34	0.08	4.47[a]	
RRS Brooding (n-1 lag)	-0.08	0.67	-0.12	-0.09	0.67	-0.14	
Age	0.10	0.21	0.50	0.11	0.21	0.51	
Sex	-4.67	5.21	-0.90	-4.81	5.19	-0.93	
IMD	-0.67	0.86	-0.79	-0.68	0.85	-0.79	
Q1 ESSI	0.76	0.33	2.27[c]	0.77	0.33	2.33[c]	$X^2(2)=0.19$
Q1 NYHA	-4.39	3.96	-1.11	-4.29	3.95	-1.09	
Days since index event	0.02	0.02	0.74	0.02	0.02	0.71	
Random							
Participant √ψ	38.29	506.96		7.52	5.47		
Participant √θ	19.32	77.38		22.25	2.03		
Time √ψ	15.36	194.44					
Overall model	Wald $\chi^2(9)=43.51$[a], Log likelihood=-868.80			Wald $\chi^2(9)=45.61$[a], Log likelihood=-868.89			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

C: Multilevel (repeated measures) models of worry with SAQ Angina stability

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=200)							
Fixed							
Time	-6.07	3.23	-1.88[p=0.060]	-5.91	3.23	-1.83[p=0.067]	
SAQ Angina stability (n-1 lag)	0.32	0.07	4.44[a]	0.35	0.07	4.73[a]	
Total PSWQ (n-1 lag)	-0.26	0.13	-2.02[c]	-0.24	0.13	-1.88[p=0.061]	
Random							$X^2(2)=1.40$
Participant √ψ	39.94	3351.10		9.54	4.17		
Participant √θ	18.45	558.04		22.08	1.90		
Time √ψ	16.82	1223.82					
Overall model	Wald $\chi^2(3)=35.88$[a], Log likelihood=-918.09			Wald $\chi^2(3)=38.68$[a], Log likelihood=-918.79			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=189)							
Fixed							
Time	-6.90	3.16	-2.18[a]	-6.76	3.16	-2.14[c]	
SAQ Angina stability (n-1 lag)	0.27	0.08	3.61[a]	0.29	0.08	3.86[a]	
Total PSWQ (n-1 lag)	-0.18	0.14	-1.29	-0.16	0.14	-1.15	
Age	0.12	0.22	0.57	0.13	0.22	0.58	
Sex	-3.62	5.38	-0.67	-3.93	5.37	-0.73	
IMD	-0.86	0.89	-0.96	-0.85	0.89	-0.96	
Q1 ESSI	0.63	0.34	1.86[p=0.062]	0.68	0.34	2.02[c]	$X^2(2)=0.60$
Q1 NYHA	-3.59	4.12	-0.87	-3.43	4.11	-0.84	
Days since index event	0.02	0.02	0.66	0.01	0.02	0.61	
Random							
Participant √ψ	38.90	2075.05		10.40	3.83		
Participant √θ	17.62	352.51		20.99	1.89		
Time √ψ	15.80	785.98					
Overall model	Wald $\chi^2(9)=39.13^a$, Log likelihood=-862.35			Wald $\chi^2(9)=42.06^a$, Log likelihood=-862.64			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 42: Results of multilevel (repeated measures) models with SAQ Treatment satisfaction as the outcome variable

A: Simple multilevel (repeated measures) models for SAQ Treatment satisfaction

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
model i (N=214)							
Fixed							
Time	-0.08	1.41	-0.05	-0.07	1.42	-0.05	
SAQ Treatment satisfaction (n-1 lag)	0.55	0.06	8.87[a]	0.57	0.06	9.28[a]	
Random							
Participant √ψ	15.10	326.13		1.66	2.77		$X^2(2)=1.22$
Participant √θ	9.05	41.89		10.26	0.84		
Time √ψ	6.45	117.53					
Overall model	Wald $\chi^2(2)=78.92$[a], Log likelihood=-823.71			Wald $\chi^2(2)=86.33$[a], Log likelihood=-824.32			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

B: Multilevel (repeated measures) models of brooding with SAQ Treatment satisfaction

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=210)							
Fixed							
Time	-0.22	1.41	-0.16	-0.18	1.42	-0.13	
SAQ Treatment satisfaction (n-1 lag)	0.50	0.06	7.71[a]	0.53	0.07	8.16[a]	
RRS Brooding (n-1 lag)	-0.72	0.30	-2.43[c]	-0.68	0.30	-2.24[c]	
Random							$X^2(2)=2.12$
Participant √ψ	19.04	1187.55		5.28	1.56		
Participant √θ	8.11	214.55		10.07	0.81		
Time √ψ	8.08	430.64					
Overall model	Wald $\chi^2(3)=86.06$[a], Log likelihood=-805.23			Wald $\chi^2(3)=93.67$[a], Log likelihood=-806.29			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=199)							
Fixed							
Time	-0.13	1.44	-0.09	-0.09	1.45	-0.06	
SAQ Treatment satisfaction (n-1 lag)	0.49	0.07	7.40[a]	0.51	0.07	7.74[a]	
RRS Brooding (n-1 lag)	-0.38	0.31	-1.21	-0.32	0.32	-1.02	
Age	0.00	0.10	0.01	-0.01	0.10	-0.08	
Sex	-6.46	2.42	-2.67[b]	-6.36	2.42	-2.63[b]	
IMD	-0.33	0.39	-0.84	-0.35	0.39	-0.90	
Q1 ESSI	0.47	0.16	2.89[b]	0.47	0.16	2.89[b]	$X^2(2)=2.15$
Q1 NYHA	-1.99	1.83	-1.09	-1.77	1.82	-0.97	
Days since index event	0.00	0.01	-0.18	0.00	0.01	-0.18	
Random							
Participant √ψ	15.17	1093.70		4.36	1.83		
Participant √θ	8.66	147.33		10.03	0.84		
Time √ψ	6.76	377.50					
Overall model	Wald $\chi^2(9)=111.26$[a], Log likelihood=-756.13			Wald $\chi^2(9)=117.78$[a], Log likelihood=-757.21			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

C: Multilevel (repeated measures) models of worry with SAQ Treatment satisfaction

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=210)							
Fixed							
Time	-0.33	1.41	-0.23	-0.32	1.42	-0.22	
SAQ Treatment satisfaction (n-1 lag)	0.53	0.06	8.45[a]	0.55	0.06	8.74[a]	
Total PSWQ (n-1 lag)	-0.11	0.06	-1.83[p=0.067]	-0.11	0.06	-1.87[p=0.062]	
Random							$X^2(2)=1.19$
Participant √ψ	16.37	1143.21		5.32	1.59		
Participant √θ	8.74	1143.22		10.12	0.83		
Time √ψ	6.88	418.66					
Overall model	Wald $\chi^2(3)=83.77$[a], Log likelihood=-806.79			Wald $\chi^2(3)=90.47$[a], Log likelihood=-807.38			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=198)							
Fixed							
Time	-0.47	1.43	-0.33	-0.46	1.44	-0.32	
SAQ Treatment satisfaction (n-1 lag)	0.49	0.07	7.55[a]	0.51	0.07	7.80[a]	
Total PSWQ (n-1 lag)	-0.03	0.06	-0.51	-0.03	0.06	-0.52	
Age	0.05	0.10	0.46	0.03	0.10	0.33	
Sex	-6.05	2.48	-2.44[c]	-6.00	2.48	-2.43[c]	
IMD	-0.46	0.40	-1.13	-0.46	0.40	-1.15	
Q1 ESSI	0.45	0.17	2.74[b]	0.45	0.17	2.73[b]	$X^2(2)=1.57$
Q1 NYHA	-1.83	1.89	-0.97	-1.67	1.88	-0.89	
Days since index event	0.00	0.01	-0.38	0.00	0.01	-0.36	
Random							
Participant √ψ	15.20	529.33		4.81	1.70		
Participant √θ	8.70	71.17		9.97	0.84		
Time √ψ	6.60	187.62					
Overall model	Wald $\chi^2(9)=101.79$[a], Log likelihood=-754.57			Wald $\chi^2(9)=107.78$[a], Log likelihood=-755.36			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 43: Results of multilevel (repeated measures) models with SAQ Disease perception as the outcome variable

A: Simple multilevel (repeated measures) models for SAQ Disease perception

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
model i (N=210)							
Fixed							
Time	-2.58	2.07	-1.25	-2.55	2.04	-1.25	
SAQ Disease perception (n-1 lag)	0.66	0.04	15.42[a]	0.65	0.04	15.15[a]	
Random							
Participant √ψ	25.89	-		0.00	0.00		$X^2(1)=0.10$
Participant √θ	12.88	1.27		14.61	0.71		
Time √ψ	10.36	0.80					
Overall model	Wald $\chi^2(2)=238.74$[a], Log likelihood=-861.06			Wald $\chi^2(2)=230.64$[a], Log likelihood=-861.11			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

B: Multilevel (repeated measures) models of brooding with SAQ Disease perception

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=207)							
Fixed							
Time	-2.32	2.01	-1.15	-2.33	2.01	-1.16	
SAQ Disease perception (n-1 lag)	0.59	0.05	12.39[a]	0.60	0.05	12.35[a]	
RRS Brooding (n-1 lag)	-1.07	0.39	-2.75[b]	-1.07	0.39	-2.74[b]	
Random							$X^2(2)=0.21$
Participant √ψ	24.37	1955.00		0.88	13.61		
Participant √θ	12.41	295.22		14.25	1.10		
Time √ψ	9.92	739.02					
Overall model	Wald $\chi^2(3)=252.88$[a], Log likelihood=-844.00			Wald $\chi^2(3)=251.78$[a], Log likelihood=-844.10			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=196)							
Fixed							
Time	-2.08	2.04	-1.02	-2.04	2.00	-1.02	
SAQ Disease perception (n-1 lag)	0.53	0.05	10.38[a]	0.53	0.05	10.07[a]	
RRS Brooding (n-1 lag)	-0.77	0.40	-1.92[p=0.054]	-0.79	0.41	-1.94[p=0.052]	
Age	0.10	0.12	0.88	0.11	0.12	0.95	
Sex	-4.02	2.79	-1.44	-3.92	2.85	-1.38	
IMD	-0.17	0.45	-0.39	-0.14	0.46	-0.31	
Q1 ESSI	0.56	0.19	2.96[b]	0.56	0.19	2.92[b]	$X^2(2)=0.35$
Q1 NYHA	-4.28	2.20	-1.94[p=0.052]	-4.39	2.24	-1.96[c]	
Days since index event	-0.01	0.01	-0.72	-0.01	0.01	-0.69	
Random							
Participant √ψ	23.88	1852.54		0.00	0.00		
Participant √θ	12.19	279.18		13.77	0.70		
Time √ψ	9.82	692.62					
Overall model	Wald $\chi^2(9)=291.20$[a], Log likelihood=-791.70			Wald $\chi^2(9)=278.74$[a], Log likelihood=-792.14			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

C: Multilevel (repeated measures) models of worry with SAQ Disease perception

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model ii (N=207)							
Fixed							
Time	-2.33	2.07	-1.12	-2.30	2.04	-1.13	
SAQ Disease perception (n-1 lag)	0.63	0.05	13.96a	0.63	0.05	13.67[a]	
Total PSWQ (n-1 lag)	-0.15	0.08	-1.99[c]	-0.15	0.08	-1.97[c]	
Random							$X^2(1)=0.15$
Participant √ψ	31.23	-		0.00	0.00		
Participant √θ	11.82	1.37		14.50	0.71		
Time √ψ	12.46	0.66					
Overall model	Wald $\chi^2(3)=248.99$[a], Log likelihood=-847.20			Wald $\chi^2(3)=239.31$[a], Log likelihood=-847.28			

Table continues on following page…

	Random coefficient model			Random intercept model			Likelihood ratio test*
	β	SE	z	β	SE	z	
Model iii (N=195)							
Fixed							
Time	-2.31	2.11	-1.10	-2.23	2.06	-1.08	
SAQ Disease perception (n-1 lag)	0.57	0.05	11.33[a]	0.56	0.05	10.94[a]	
Total PSWQ (n-1 lag)	-0.09	0.08	-1.14	-0.09	0.08	-1.12	
Age	0.12	0.12	0.97	0.12	0.12	1.01	
Sex	-3.36	2.85	-1.18	-3.37	2.91	-1.16	
IMD	-0.16	0.46	-0.34	-0.14	0.47	-0.30	
Q1 ESSI	0.51	0.19	2.68[b]	0.52	0.20	2.67[b]	$X^2(2)=0.23$
Q1 NYHA	-3.58	2.25	-1.59	-3.74	2.30	-1.62	
Days since index event	-0.01	0.01	-1.00	-0.01	0.01	-0.96	
Random							
Participant √ψ	25.49	1787.67		0.00	0.00		
Participant √θ	12.52	279.98		14.11	0.71		
Time √ψ	10.26	683.11					
Overall model	Wald $\chi^2(9)=272.37$[a], Log likelihood=-792.75			Wald $\chi^2(9)=257.38$[a], Log likelihood=-792.86			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Random intercept model nested in random coefficient model.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

Appendix 44: Example of random intercept model with and without days from baseline as covariate

	Random intercept model not including days from baseline as a covariate			Random intercept model including days from baseline as a covariate		
	β	SE	z	β	SE	z
Model iii (N=212)						
Fixed						
Time	-0.03	0.37	-0.07	0.05	0.78	0.07
Total PHQ (n-1 lag)	0.64	0.06	10.35[a]	0.64	0.06	10.35[a]
RRS Brooding (n-1 lag)	0.15	0.09	1.77[p=0.076]	0.15	0.09	1.78 [p=0.076]
Age	-0.02	0.02	-0.76	-0.02	0.02	-0.77
Sex	0.35	0.52	0.67	0.33	0.54	0.62
IMD	0.01	0.09	0.13	0.01	0.09	0.11
Q1 ESSI	-0.11	0.04	-2.89[b]	-0.11	0.04	-2.85[b]
Q1 NYHA	0.84	0.42	2.01[c]	0.84	0.42	2.01[c]
History of depression	0.36	0.69	0.52	0.36	0.69	0.52
Days since index event	0.00	0.00	0.44	0.00	0.00	0.42
Days from baseline				0.00	0.01	-0.12
Random						
Participant √ψ	0.00	0.00		0.00	0.00	
Participant √θ	2.69	0.13		2.67	0.13	
Time √ψ						
Overall model	Wald $\chi^2(10)=830.74$[a], Log likelihood=-498.45			Wald $\chi^2(11)= 387.83$[a], Log likelihood=-510.26		

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

√ψ=between-subjects standard deviation.

√θ=within-subject standard deviation.

Q1=baseline.

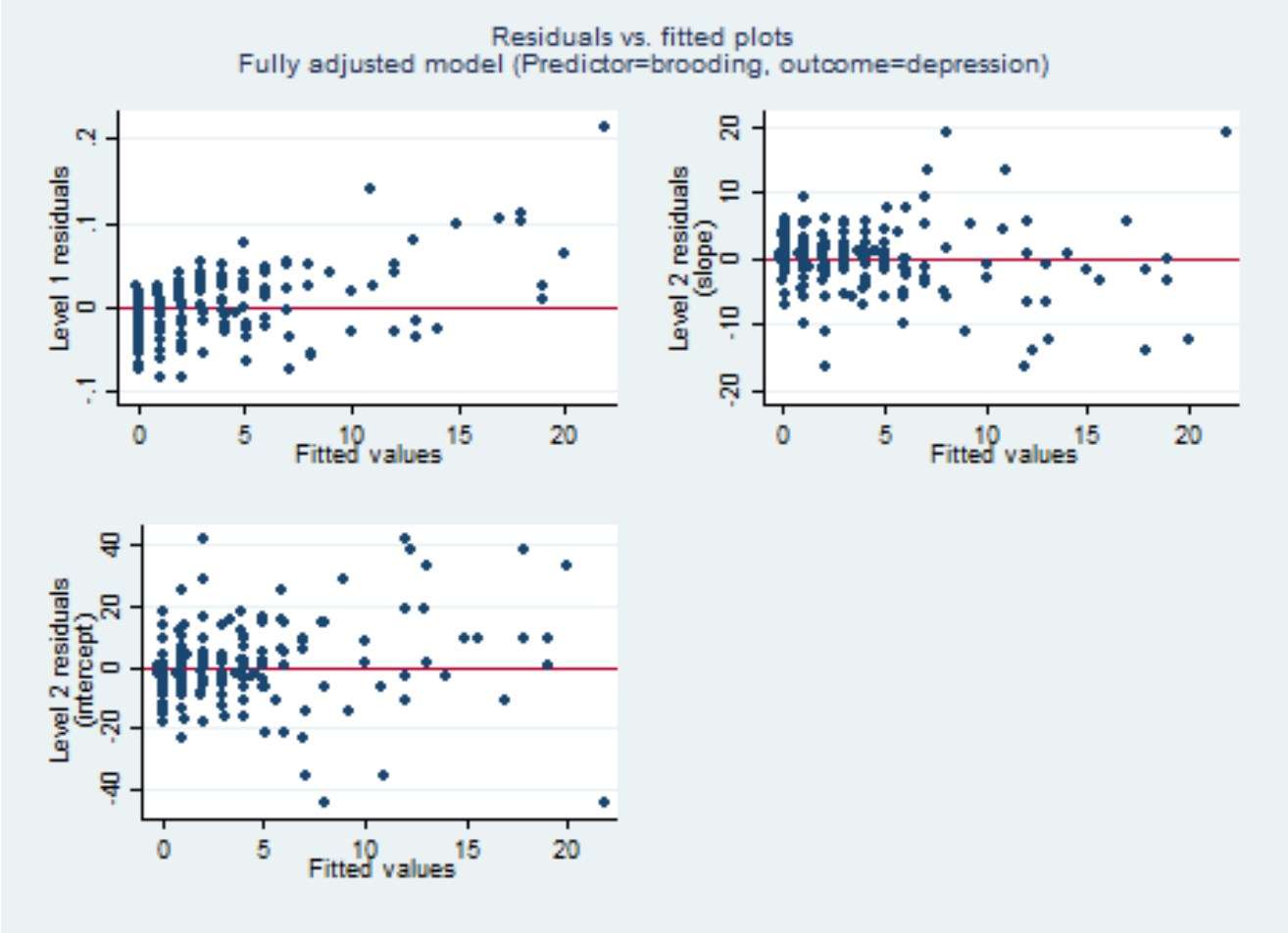
Appendix 45: Summary of Shapiro Wilk tests (W) of normality for multilevel (repeated measures) models (model iii)

Model	Random coefficient model*			Random intercept model*	
	Level 1	Level 2 (Slope)	Level 2 (Intercept)	Level 1	Level 2 (Intercept)
RRS brooding→ PHQ	0.92[a]	0.90[a]	0.91[a]		
PSWQ→ PHQ	0.92[a]	0.90[a]	0.91[a]		
RRS brooding → BAI	0.95[a]	0.95[a]	0.92[a]		
PSWQ → BAI	0.94[a]	0.95[a]	0.92[a]		
RRS brooding → EQ5D VAS				0.87[a]	0.92[a]
PSWQ → EQ5D VAS				0.88[a]	0.93[a]
RRS brooding → EQ5D Index value				0.92[a]	0.93[a]
PSWQ → EQ5D Index value				0.92[a]	0.93[a]
RRS brooding → SAQ Physical limitations				0.95[a]	0.97[a]
PSWQ → SAQ Physical limitations				0.95[a]	0.97[a]
RRS brooding → SAQ Angina frequency				0.86[a]	0.86[a]
PSWQ → SAQ Angina frequency				0.86[a]	0.86[a]
RRS brooding → SAQ Angina stability				0.97[a]	0.96[a]
PSWQ → SAQ Angina stability				0.97[a]	0.96[a]
RRS brooding → SAQ Treatment satisfaction				0.83[a]	0.90[a]
PSWQ → SAQ Treatment satisfaction				0.83[a]	0.91[a]
RRS brooding → SAQ Disease perception				0.97[a]	0.98[a]
PSWQ → SAQ Disease perception				0.97[a]	0.98[a]

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Normality tests reported for selected model only.

Appendix 46: Example of residuals versus fitted values plot (homoscedasticity assumption check)



Appendix 47: Description of missing data (potential mediator variables) at baseline (total N=169)

	N	% missing cases	% cases with missing items			Total number of missing items	% missing items
			Total	Item/s substituted	Scale/subscale excluded		
Social support							
ESSI social support	169	0.00	0.59	0.59	0.00	1.00	0.10
Problem solving							
SPSI Positive problem orientation	167	1.18	2.37	1.18	1.18	9.00	1.07
SPSI Rational problem solving	167	1.18	1.78	0.59	1.18	10.00	1.18
SPSI Negative problem orientation	167	1.18	2.37	1.18	1.18	8.00	0.95
SPSI Impulsivity	167	1.18	1.78	0.59	1.18	10.00	1.18
SPSI Avoidance	167	1.18	1.18	0.00	1.18	8.00	0.95
SPSI Total score	167	1.18	4.73	3.55	1.18	45.00	1.07
Pleasant events							
PES Frequency	169	0.00	11.24	11.24	0.00	33.00	0.98
PES Pleasantness	164	2.96	22.49	19.53	2.96	179.00	5.30
PES Obtained pleasure	164	2.96	24.85	21.89	2.96	188.00	5.56
Negative biases							
Memory task	88	47.93	n/a	n/a	n/a	n/a	n/a
Interpretation task	88	47.93	n/a	n/a	n/a	n/a	n/a

Appendix 48: Correlations between sample characteristics and potential mediator variables at baseline

	ESSI social support	SPSI Positive problem orientation	SPSI Rational problem solving	SPSI Negative problem orientation	SPSI Impulsivity	SPSI Avoidance	SPSI Total	PES Frequency	PES Pleasantness
Demographic variables									
Age	0.12	0.02	0.13	-0.10	-0.05	-0.13	0.14	-0.15	0.13
Years of education	-0.09	0.03	0.18[c]	-0.12	-0.21[c]	-0.01	0.16[c]	0.09	-0.09
Index of multiple deprivation	0.07	0.08	0.10	-0.19[a]	-0.11	-0.19[a]	0.18[a]	0.11	0.10
Disease variables									
Time since index event	-0.10	-0.05	-0.12	0.11	0.04	0.11	-0.09	-0.08	0.07
Left ventricular function	0.13	0.06	0.05	-0.13	-0.05	-0.05	0.07	0.00	0.06
NYHA classification	-0.17[b]	-0.10	-0.02	0.17[b]	0.21[a]	0.14[c]	-0.20[a]	-0.17	-0.09
Number of diseased vessels	0.02	-0.04	0.09	-0.11	-0.05	-0.08	0.08	-0.12[c]	-0.03
Comorbidity score	0.03	-0.08	0.00	0.04	0.15[c]	0.06	-0.09	-0.19[c]	0.02
Troponin	0.10	0.05	0.05	0.00	-0.06	0.21[c]	-0.02	0.06	0.12

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	PES Obtained pleasure	Negative words endorsed	Negative words recalled (%)	Endorsed negative words recalled (%)	Positive affective homophones (%)	Negative affective homophones (%)
Demographic variables						
Age	-0.02	-0.01	0.01	-0.23[c]	-0.15	-0.02
Years of education	-0.01	-0.04	0.16	0.14	-0.17	-0.17
Index of multiple deprivation	0.10	-0.09	0.13	0.09	0.19[c]	0.01
Disease variables						
Time since index event	-0.03	0.01	-0.11	0.11	-0.02	0.13
Left ventricular function	0.00	0.01	0.04	-0.08	0.05	-0.13
NYHA classification	-0.14[c]	0.16	0.06	-0.14	-0.04	0.14
Number of diseased vessels	-0.09	-0.02	-0.09	0.00	-0.05	0.09
Comorbidity score	-0.09	0.02	0.02	0.02	-0.08	0.04
Troponin	0.14	0.14	-0.03	0.01	0.04	-0.24

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 49: Summary of differences in potential mediators at baseline according to sample characteristics

	z	Median	
Sex		Male	Female
ESSI social support	-2.72[b]	29.00	26.00
Positive affective homophones (%)	2.11[c]	60.00	70.00
Employment status		Working	Not working
Endorsed negative words recalled (%)	-2.22[c]	11.49	4.33
Relationship status		Partner	No partner
ESSI social support	-6.28[a]	29.00	23.50
PES Frequency	-1.98[c]	1.65	1.55
History of depression		Yes	No
SPSI Total score	2.07[c]	11.70	14.00
PES Pleasantness	3.02[b]	1.40	1.75
PES Obtained pleasure	2.89[b]	2.36	3.05
Negative words endorsed	-2.69[b]	1.00	0.00
Endorsed negative words recalled (%)	-2.76[b]	33.33	0.00
Negative affective homophones (%)	-1.96[c]	62.50	50.00
Smoking status		Smoker	Non-smoker
SPSI Total score	2.24[c]	11.80	14.00
Alcohol use		Frequent	Infrequent
No significant differences			
Recreational drug use		Frequent	Infrequent
No significant differences			
Exercise frequency		Frequent	Infrequent
ESSI social support	-2.13[c]	29.00	26.00
SPSI Rational problem solving	-2.13[c]	10.00	9.00
SPSI Total score	-2.64[b]	14.20	13.00
PES Frequency	-2.32[c]	1.70	1.55
Diagnosis type			
No significant differences			
C-reactive protein		Inflammation	No inflammation
Negative words endorsed	-2.14	1.00	0.00
White cell count		Raised	Normal
No significant differences			

[a]p<0.001, [b]p≤0.01, [c]p≤0.05.

Non-significant findings not reported for brevity.

Appendix 50: Correlation matrix of mediator variables at baseline

	1	2	3	4	5	6	7	8	9
1.ESSI social support	1								
2.SPSI Positive problem orientation	0.14	1							
3.SPSI Rational problem solving	0.09	0.47[a]	1						
4.SPSI Negative problem orientation	-0.20[b]	-0.33[a]	-0.12	1					
5.SPSI Impulsivity	-0.12	-0.22[b]	-0.35[a]	0.45[a]	1				
6.SPSI Avoidance	-0.10	-0.20[c]	-0.17[c]	0.56[a]	0.33[a]	1			
7.SPSI Total score	0.20[b]	0.67[a]	0.67[a]	-0.66[a]	-0.65[a]	-0.60[a]	1		
8.PES Frequency	0.36[a]	0.24[b]	0.18[c]	-0.26[a]	-0.18[c]	-0.21[b]	0.31[a]	1	
9.PES Pleasantness	0.39[a]	0.14	0.14	-0.29[a]	-0.16[c]	-0.23[b]	0.29[a]	0.62[a]	1
10.PES Obtained pleasure	0.38[a]	0.21[b]	0.19[c]	-0.26[a]	-0.16[c]	-0.20[c]	0.32[a]	0.89[a]	0.84[a]
11.Negative words endorsed	0.09	-0.17	-0.09	0.41[a]	0.19	0.37[a]	-0.38[a]	-0.16	-0.25[c]
12.Negative words recalled (%)	0.05	-0.08	0.04	0.04	-0.14	0.10	-0.02	0.04	0.09
13.Endorsed negative words recalled (%)	-0.07	-0.07	0.07	0.35[b]	0.00	0.37[a]	-0.23[c]	-0.09	-0.23[c]
14.Positive affective homophones (%)	-0.03	-0.02	0.00	-0.10	-0.05	-0.22[c]	0.07	0.19	0.09
15.Negative affective homophones (%)	-0.23[c]	-0.31[c]	-0.14	-0.04	0.11	-0.07	-0.16	-0.12	-0.11

	10	11	12	13	14	15
10.PES Obtained pleasure	1					
11.Negative words endorsed	-0.17	1				
12.Negative words recalled (%)	0.06	-0.06	1			
13.Endorsed negative words recalled (%)	-0.19	0.57[a]	0.25[c]	1		
14.Positive affective homophones (%)	0.15	-0.03	-0.15	-0.23[c]	1	
15.Negative affective homophones (%)	-0.10	0.13	0.10	0.10	0.02	1

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

Appendix 51: Description of missing data (potential mediator variables) at 2 months (total N=125)

	N	% missing cases	% cases with missing items			Total number of missing items	% missing items
			Total	Item/s substituted	Scale/subscale excluded		
Social support							
ESSI social support	123	1.60	1.60	0.00	1.60	12.00	1.92
Problem solving							
SPSI Positive problem orientation	121	3.20	4.00	0.80	3.20	12.00	1.92
SPSI Rational problem solving	121	3.20	4.00	0.80	3.20	13.00	2.08
SPSI Negative problem orientation	121	3.20	4.00	0.80	3.20	13.00	2.08
SPSI Impulsivity	121	3.20	3.20	0.00	3.20	14.00	2.24
SPSI Avoidance	121	3.20	4.00	0.80	3.20	12.00	1.92
SPSI Total score	121	3.20	4.80	1.60	3.20	64.00	2.05
Pleasant events							
PES Frequency	123	1.60	8.00	6.40	1.60	58.00	2.32
PES Pleasantness	123	1.60	15.20	13.60	1.60	78.00	3.12
PES Obtained pleasure	123	1.60	15.20	13.60	1.60	78.00	3.12
Negative biases							
Memory task	35	72.00	n/a	n/a	n/a	n/a	n/a
Interpretation task	34	72.80	n/a	n/a	n/a	n/a	n/a

Appendix 52: Description of missing data (potential mediator variables) at 6 months (total N=111)

	N	% missing cases	% cases with missing items			Total number of missing items	% missing items
			Total	Item/s substituted	Scale/subscale excluded		
Social support							
ESSI social support	111	0.00	0.00	0.00	0.00	0.00	0.00
Problem solving							
SPSI Positive problem orientation	109	1.80	1.80	0.00	1.80	10.00	1.80
SPSI Rational problem solving	109	1.80	1.80	0.00	1.80	7.00	1.26
SPSI Negative problem orientation	109	1.80	1.80	0.00	1.80	9.00	1.62
SPSI Impulsivity	109	1.80	1.80	0.00	1.80	7.00	1.26
SPSI Avoidance	109	1.80	1.80	0.00	1.80	7.00	1.26
SPSI Total score	109	1.80	1.80	0.00	1.80	40.00	1.44
Pleasant events							
PES Frequency	109	1.80	9.01	7.21	1.80	31.00	1.40
PES Pleasantness	108	2.70	19.82	17.12	2.70	83.00	3.74
PES Obtained pleasure	108	2.70	20.72	18.02	2.70	85.00	3.83
Negative biases							
Memory task	14	87.39	n/a	n/a	n/a	n/a	n/a
Interpretation task	14	87.39	n/a	n/a	n/a	n/a	n/a

Appendix 53: Results of regression analyses exploring mediators of the association between brooding and depression

	B	SE*	t	95% CI
ESSI Social support				
Unadjusted model (n=103)				
Path c' (total effect)	1.00	0.11	8.83[a]	
Path a (direct effect)	-0.41	0.19	-2.12[c]	
Path b (direct effect)	-0.25	0.05	-4.84[a]	
Indirect effect	0.10	0.07		0.00, 0.29
Adjusted model (n=102)				
Path c' (total effect)	0.32	0.13	2.45[c]	
Path a (direct effect)	0.20	0.27	0.76	
Path b (direct effect)	-0.15	0.05	-3.20[b]	
Indirect effect	-0.03	0.05		-0.14, – 0.06
SPSI Positive problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	-0.50	0.11	-4.58[a]	
Path b (direct effect)	-0.09	0.11	-0.90	
Indirect effect	0.05	0.06		-0.05, .21
SPSI Rational problem solving				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	-0.26	0.14	-1.87[p=0.064]	
Path b (direct effect)	-0.03	0.08	-0.36	
Indirect effect	0.01	0.03		-0.03, 0.08
SPSI Negative problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	0.88	0.09	9.75[a]	
Path b (direct effect)	0.46	0.12	3.87[a]	
Indirect effect	0.40	0.14		0.16, 0.73
Adjusted model (n=101)				
Path c' (total effect)	0.32	0.13	2.46[c]	
Path a (direct effect)	0.51	0.12	4.09[a]	
Path b (direct effect)	0.17	0.11	1.56	
Indirect effect	0.09	0.06		-0.01, 0.25
SPSI Impulsivity				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	0.28	0.10	2.81[b]	
Path b (direct effect)	0.01	0.12	0.11	
Indirect effect	0.00	0.04		-0.07, 0.11

Table continues on following page…

	B	SE*	t	95% CI
SPSI Avoidance				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	0.27	0.11	2.51[b]	
Path b (direct effect)	0.04	0.10	0.40	
Indirect effect	0.01	0.05		-0.05, 0.16
SPSI Total score				
Unadjusted model (n=102)				
Path c' (total effect)	1.00	0.11	8.78[a]	
Path a (direct effect)	-0.44	-0.07	-6.06[a]	
Path b (direct effect)	-0.23	0.15	-1.48	
Indirect effect	0.10	0.10		-0.07, 0.34
PES Frequency				
Unadjusted model (n=103)				
Path c' (total effect)	1.00	0.11	8.83[a]	
Path a (direct effect)	-0.03	0.01	-2.75[b]	
Path b (direct effect)	-1.80	1.12	-1.61	
Indirect effect	0.05	0.05		-0.00, 0.21
PES Pleasantness				
Unadjusted model (n=103)				
Path c' (total effect)	1.00	0.11	8.83[a]	
Path a (direct effect)	-0.03	0.01	-3.46[a]	
Path b (direct effect)	-3.21	1.28	-2.50[c]	
Indirect effect	0.09	0.05		0.02, 0.24
Adjusted model (n=102)				
Path c' (total effect)	0.32	0.13	2.45[c]	
Path a (direct effect)	-0.02	0.01	-1.43	
Path b (direct effect)	-1.51	1.14	-1.34	
Indirect effect	0.03	0.03		-0.01, 0.12
PES Obtained pleasure				
Unadjusted model (n=103)				
Path c' (total effect)	1.00	0.11	8.83[a]	
Path a (direct effect)	-0.08	0.02	-3.41[a]	
Path b (direct effect)	-1.13	0.46	-2.49[c]	
Indirect effect	0.09	0.06		0.02, 0.26
Adjusted model (n=102)				
Path c' (total effect)	0.32	0.13	2.45[c]	
Path a (direct effect)	-0.04	0.03	-1.31	
Path b (direct effect)	0.47	0.41	-1.13	
Indirect effect	0.02	0.03		-0.01, 0.11

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	B	SE*	t	95% CI
Negative words endorsed				
Unadjusted model (n=86)				
Path c' (total effect)	0.99	0.12	8.61[a]	
Path a (direct effect)	0.30	0.06	4.75[a]	
Path b (direct effect)	0.22	0.20	1.08	
Indirect effect	0.06	0.11		-0.09, 0.37
Negative words recalled (%)				
Unadjusted model (n=83)				
Path c' (total effect)	0.95	0.12	8.03[a]	
Path a (direct effect)	0.27	0.88	0.31	
Path b (direct effect)	0.02	0.01	1.54	
Indirect effect	0.01	0.02		-0.02, 0.05
Endorsed negative words recalled (%)				
Unadjusted model (n=74)				
Path c' (total effect)	0.96	0.13	7.60[a]	
Path a (direct effect)	3.17	0.57	5.34[a]	
Path b (direct effect)	0.07	0.02	2.82[b]	
Indirect effect	0.21	0.16		-0.02, 0.65
Adjusted model (n=72)				
Path c' (total effect)	0.71	0.12	5.81[a]	
Path a (direct effect)	2.68	0.61	4.40[a]	
Path b (direct effect)	0.03	0.02	1.23	
Indirect effect	0.08	0.11		-0.08, 0.37
Positive affective homophones (%)				
Unadjusted model (n=86)				
Path c' (total effect)	0.99	0.12	8.61[a]	
Path a (direct effect)	-0.11	0.46	-0.24	
Path b (direct effect)	-0.04	0.03	-1.45	
Indirect effect	0.00	0.02		-0.03, 0.06
Negative affective homophones (%)				
Unadjusted model (n=86)				
Path c' (total effect)	0.99	0.12	8.61[a]	
Path a (direct effect)	0.99	0.63	1.57	
Path b (direct effect)	0.02	0.02	0.99	
Indirect effect	0.02	0.02		-0.01, 0.09

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Bootstrapped standard error for indirect effect.

CI=95% bias corrected confidence interval.

Appendix 54: Results of regression analyses exploring mediators of the association between brooding and EQ5D index value

	B	SE*	t	95% CI
ESSI Social support				
Unadjusted model (n=102)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.40	0.20	-2.07[c]	
Path b (direct effect)	0.02	0.00	5.65[a]	
Indirect effect	-0.01	0.00		-0.02, 0.00
SPSI Positive problem orientation				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.51	0.11	-4.68[a]	
Path b (direct effect)	0.01	0.01	1.34	
Indirect effect	-0.00	0.00		-0.01, 0.00
SPSI Rational problem solving				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.26	0.14	-1.87[p=0.064]	
Path b (direct effect)	0.00	0.00	-0.31	
Indirect effect	0.00	0.00		-0.00, 0.00
SPSI Negative problem orientation				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	0.88	0.09	9.71[a]	
Path b (direct effect)	-0.01	0.01	-0.96	
Indirect effect	-0.01	0.01		-0.02, 0.01
SPSI Impulsivity				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	0.28	0.10	2.86[b]	
Path b (direct effect)	-0.01	0.01	-1.76[p=0.081]	
Indirect effect	-0.00	0.00		-0.01, 0.00
SPSI Avoidance				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	0.28	0.11	2.51[c]	
Path b (direct effect)	-0.00	0.01	-0.79	
Indirect effect	-0.00	0.00		-0.01, 0.00

Table continues on following page…

	B	SE*	t	95% CI
SPSI Total score				
Unadjusted model (n=101)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	0.44	0.07	-6.11[a]	
Path b (direct effect)	0.01	0.01	1.25	
Indirect effect	-0.00	0.00		-0.02, 0.00
PES Frequency				
Unadjusted model (n=102)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.03	0.01	2.88[b]	
Path b (direct effect)	0.16	0.06	2.75[b]	
Indirect effect	-0.00	0.00		-0.01, -0.00
PES Pleasantness				
Unadjusted model (n=102)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.03	0.01	3.49[a]	
Path b (direct effect)	0.17	0.07	2.52[c]	
Indirect effect	-0.01	0.00		-0.01, -0.00
PES Obtained pleasure				
Unadjusted model (n=102)				
Path c' (total effect)	-0.02	0.01	-3.11[b]	
Path a (direct effect)	-0.08	0.02	-3.45[a]	
Path b (direct effect)	0.08	0.02	3.38[c]	
Indirect effect	-0.01	0.00		-0.02, -0.00
	B	SE*	t	95% CI
Negative words endorsed				
Unadjusted model (n=85)				
Path c' (total effect)	-0.03	0.01	-5.12[a]	
Path a (direct effect)	0.29	0.06	4.69[a]	
Path b (direct effect)	-0.00	0.01	-0.25	
Indirect effect	-0.00	0.00		-0.01, 0.00
Negative words recalled (%)				
Unadjusted model (n=82)				
Path c' (total effect)	-0.03	0.01	-4.61[a]	
Path a (direct effect)	0.26	0.89	0.29	
Path b (direct effect)	-0.00	0.00	-0.86	
Indirect effect	-0.00	0.00		-0.01, 0.00
Endorsed negative words recalled (%)				
Unadjusted model (n=73)				
Path c' (total effect)	-0.03	0.01	-4.53[a]	
Path a (direct effect)	3.18	0.60	5.29[a]	
Path b (direct effect)	0.00	0.00	1.31	
Indirect effect	0.01	0.01		-0.00, 0.02

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	B	SE*	t	95% CI
Positive affective (%)				
Unadjusted model (n=85)				
Path c' (total effect)	-0.03	0.01	-5.12[a]	
Path a (direct effect)	-0.14	0.46	-0.30	
Path b (direct effect)	0.00	0.00	0.13	
Indirect effect	0.00	0.00		-0.00, 0.00
Negative affective (%)				
Unadjusted model (n=85)				
Path c' (total effect)	-0.03	0.01	-5.12[a]	
Path a (direct effect)	0.91	0.63	1.44	
Path b (direct effect)	-0.00	0.00	-0.85	
Indirect effect	-0.00			

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Bootstrapped standard error for indirect effect.

CI=95% bias corrected confidence interval.

Appendix 55: Results of regression analyses exploring mediators of the association between brooding and SAQ disease perception

	B	SE*	t	95% CI
ESSI social support				
Unadjusted model (n=97)				
Path c' (total effect)	-2.35	0.65	-3.63[a]	
Path a (direct effect)	-0.41	0.20	-2.06[c]	
Path b (direct effect)	1.44	0.30	4.75[a]	
Indirect effect	-0.59	0.36		-1.54, -0.03
SPSI Positive problem orientation				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64[a]	
Path a (direct effect)	-0.49	0.11	-4.28[a]	
Path b (direct effect)	0.31	0.59	0.53	
Indirect effect	-0.15	0.33		-0.86, 0.46
SPSI Rational problem solving				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64[a]	
Path a (direct effect)	-0.23	0.13	-1.70	
Path b (direct effect)	0.35	0.50	0.70	
Indirect effect	-0.08	0.14		-0.52, 0.10
SPSI Negative problem orientation				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64[a]	
Path a (direct effect)	0.88	0.09	9.52[a]	
Path b (direct effect)	-1.49	0.71	-2.09[c]	
Indirect effect	-1.31	0.72		-3.01, -0.12
SPSI Impulsivity				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64[a]	
Path a (direct effect)	0.28	0.10	2.89[b]	
Path b (direct effect)	-1.00	0.69	-1.46	
Indirect effect	-0.28	0.28		-1.11, 0.07
SPSI Avoidance				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64a	
Path a (direct effect)	0.31	0.11	2.76b	
Path b (direct effect)	-0.17	0.60	-0.28	
Indirect effect	-0.05	0.24		-0.71, 0.31
SPSI Total score				
Unadjusted model (n=96)				
Path c' (total effect)	-2.37	0.65	-3.64[a]	
Path a (direct effect)	-0.44	0.07	-5.91[a]	
Path b (direct effect)	1.27	0.90	1.41	
Indirect effect	-0.56	0.49		-1.61, 0.32

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	B	SE*	t	95% CI
PES Frequency				
Unadjusted model (n=97)				
Path c' (total effect)	-2.35	0.65	3.63[a]	
Path a (direct effect)	-0.03	0.01	-2.83[b]	
Path b (direct effect)	18.32	6.14	2.98[b]	
Indirect effect	-0.54	0.30		-1.34, -0.13
PES Pleasantness				
Unadjusted model (n=97)				
Path c' (total effect)	-2.35	0.65	3.63[a]	
Path a (direct effect)	-0.03	0.01	-3.69[a]	
Path b (direct effect)	18.07	7.43	2.43[c]	
Indirect effect	-0.58	0.34		-1.49, -0.10
PES Obtained pleasure				
Unadjusted model (n=97)				
Path c' (total effect)	-2.35	0.65	3.63[a]	
Path a (direct effect)	-0.09	0.02	-3.55[a]	
Path b (direct effect)	8.80	2.25	3.46[a]	
Indirect effect	-0.77	0.35		-1.71, -0.28
Negative words endorsed				
Unadjusted model (n=82)				
Path c' (total effect)	-3.17	0.78	-4.05[a]	
Path a (direct effect)	0.29	0.07	4.49[a]	
Path b (direct effect)	2.20	1.30	1.70	
Indirect effect	0.66	0.35		0.05, 1.42
Negative words recalled (%)				
Unadjusted model (n=82)				
Path c' (total effect)	-3.20	0.80	-4.02[a]	
Path a (direct effect)	0.16	0.91	0.18	
Path b (direct effect)	-0.16	0.10	-1.59	
Indirect effect	-0.03	0.14		-0.39, 0.20
Endorsed negative words recalled (%)				
Unadjusted model (n=71)				
Path c' (total effect)	-3.09	0.84	-3.70[a]	
Path a (direct effect)	3.11	0.61	5.09[a]	
Path b (direct effect)	0.32	0.16	1.96[p=0.054]	
Indirect effect	0.99	0.60		0.15, 2.58
Positive affective homophones (%)				
Unadjusted model (n=82)				
Path c' (total effect)	-3.17	0.78	-4.05[a]	
Path a (direct effect)	0.04	0.47	0.09	
Path b (direct effect)	-0.03	0.19	-0.15	
Indirect effect	-0.00	0.09		-0.22, 0.18

Table continues on following page…

	B	SE*	t	95% CI
Negative affective homophones (%)				
Unadjusted model (n=82)				
Path c' (total effect)	-3.17	0.78	-4.05[a]	
Path a (direct effect)	0.77	0.66	1.16	
Path b (direct effect)	-0.04	0.13	-0.30	
Indirect effect	-0.03	0.12		-0.44, 0.12

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Bootstrapped standard error for indirect effect.

CI=95% bias corrected confidence interval.

Appendix 56: Results of regression analyses exploring mediators of the association between worry and EQ5D VAS

	B	SE*	t	95% CI
ESSI social support				
Unadjusted model (n=103)				
Path c' (total effect)	-0.48	0.12	-3.88[a]	
Path a (direct effect)	-0.07	0.04	-1.66	
Path b (direct effect)	1.29	0.25	5.08[a]	
Indirect effect	-0.09	0.07		-0.27, 0.01
SPSI Positive problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	-0.12	0.02	-4.88[a]	
Path b (direct effect)	0.70	0.52	1.33	
Indirect effect	-0.08	0.06		-0.21, 0.03
SPSI Rational problem solving				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	-0.06	0.03	-2.13[c]	
Path b (direct effect)	-0.16	0.41	-0.38	
Indirect effect	0.01	0.03		-0.04, 0.07
SPSI Negative problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	0.17	0.02	7.70[a]	
Path b (direct effect)	-1.07	0.56	-1.91[p=0.059]	
Indirect effect	-0.18	0.12		-0.40, 0.08
SPSI Impulsivity				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	0.04	0.02	1.66	
Path b (direct effect)	-0.02	0.58	-0.03	
Indirect effect	-0.00	0.03		-0.06, 0.05
SPSI Avoidance				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	0.05	0.02	2.02[c]	
Path b (direct effect)	-0.32	0.51	-0.63	
Indirect effect	-0.02	0.03		-0.13, 0.03
SPSI Total score				
Unadjusted model (n=102)				
Path c' (total effect)	-0.48	0.12	-3.68[a]	
Path a (direct effect)	-0.09	0.02	-5.24[a]	
Path b (direct effect)	0.70	0.75	0.93	
Indirect effect	-0.06	0.08		-0.21, 0.09

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	B	SE*	t	95% CI
PES Frequency				
Unadjusted model (n=103)				
Path c' (total effect)	-0.48	0.12	-3.98[a]	
Path a (direct effect)	-0.00	0.00	-0.56	
Path b (direct effect)	16.90	5.11	3.31[a]	
Indirect effect	-0.02	0,04		-0.12, 0.04
PES Pleasantness				
Unadjusted model (n=103)				
Path c' (total effect)	-0.48	0.12	-3.98[a]	
Path a (direct effect)	-0.00	0.00	-1.95[p=0.054]	
Path b (direct effect)	19.17	5.99	3.20[b]	
Indirect effect	-0.07	0.05		-0.20,-0.00
PES Obtained pleasure				
Unadjusted model (n=103)				
Path c' (total effect)	-0.48	0.12	-3.98[a]	
Path a (direct effect)	-0.01	0.01	-1.58	
Path b (direct effect)	7.87	2.07	3.80[a]	
Indirect effect	-0.07	0.05		-0.19, -0.00
Negative words endorsed				
Unadjusted model (n=83)				
Path c' (total effect)	-0.34	0.14	-2.45[c]	
Path a (direct effect)	0.05	0.01	3.56[a]	
Path b (direct effect)	-0.77	1.12	-0.69	
Indirect effect	0.04	0.07		-0.22, 0.07
Negative words recalled (%)				
Unadjusted model (n=81)				
Path c' (total effect)	-0.33	0.14	-2.36[c]	
Path a (direct effect)	-0.15	0.20	-0.74	
Path b (direct effect)	-0.15	0.08	-1.88[p=0.064]	
Indirect effect	0.02	0.03		-0.02, 0.11
	B	SE*	t	95% CI
Endorsed negative words recalled (%)				
Unadjusted model (n=72)				
Path c' (total effect)	-0.39	0.14	-2.81[b]	
Path a (direct effect)	0.48	0.15	3.17[b]	
Path b (direct effect)	-0.18	0.11	-1.70	
Indirect effect	-0.09	0.07		-0.28, 0.02
Positive affective homophones (%)				
Unadjusted model (n=83)				
Path c' (total effect)	-0.34	0.14	-2.45[c]	
Path a (direct effect)	-0.00	0.11	-0.05	
Path b (direct effect)	0.22	0.14	1.53	
Indirect effect	0.00	0.03		-0.06, 0.06

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	B	SE*	t	95% CI
Negative affective homophones (%)				
Unadjusted model (n=83)				
Path c' (total effect)	-0.34	0.14	-2.45[c]	
Path a (direct effect)	-0.01	0.15	-0.09	
Path b (direct effect)	-0.06	0.10	-0.61	
Indirect effect	0.00	0.02		-0.03, 0.05

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Bootstrapped standard error for indirect effect.

CI=95% bias corrected confidence interval.

Appendix 57: Results of regression analyses exploring mediators of the association between worry and EQ5D index value

	B	SE*	t	95% CI
ESSI social support				
Unadjusted model (n=103)				
Path c' (total effect)	-0.00	0.00	-3.66[a]	
Path a (direct effect)	-0.07	0.04	-1.66	
Path b (direct effect)	0.01	0.00	5.69[a]	
Indirect effect	-0.00	0.00		-0.00, 0.00
SPSI Positive problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	-0.12	0.02	-4.88[a]	
Path b (direct effect)	0.01	0.01	0.99	
Indirect effect	-0.00	0.00		-0.00, 0.00
SPSI Rational problem solving				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	-0.06	0.03	-2.13[c]	
Path b (direct effect)	-0.00	0.00	-0.49	
Indirect effect	0.00	0.00		-0.00, 0.00
SPSI Negative problem orientation				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	0.17	0.02	7.70[a]	
Path b (direct effect)	-0.01	0.01	-0.95	
Indirect effect	-0.00	0.00		-0.00, 0.00
SPSI Impulsivity				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	0.02	0.04	1.66	
Path b (direct effect)	-0.01	0.01	-1.92[p=0.058]	
Indirect effect	-0.00	0.00		-0.00, 0.00
SPSI Avoidance				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	0.05	0.02	2.02[c]	
Path b (direct effect)	-0.00	0.01	-0.84	
Indirect effect	-0.00	0.00		-0.00, 0.00
SPSI Total score				
Unadjusted model (n=102)				
Path c' (total effect)	-0.00	0.00	-3.64[a]	
Path a (direct effect)	-0.09	0.02	-5.24[a]	
Path b (direct effect)	0.01	0.01	1.11	
Indirect effect	-0.00	0.00		-0.00, 0.00

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	B	SE*	t	95% CI
PES Frequency				
Unadjusted model (n=103)				
Path c' (total effect)	-0.00	0.00	3.36[a]	
Path a (direct effect)	-0.00	0.00	-0.56	
Path b (direct effect)	0.18	0.05	3.31[a]	
Indirect effect	-0.00	0.00		-0.00, 0.00
PES Pleasantness				
Unadjusted model (n=103)				
Path c' (total effect)	-0.00	0.00	3.36[a]	
Path a (direct effect)	-0.00	0.00	-1.95[p=0.054]	
Path b (direct effect)	0.18	0.06	2.86[b]	
Indirect effect	-0.00	0.00		-0.00, 0.00
PES Obtained pleasure				
Unadjusted model (n=103)				
Path c' (total effect)	-0.00	0.00	3.36[a]	
Path a (direct effect)	-0.01	0.01	-1.58	
Path b (direct effect)	0.08	0.02	3.75[a]	
Indirect effect	-0.00	0.00		-0.00, -0.00
Negative words endorsed				
Unadjusted model (n=83)				
Path c' (total effect)	-0.00	0.00	-3.07[b]	
Path a (direct effect)	0.05	0.01	3.44[a]	
Path b (direct effect)	-0.02	0.01	-1.92[p=0.058]	
Indirect effect	-0.00	0.00		-0.00, 0.00
Negative words recalled (%)				
Unadjusted model (n=81)				
Path c' (total effect)	-0.00	0.00	-2.88[b]	
Path a (direct effect)	-0.16	0.20	-0.69	
Path b (direct effect)	-0.00	0.00	-1.13	
Indirect effect	0.00	0.00		-0.00, 0.00
Endorsed negative words recalled (%)				
Unadjusted model (n=72)				
Path c' (total effect)	-0.00	0.00	-2.87[b]	
Path a (direct effect)	0.49	0.15	3.17[b]	
Path b (direct effect)	-0.00	0.00	-0.15	
Indirect effect	-0.00	0.00		-0.00, 0.00
Positive affective homophones (%)				
Unadjusted model (n=83)				
Path c' (total effect)	-0.00	0.00	-3.07[b]	
Path a (direct effect)	-0.03	0.11	-0.26	
Path b (direct effect)	0.00	0.00	0.25	
Indirect effect	0.00	0.00		-0.00, 0.00

Table continues on following page…

	B	SE*	t	95% CI
Negative affective homophones (%)				
Unadjusted model (n=83)				
Path c' (total effect)	-0.00	0.00	-3.07b	
Path a (direct effect)	0.49	0.15	-0.33	
Path b (direct effect)	-0.00	0.00	-1.64	
Indirect effect	0.00	0.00		-0.00, 0.00

[a]p≤0.001 [b]p≤0.01 [c]≤0.05.

*Bootstrapped standard error for indirect effect.

CI=95% bias corrected confidence interval.

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