School of Public Health and Preventive Medicine

Monash University

Improving the health and well-being of people with depression following a cardiac event

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TABLE OF CONTENTS

ABSTRACT

Background: Depression is highly prevalent in cardiac populations. While depression can lead to a range of clinical and psychological impairments, its impact on vocational, mental and physical health functioning remains under-researched in this population. Also unclear is whether targeted treatment can improve these outcomes. Combining depression management with a Coronary Heart Disease (CHD) secondary prevention program using a flexible mode of delivery could facilitate access to treatment, improving these patient outcomes and minimising the burden of this co-morbidity. The purpose of this thesis was to assess *the impact of depression on mental, physical and vocational functioning in those with cardiovascular disease (CVD),* and *determine whether targeted treatment can improve these outcomes.*

Methods: Australian population-based data were used to assess the burden of, and interaction between, major depressive disorder (MDD) and CVD on vocational and health related quality of life (HRQOL) outcomes. Further, a novel systematic review was conducted to determine the predictive role of depression on return to work (RTW) after a cardiac event. In order to determine the effectiveness of depression treatment on mental and physical HRQOL outcomes of cardiac patients, a meta-analysis was conducted. Finally, data from a two-arm, 24-week randomised feasibility trial, with 6-month evaluation outcomes, were used to assess the effectiveness of a telephone-delivered, depression and lifestyle management program ('MoodCare') on mental and physical HRQOL and vocational functioning of depressed Acute Coronary Syndrome patients.

Results: First, Australians with co-morbid MDD and CVD were least likely to be participating in the workforce (adj. Odds Ratio (OR): 0.4, 95% CI:0.3-0.6), and most likely to experience work functioning impairments (adj. OR:8.1, 95% CI:3.8-17.3) and absenteeism (adj. OR:3.0, 95% CI:1.4-6.6) when compared with individuals with one or neither condition. Second, depression predicted RTW after a cardiac event in over half of the 12 studies reviewed. Third, Australians with co-morbid MDD and CVD reported the greatest deficits in Assessment of Quality of Life (AQOL) utility scores (adj. Coefficient:-0.32, 95% CI:-0.40,-0.23) when compared with those with one or neither condition. Fourth, a meta-analysis demonstrated that depression treatment administered after a cardiac event significantly improved both mental and physical health functioning. Effect sizes were greatest for mental (standardised mean difference [SMD]=-0.29, 95% CI:-0.38,-0.20) versus physical HRQOL (SMD:-0.14, 95% CI:-0.24,-0.04). Finally, the MoodCare program yielded significant improvements in physical health functioning after 6-months (SF-12 mean difference=6.7; 95% CI:1.1, 12.3), compared with a control condition. Significant improvements in mental health functioning were also observed for those with a history of MDD. No intervention effects were observed for vocational outcomes.

Conclusions: These findings confirm co-morbid depression and CVD as a significant public health issue. The benefits of treating depression in this population can go beyond psychological outcomes to improve HRQOL. These findings provide support for the use of a combined depression management and lifestyle program which is delivered over the telephone to improve key functioning outcomes of cardiac patients. Further

research is required to determine the most effective way to impact vocational outcomes. Several clinically- and policy-relevant recommendations are discussed in light of these findings.

DECLARATION

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17 / Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published in peer reviewed journals and three unpublished publications. The core theme of the thesis is: ***Improving the health and well-being of people with depression following a cardiac event.*** The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Public Health and Preventive Medicine under the supervision of ***Professor Brian Oldenburg***.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of [Chapters 2,3,4,6,7] my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
2	Co-morbid depression is associated with poor work outcomes in persons with cardiovascular disease (CVD): A large, nationally representative survey in the Australian population.	Published	Conceptualisation of manuscript, data analysis and interpretation, drafting of original and subsequent versions of manuscript
3	Depression as a predictor of work resumption following myocardial infarction (MI): a review of the research evidence	Published	Conceptualisation of the paper, synthesis, analysis and interpretation of data, and drafting of original and subsequent versions of manuscript
4	The Health Related Quality of Life burden of co-morbid Cardiovascular Disease and major depressive disorder in Australia. Findings from a population-based, cross-sectional study.	Accepted, 20 January 2012	Data analysis and interpretation, and drafting of original and subsequent versions of manuscript

6	The impact of depression treatment of mental and physical health related quality of life: a meta-analysis	Published	Conceptualisation of the paper, synthesis, data analysis and interpretation, and drafting of original and subsequent versions of manuscript
7	A randomised, feasibility trial of a tele-health intervention for Acute Coronary Syndrome patients with depression ('MoodCare'): study protocol	Published	Contribution to original research proposal and amendments to protocol, drafting of original and subsequent versions of manuscript

[* For example, 'published' / 'in press' / 'accepted' / 'returned for revision']

Signed: **……**

Date: 27.1.2012

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ABBREVIATIONS

ACS = Acute Coronary Syndrome; **ANS** = Autonomic Nervous System; **APACHE III** = Acute Physiology And Chronic Health Evaluation III; **ARIC** = Atherosclerosis Risk in Communities; **BDI** = Beck Depression Inventory; **BDI-FS** = Beck Depression Inventory Fast Scale; **BMI** = Body Mass Index; **BP** = Bodily Pain; **β-TG** = beta-thromboglobulin; **CABG** = Coronary Artery Bypass Graft; **CAD** = Coronary Artery Disease; **CATI** = Computer Assisted Telephone Interview; **CBT** = Cognitive Behavioral Therapy; **CEA** = Cost-effectiveness analysis; **CES-D** = Center for Epidemiologic Studies Depression Scale (CES-D/AC German version); **CDS** = Cardiac Depression Scale; **CGI** = Clinical Global Impression Scale; **CHD** = Coronary Heart Disease; **CHF** = Chronic Heart Failure; **CI** = Confidence Intervals; **CIDI** = Composite International Diagnostic Interview; **CONSORT** = Consolidated Standards of Reporting Trials; **COPD** = Chronic Obstructive Pulmonary Disease; **CRP** = C-Reactive protein; **CVD** = Cardiovascular disease; **DM** = Diabetes Mellitus; **DSM-IV** = Diagnostic Statistics Manual IV; **ENRICHD** = Enhancing Recovery in Coronary Heart Disease Patients; **GAD** = Generalised Anxiety Disorder; **GH** = General health; **GP** = General Practitioner; **HADS** = Hospital Anxiety and Depression Scale; **HbA1c** = Haemoglobin A1C; **HCU** = Health Care Utilisation; **HF** = Health related functioning; **HPA** = Hypothalamic-pituitary-adrenocortical; **HR** = Hazard Ratio; **HRQOL** = Health Related Quality of Life; **HRV** = Heart rate variability; **IFG** = Impaired Fasting Glucose; **IGT** = Impaired Glucose Tolerance; **IL-6** = Interleukin-6; **MDD** = Major Depressive Disorder; **MI** = Myocardial Infarction; **MIND-IT** = Myocardial Infarction and Depression Intervention Trial; **MMPI** = Minnesota Multiphasic Personality Inventory; **NDM** = Newly Diagnosed type 2 diabetes mellitus; **NGT** = normal glucose tolerance; **OR** = Odds ratio; **PBS** = Pharmaceutical Benefits Scheme; **PCI** = Percutaneous Coronary

Intervention; **PF** = Physical functioning; **PF4** = Platelet factor 4; **PHQ 2/9** = Patient Health Questionnaire 2/9; **PRIMSA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PTCA** = Percutaneous Transluminal Coronary Angioplasty; **PUFA** = Polyunsaturated Fatty Acids; **QALY** = Quality Adjusted Life Years; **QOL** = Quality of Life; **RCT** = Randomised Controlled Trial; **REVMAN** = Review Manager 5; **RTW** = Return to Work; **SADHART** = Sertraline Anti Depressant Heart Attack Trial; **SES** = Social Economic Status; **SF12/36** = Short Form 12/36; **SMD** = Standard Mean Differences; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **TBXB2** = 11-dehydro-thromboxane B2; **T2DM** = Type 2 Diabetes Mellitus; **UC** = Usual Care; **VT** = vitality; **WLC** = Wait list control

ORIGINAL ARTICLES

O'Neil A, Williams ED, Stevenson CE, Oldenburg B, Sanderson K (2012). Co-morbid depression is associated with poor work outcomes in persons with cardiovascular disease (CVD): A large, nationally representative survey in the Australian population. *BMC Public Health.* 12:47.

O'Neil A, Sanderson K, Oldenburg B. (2010). Depression as a predictor of work resumption following myocardial infarction (MI): a review of recent research evidence, *BMC Quality of Life and Health Outcomes.* 8:95. doi:10.1186/1477-7525-8-95

O'Neil A, Stevenson CE, Williams ED, Mortimer D, Oldenburg B, Sanderson K. The Health Related Quality of Life burden of co-morbid Cardiovascular Disease and major depressive disorder in Australia. Findings from a population-based, cross-sectional study. *Quality of Life Research*. Accepted, 20 January 2012.

O'Neil A, Sanderson K, Oldenburg B, Taylor CB. (2011). The impact of depression treatment on mental and physical health-related quality of life of cardiac patients: A meta-analysis. *Journal of Cardiopulmonary Rehabilitation & Prevention.* 31, 3: 146–156.

O'Neil A, Hawkes AL, Chan B, Sanderson K, Forbes A, Hollingsworth B, Atherton J, Hare DL, Jelinek M, Eadie K, Taylor CB, Oldenburg B (2011). A randomised, feasibility trial of a tele-health intervention for Acute Coronary Syndrome patients with depression ('MoodCare'): study protocol. *BMC Cardiovascular Disorders*. 2011, 11:8.

OTHER RELATED ORIGINAL ARTICLES

O'Neil A, Williams ED, Stevenson CE, Oldenburg B, Berk M, Sanderson K (2011). Co-morbid cardiovascular disease (CVD) and depression: sequence of disease onset is linked to mental but not physical self-rated health. Results from a cross-sectional, population-based study. *Social Psychiatry and Psychiatric Epidemiology.* Published ahead of print, DOI: 10.1007/s00127-011-0421-5. (APPENDIX A1).

O'Neil A, & Sanderson K (2011). The use of Cognitive Behavioral Therapy (CBT) for secondary prevention in patients with Coronary Heart Disease (CHD)[letter]. *Archives of Internal Medicine.* 171, 16. (APPENDIX A2).

O'Neil A, & Sanderson K (2011). Improving the identification and treatment of depression in women after acute myocardial infarction [letter]. *Circulation: Cardiovascular Quality and Outcomes*. Published online

http://circoutcomes.ahajournals.org/cgi/eletters/4/3/283#288. July 14, 2011. (APPENDIX A3).

STRUCTURE OF THESIS

This thesis combines five peer-reviewed publications (Chapters 2, 3, 4, 6, 7) with four traditional thesis chapters (Chapters 1, 5, 8, 9). Before the burden of cardiovascular disease and depression is established and a treatment program evaluated, the various mechanisms thought to underpin this relationship need to be understood. Therefore, Chapter 1 comprises a literature review of the complex, aetiological relationships between Coronary Heart Disease and depression, with a focus on the way in which these conditions impact Health Related Quality of Life and vocational functioning. After identifying the research gaps, the thesis aims are described. Chapter 2 presents key data regarding the current burden of co-morbid cardiovascular disease and major depressive disorder on workforce participation, productivity and absenteeism in Australia. Chapter 3 establishes whether depression acts as a prognostic indicator of return to work after a cardiac event. Chapter 4 assesses the burden of, and interaction between, co-morbid cardiovascular disease and depression on Health Related Quality of Life in Australia. In doing so, the synergistic effect of the two conditions is established. This chapter also assesses whether the dose-response relationship previously observed between Health Related Quality of Life and depression differs with the presence of cardiovascular disease. Chapter 5 introduces and reviews the different types of depression management programs which have been evaluated for cardiac patients experiencing depression. Chapter 6 presents a meta-analytic review which assesses and measures the impact of depression treatment on Health Related Quality of Life outcomes of cardiac patients. Chapter 7 presents the methodology of a feasibility trial evaluating a telephone-delivered, depression management and Coronary Heart Disease secondary prevention program which aims to enhance key mood and functional

outcomes of cardiac patients with depression. Chapter 8 presents preliminary findings from this study related to mental, physical and vocational functioning outcomes. The thesis culminates in a discussion chapter in which key findings are used to present clinically- and policy-salient recommendations (Chapter 9).

LIST OF FIGURES

LIST OF TABLES

Chapter 1: INTRODUCTION

Chapter Overview

Various trials have been conducted evaluating depression management programs in cardiac populations. However, to date, the most effective way to manage this co-morbidity in the real world setting remains unclear. To better understand the past successes and failures of previous trials and subsequently develop suitable interventions that target mental, physical and related components of functioning, we first need to understand the mechanisms underpinning the relationship between the two conditions. In terms of discussing the aetiological patterns of cardiovascular disease and depression, there is evidence that major depressive disorder often occurs prior to the onset of cardiovascular disease (APPENDIX A1). While this distinction is of some importance and will be noted, reviewing every possible permutation of the association between depression and cardiovascular disease is beyond the scope of this literature review. Therefore, this chapter, and ultimately this thesis, will focus predominantly on individuals for whom depression manifests following a cardiac event. In addition to exploring the aetiological relationship between the two conditions, this chapter will cover: the relationship between heart disease, depression and Health Related Quality of Life; the relationship between heart disease, depression and vocational functioning; and the impact of depression treatment on these outcomes. Finally, having identified the research gaps in the literature, the study rationale, research questions and hypotheses will be outlined.

1.1. Relationship between heart disease and depression

The relationship between coronary heart disease (CHD) and major depressive disorder (MDD) has been investigated extensively over recent decades, as the prevalence of both conditions has risen around the world (**1**). Each condition remains a major contributor to the global burden of disease; CHD is the leading cause of death (**2**), while MDD (defined as the presence of severely depressed mood persisting for at least two weeks), is the top-ranking cause of disability (**3**). Similarly, in Australia, heart disease is the leading cause of disease burden and death, and depression is the top-ranking cause of non-fatal burden (**4**). Increasing rates of obesity and metabolic syndrome, an ageing population, sedentary lifestyles and chronic life stressors (among other factors) have all contributed to this rising trend. While depression and heart disease commonly occur in the general population as individual conditions, the two often coexist. For example, depression is highly prevalent among individuals with CHD. This condition has been estimated to affect one in five hospitalised myocardial infarct (MI) patients (**5**). This co-morbidity is particularly problematic because CHD patients with depressive symptoms are more likely to experience poorer behavioural, psychological and clinical outcomes, including increased likelihood of morbidity and mortality, compared with those who are not depressed. In MI patients, a landmark study by Frasure-Smith and colleagues (1995) revealed that the presence of depression was significantly related to 18-month cardiac mortality (**6**). This finding has since been corroborated; others have demonstrated that even mild to moderate depressive symptoms in post-MI populations are associated with decreased survival (**7**). While it may seem intuitive that individuals who have experienced a life threatening event would report negative emotions such as low mood in the ensuing recovery period, the relationship between cardiovascular disease (CVD) and depression is much more complex; the conditions may act

bi-directionally rather than causally. Gaining a better understanding of the nature of these two conditions will be of importance; both in understanding the role of psychosocial factors in the relationship between CVD and depression and for the development of appropriate treatment programs if they are to effectively impact on mental, physical and related functioning outcomes.

1.1.1 Depression as a risk factor for CVD

While depression is a prognostic indicator for a range of outcomes in patients with existing CHD including increased risk of heart failure (**8**) suicide (**9**), reduced health service utilisation (**10**) and medication adherence, depression is also considered an independent risk factor for the onset of heart disease (**11**). The presence of depressive symptoms before the onset of a cardiac condition appears to increase the risk of cardiac fatality (**12**). In fact, those with a history of depression are four times more likely to have a MI than those without (**13**). Indeed, there is evidence that the presence of depressed mood in the preceding hour may trigger potentially life-threatening cardiac events (**14**). For example, by comparing the depressed mood of 295 Acute Coronary Syndrome (ACS) patients two hours prior to ACS symptom onset with the same period 24 hours earlier and with usual levels of depressed mood, Steptoe et al (2006) found that the odds of ACS were 2.5 following depressed mood, and the relative risk of ACS onset following depressed mood was 4.3 compared with usual levels of mood (**14**). A meta-analysis has further demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without depression (**11**). The bi-directional nature of this co-morbidity would suggest that depression is not purely reactionary to a life threatening cardiac event and the association is, in fact, much more complex.

While the pathways that play a role in the initiation of depression and/or in the pathogenesis of heart disease remain largely undetermined, a number of causal pathways have been proposed. A comprehension of this network is important if we are to understand the overall impact of co-morbid heart disease and depression on key aspects of functioning. In order to provide a more comprehensive review of their association, the aetiological relationships between the two conditions including hypothalamic-pituitary-adrenocortical (HPA) axis, cortisol elevation, heart rate variability, pro-inflammatory cytokines, platelet activation, genetics, risk factor clustering, medication non-compliance, anger and anxiety, demographics and psychosocial factors will now be explored in more detail and are illustrated in Figure 1.

1.2. Aetiological relationships between depression & heart disease

1.2.1 Hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation

There is evidence to suggest that depression elicits the same biological responses that contribute to ACS (**14**). Firstly, it should be noted that depression has traditionally been associated with hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis, as an extension of the 'fight or flight response.' This term was coined to explain the response of a person to threat, characterised by a discharge of the sympathetic nervous system enabling a person to either fight or flee danger (**15**). The result is an overstimulation of the sympathetic nervous system, which increases circulating levels of adrenaline, noradrenaline and serum cortisol. This response has the potential to contribute to increased cardiovascular risk through a variety of related risk factors, including those consistent with the metabolic syndrome (high lipid levels, obesity, elevated blood pressure, insulin resistance). It is possible, however, that these physiologic responses may vary for different severities of depression. Abnormal HPA axis function resulting in hypercortisolaemia (high amounts of circulating cortisol) has been associated with severe depression. Evidence suggests that those with MDD

exhibit blunted reactivity (**16**), whereas this process may differ for those with milder cases of depression. It is likely that patients with less severe depression show a reduced cortisol response to stress and have low or normal ambulatory measures of cortisol (**17**).

Despite these advances in knowledge, the extent to which HPA activity mediates the relationship between CHD and depression (of varying degrees) remains unclear. Disentangling this relationship by observing the effects of depression treatment on HPA activity has failed to provide clarity; this may be because altering HPA activity via psychological interventions is considered particularly difficult to achieve. For example, Taylor et al (2009) (**18**) randomised 48 depressed participants with elevated cardiovascular risk factors to a cognitive behavioural therapy (CBT) intervention or a wait list control (WLC) condition to determine whether achieving improvements in mood would ameliorate autonomic dysregulation, HPA dysfunction, typical risk factors and C-reactive protein (CRP). Traditional risk factors (such as lipids and blood pressure), CRP and psychophysiological stress tests were assessed pre- and post-treatment after six months. Results indicated that, while the CBT subjects were significantly less depressed than those assigned to the WLC (post-intervention Hamilton Rating Scale for Depression (HRSD) mean scores were 5.5 versus 15.5, respectively), no significant differences in any of the traditional risk factors or psychophysiological measures (with the exception of triglyceride levels and heart rate) were observed. Further, 20 non-depressed, age and risk-matched controls exhibited no change in the variables measured during the same time (**18**). Despite limited generalisability due to the small sample, the authors concluded that alterations in mood have limited impact on HPA activity, traditional or atypical risk factors, cortisol or cardiophysiology; a finding which contradicts the conventional wisdom that depression is linked to increased cortisol levels and HPA dysfunction (**19**). Interestingly, this study did, however, highlight the role of another key

mechanism thought to underpin the relationship between heart disease and depression, Heart Rate Variability (HRV).

1.2.2 Decreased heart rate variability

HRV has been defined as the varying time interval between heart beats. Decreased HRV has previously been associated with a heightened risk of mortality (**20**). More specifically, along with other alterations of the Autonomic Nervous System (ANS), it has long been considered a fundamental mechanism linking heart disease and major depression. Changes in the ANS, such as heart rate variability, are commonly linked with cardiac function (**21**). It is also well established that depression can impact the autonomic control of the cardiovascular system, thereby impeding cardiac functioning. Typically, depressed patients have been found to experience elevated resting heart rate, even when adjusting for confounding factors such as medication usage. In a review, Carney and Freedland (2009) (**22**) identified higher resting heart rate as a common feature of both CHD patients with depression, and medically well patients with depression. The mechanism linking the two conditions has been identified as excessive sympathetic activity (or, alternatively, reduced parasympathetic nervous system activity) found in depressed patients, which can promote myocardial ischaemia or other related cardiac conditions. However, research in support of this remains inconsistent. Findings from the Heart and Soul study, comprising a sample of 873 outpatients with stable CHD found little evidence of an association between depression and HRV, leading the authors to question HRV as the fundamental mechanism linking depression and CVD (**23**). Several limitations have been associated with this study, however, including its cross-sectional design. Others have examined the effects of depression treatment on cardiovascular outcomes as another means by which to explore the role of HRV. Studies evaluating the use of psychological interventions in patients with high CVD risk (**18, 24**) have demonstrated some

benefits; depression treatment can effectively reduce HRV in this population. However, meta-analyses and other studies have revealed that, in spite of the benefits, the effects of psychological therapy do not translate to reduced cardiovascular mortality or morbidity (**25**).

1.2.3 Elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis

Another mechanism thought to be associated with CHD and depression is inflammation. Inflammatory changes are common characteristics of both heart disease and depression. The underlying inflammatory component of ACS is atherosclerosis- the build up of plaque in the arteries. This inflammatory component is also a physiological characteristic associated with depression. For example, patients with depression have been found to exhibit elevated inflammatory markers, including interleukin-6 (IL-6) and CRP (a non-specific measure of inflammation). Moreover, IL-6 and CRP are significant predictors of various outcomes in patients with ACS (**26**) and other inflammatory conditions (e.g. stroke (**27**)). Circulating IL-6 induces the release of CRP, as well as other inflammatory markers, making IL-6 a strong independent marker of increased mortality in those with unstable Coronary Artery Disease (CAD)(**28**). Interestingly, the presence of high levels of CRP has also been found in non-depressed patients at risk of CVD, as well as in depressed samples without known CVD. A meta-analysis has demonstrated that both CRP and IL-6 are positively associated with depression (CRP: Standardised mean difference (SMD)=0.15, 95% CI =0.10,0.21; IL-6: SMD=0.25, 95% CI=0.18,0.31, indicating a high level of significance). Sub-group analyses revealed similar results both in clinical and community samples (**29**).

In cardiac patients with co-morbid depression, the association with IL-6 and CRP is complex. Patients with severe post-ACS depressive symptoms exhibit higher levels of CRP and IL-6 than those with mild symptoms. In fact, it has been estimated that patients with the most severe depression record CRP levels >50% higher than patients in the middle and lowest range (**30**).

It has been argued that such trends are responsible for the effect of atherosclerosis on ACS. Reasons for these elevated levels of cytokines may be due to mildly depressed patients demonstrating flatter cortisol levels (**17**) (as discussed previously). As cortisol is responsible for suppressing pro-inflammatory cytokines, the hypo-pituitary response to stress exhibited by these patients is subsequently inadequate, making individuals with depression more susceptible to, or less equipped to respond to stress. A review by Von Kanel et al (2001) highlighted the common pathophysiologic characteristics of depression and stress reactivity (**31**). In addition to elevated plasma levels, other common features include increased blood pressure, heart rate, arousal mobilisation of energy stores and elevated risk of ventricular fibrillation. Recently, evidence has emerged suggesting that increased inflammation explains only a small proportion of the relationship between heart disease and depression (**32**). This is supported by earlier data from the Heart and Soul study which suggest that inflammation is unlikely to explain the adverse CVD outcomes linked to depression in those with heart disease (**33**). These findings have led researchers to focus on other possible mechanisms linking depression and heart disease such as platelet activation and hypercoagulability.

1.2.4 Platelet activation and hypercoagulability

Increased platelet activation is another common physiological feature of both ACS and depression. There is evidence that depression is associated with increased platelet activation (**34**), leading to thrombus formation, vascular damage and an increased risk of a cardiac event. Enhanced platelet reactions are often the result of psychologic stress, and a common characteristic of MI. In a 2001 review comprising 68 articles, Von Kanel (2001) found that pro-coagulant responses to stressors induced blood clotting (hypercoagulability) in patients with atherosclerosis but not in healthy subjects (**31**). More specifically, the authors found that chronic psychosocial stressors, namely job strain and those associated with low

socioeconomic status, were found to be related to a hypercoagulable state, which may be responsible for, or contribute to, a depressed state and/or atherosclerosis (**31**) (the role of demographic and psychosocial factors in the relationship between heart disease and depression will be discussed in further detail in Section 1.3.4).

However, evidence from large scale studies (e.g. the Heart and Soul study (**35**)) has challenged the idea that increased platelet activation, a previously putative mechanism, is the underlying mechanism linking depression to CVD. Using a cross-sectional design, Gehi and colleagues (2010) assessed platelet activation in 104 patients with stable CHD (n=58 with a current episode of major depression and n=46 without past or current major depression). Platelet activation was measured by plasma concentrations of platelet factor 4 (PF4) and beta-thromboglobulin (β-TG), and by urinary concentrations of 11-dehydro-thromboxane B2 (TBXB2). The authors found no differences in mean levels of PF4, B-TG or TBXB2 in patients with and without major depression, even after adjusting for covariates such as medication and aspirin usage, age, and smoking. The authors concluded that the association between depression and cardiovascular disease is not attributable to platelet activation among patients with stable CHD (**35**).

1.2.5 Genetic factors and predispositions

It is known that genetic predisposition plays a role in the initiation of depression and in the pathogenesis of heart disease, either independently or via interactions with extraneous factors. First, there is strong evidence that depression has a hereditary component. For example, in the largest sample to date, a Swedish national twin study found that lifetime MDD was heritable (**36**); first-degree relatives of individuals with MDD were two to three times more likely to develop depression when compared with the first-degree relatives of controls. The mechanism underlying a potential 'depression gene' is thought to be associated with

genetic variation related to endothelial dysfunction. Endothelial dysfunction is predictive of depressive symptoms and has been proposed as another mechanism contributing to depression among cardiac patients (**37**). Animal models have demonstrated that deficits in endothelial function are associated with recent stress exposure, which persist even after stressful stimuli have been eliminated (**38**). The role of endothelial dysfunction in the relationship between CVD and depression has been associated with cytokine release. This is either as a result of, or a contributor to, various disease processes, such as those which occur in hypertension, hypercholesterolaemia or diabetes as well from environmental factors, such as smoking. These findings highlight the multi-factorial nature of the association between depression and CVD.

Indeed, it is recognised that, due to the complexity of the two conditions, it is unlikely that any single physiological mechanism can explain their relationship. Rather, it is likely that these mechanisms are inter-related (**39**).

1.2.6 Inter-relationships among psychophysiological factors

De Jonge et al (2010) argues that the aetiological relationship between depression and CVD is "best described as a complex system, consisting of many distinct but inter-related and inter-dependent components linked through multiple interconnections and feedback loops" (**40**). As examples, serotonin has been identified as a catalyst in platelet activation that leads to atherosclerosis, HPA activity which, due to elevated cortisol levels, can result in immune system changes, and the inflammatory nature of atherosclerosis can, itself, promote decreases in central serotonin. Given that the most common anti-depressants target serotonin, Chapter 5 will explore the way in which treatment that targets serotonin impacts upon the outcomes of cardiac patients.

There is evidence that key lifestyle factors, such as diet, sedentary lifestyles and alcohol, can precipitate depression, heart disease or both. The influence of such biobehavioural factors will now be explored.

1.3. Mediating factors influencing the relationship between depression and heart disease

1.3.1 Risk factor clustering

The presence of depression and its symptoms, including anhedonia (characterised by apathy and lack of pleasure), helplessness and hopelessness, can inhibit the primary prevention behaviours associated with CVD. That is, individuals with depression may be more likely to report risk factor behaviours that contribute to CHD onset, such as smoking and high alcohol consumption. Hughes and others (1986) found that the prevalence of smoking was higher in those with mental disorders than in the general population (**41**), a finding which has also been observed for alcohol use (**42**). While there is good evidence that alcohol use can precede the onset of MDD (**43**), individuals with existing depression may use alcohol as a form of self medication. In fact, depression has been found to act as a mediator between stress and excess alcohol (**44**). Interestingly, alcohol consumption has been closely associated with other risk factors for heart disease such as smoking and dietary habits, particularly in depressed populations. While there is evidence of risk factor clustering in the general population, clustering is more common among people with depression (**45**). Other studies have demonstrated that depression affects other key primary and secondary prevention behaviours such as physical activity. Not only are those experiencing depression as a sole condition more likely to be sedentary than those without, but there is evidence that for cardiac patients, depression impedes exercise regimes after a coronary event (**46**). A recent review evaluating 11 studies (representing 20,000 cardiac patients) found post-MI depressive

symptoms to be a significant risk factor for a sedentary lifestyle or poor compliance to a physical activity program (**46**).

More recently, diet has been identified as a key factor that may mediate the relationship between depression and CVD. Not only are low levels of Omega-3 fatty acids- derived from foods such as fish- associated with increased risk of CHD and high prevalence mental disorders like anxiety, but case-control studies have demonstrated that low Omega-3 levels are related to depression levels after a recent cardiac event (**47**). Conversely, CAD patients experiencing depression have been shown to report higher levels of Polyunsaturated Fatty acids (PUFAs), compared with non depressed patients. While the protective effects of Omega-3 result from its anti-inflammatory properties (**40**), evidence of the full effects of PUFAs remains conflicted. Large scale, international studies have also found no association between depression and Omega-3 deficiencies (**48**). Despite this, there remains some long standing evidence of the benefits of Omega-3 fatty acids on CVD-related risk factors including reducing blood pressure (**49**) and triglycerides.

Additionally, the association between depressive symptoms and high risk behaviour related to alcohol, smoking, physical activity and diet may precipitate other medical conditions, such as diabetes mellitus (**50**), overweight and obesity, hypertension, and hypercholesterolaemia, all associated with the onset of heart disease. Indeed, the inextricable link between depression, heart disease and lifestyle factors suggests that a multi-faceted approach may be required when developing appropriate depression management or secondary prevention interventions in this patient population (to be discussed in further detail in later chapters).

Evidently, lifestyle as a mediating factor in the relationship between depression and heart disease affects both primary CVD prevention activities, as well as secondary prevention behaviours. Important components of the latter, adherence to cardiac rehabilitation programs

and medication regimes can often be compromised by the presence of depression after a heart event, increasing the risk of recurrent CVD events.

1.3.2 Noncompliance with cardiac rehabilitation and medical regimens

The World Health Organisation (WHO) considers cardiac rehabilitation "an integral component in the overall management of patients with CVD" (**51**). While it is recommended that patients who are hospitalised with heart disease as an index admission are referred to early outpatient rehabilitation (**52**), evidence suggests that patients experiencing depression post-discharge are less likely to complete a cardiac rehabilitation program compared with their non depressed counterparts (**53**), increasing the likelihood of a recurrent CVD event. For these patients, increased attrition levels may be due to the cognitive and/or somatic symptoms of depression including hopelessness, reduced motivation, social exclusion, fatigue and helplessness. In any case, noncompliance to rehabilitation and medical regimes in this population has been identified as "a formidable problem impacting on the failure of risk-reduction therapies, on patient morbidity, and on health care costs"(**54**). The presence of depression, has been specifically linked with the under-utilisation of appropriate health services (**10**) and poorer self-care, specifically in relation to medication adherence. Kronish and others (2009) found that patients with persistent post-ACS depression differ significantly in their level of adherence to medications prescribed for their cardiac condition, compared with those who did not exhibit depression in hospital (**55**). Interestingly, the presence of other negative emotions, such as anxiety, in cardiac patients has recently been shown to be associated with better medication adherence (**56**). The relationship between depression, anxiety and CVD will now be discussed.

1.3.3 Anxiety and anger

Similarly to depression, there appears to be a bi-directional, rather than purely causal, relationship between anxiety and CVD. Anxiety is both highly prevalent in patients with existing CHD (**57**) and has been shown to independently predict subsequent CVD events over decades (**58**). Anxiety is thought to produce an activation of inflammation, coagulation and fibrinolysis (**59**), common characteristics of CVD. Given that anxiety and depression often occur co-morbidly, it is possible that anxiety may mediate the relationship between depression and CVD, or conversely that depression may mediate the relationship between anxiety and CVD. Frasure-Smith and Lesperance have demonstrated substantial overlap in MDD and generalised anxiety disorder (GAD) in patients with stable CAD, concluding that both are associated with prospective coronary events (**60**). These findings have led some to argue that clinically meaningful distinctions of distress in CAD patients need to be considered (**61**), if this relationship is to be truly understood, and should be considered in the development of treatment programs for this population.

Further, the role of personality traits, hostility and anger, have been identified as having the potential to alter one's susceptibility to CHD onset. Chida and Steptoe (2009) conducted one of the first quantitative systematic reviews in this area, and found that anger and hostility were significantly correlated with poorer prognosis in CHD patients (**62**). If appropriate treatment programs are to be provided for patients after a heart event, the role of negative mood and traits, as well as other psychosocial factors, may need to be taken into consideration.

1.3.4 Demographic and psychosocial factors

Depression has been significantly associated with social isolation (**63**), chronic life stressors (**64**) and maladaptive coping style in both cardiac (**65**) and other populations (**66**). It is well established that these factors can be mediated by demographic variables such as gender, social economic status (SES) and income, and have also been linked to cardiovascular risk. For example, a gradient exists between SES and depression risk among individuals with chronic disease (e.g. diabetes (**67**)). This trend has also been observed for those with established CHD; those reporting CHD and low SES are more likely to report depression (**68**). Those belonging to a lower SES may have accentuated cardiac risk factors simply because of their location within the SES hierarchy. Indeed, those belonging to a lower SES bracket are more likely to suffer adverse cardiovascular events than those reporting high SES (**69**). Additionally, low SES, which can translate to poorer standards of living (for example, less exposure to important resources, fresh and healthy foods, safe exercising environments) can act synergistically with other cardiac risk factors such as overweight and obesity, hyperlipidaemia or hypertension, to accelerate the course of atherosclerosis (**69**). In a similar manner, psychosocial variables like social isolation and low levels of emotional support have been related to both depression and CHD. Social isolation may adversely affect the origin, course, and outcome of heart disease (**70**). Evidence indicates that low social support confers a risk of 1.5 to 2.0 in both healthy individuals and in CHD populations (**71**). This relationship is thought to share the same risk factor pathways as the relationship between SES and onset of CHD. Moreover, recent evidence indicates that the impact of social support on mortality is comparable with other well established risk factors for mortality like smoking (**72**).

The way in which one perceives their own physical and mental health functioning- their health related quality of life (HRQOL)- is another psychosocial variable that can provide

important insights about the relationship between depression and heart disease. Depression is closely linked to HRQOL. In fact, depression has been identified as the single most important, independent predictor of HRQOL (**73**) in cardiac populations. The concept of HRQOL has been developed and defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient' (**74**). A concept traditionally encompassing physical functioning, mental health, social relationships, and happiness or global satisfaction, HRQOL has become of increasing importance in the context of disease populations for several reasons. It is considered both a determinant in the course and onset of some diseases (e.g. diabetes (**75**)) and is considered by some, a significant endpoint for evaluating the impact of a disease or treatment.

The concept of measuring HRQOL, however, is contentious. It has been argued that a quantitative instrument to measure, by its very nature, a qualitative concept is an insufficient means by which to gauge an individual's HRQOL status. In addition to the issue of subjectivity versus objectivity, there is contention surrounding HRQOL as a function-based or satisfaction-based measure. For example, HRQOL measures may be used to assess patients' satisfaction with care or the effects of therapy, or alternatively to assess one's functional status as a result of illness. In spite of these assertions, the importance of investigating the role of HRQOL in disease populations is becoming increasingly apparent. In fact, HRQOL can be predictive of clinical outcomes in patients with chronic disease. Functional components have been used to predict survival and rehospitalisation in chronic disease populations (**76**). Moreover, HRQOL is of increasing importance in the context of health economics as its derivative can often be used to capture Quality Adjusted Life Years (QALYs), a measure of disease burden encapsulating both quality and quantity of life lived.

The relationship between HRQOL, depression and CHD is a complex one. For example, while it is clear that some depressive symptoms such as hopelessness, sadness and anhedonia impact poorly on self-rated health status and thereby HRQOL status (**77**), components of HRQOL, like impaired functioning, can also intensify depression. An example of this is that loss of mental and physical functionality is a strong mediator in the association between depression and chronic disease. Those with depression possess a 34% greater attributable risk of functional limitation (95% CI: 24.8-42.7) (**78**). The effect of depression is such that symptoms impact cardiac functioning; depressive symptoms can diminish the functional benefits of interventions aimed at improving cardiac functioning (e.g. Coronary Artery Bypass Grafting (CABG) surgery (**79**)).

Despite such evidence, surprisingly, the role of HRQOL in populations with co-morbid depression and heart disease remains under-researched (**80**). Traditionally, research exploring the impact of depression or depression treatment in cardiac populations has focused predominantly on clinical outcomes. The emerging rationale for an increased focus on HRQOL as both a risk factor and an outcome in this area of research, is two-fold. First, investigating the role of HRQOL in cardiac populations has the potential to shed light on the relationship between depression and CVD, where there remains a deficit in our knowledge. Just as treating depression in CVD populations has not been shown to improve CVD-related outcomes or survival (**81**), neither can it be assumed that treating depression will alter HRQOL status. Recently, it has been argued: "As investigators move forward in attempting to unravel the intriguing relation between depression and coronary disease, it will be important to include quality of life indicators as outcomes of interest" (**80**). Second, if we are to use our existing understanding of this relationship, with the view to improve patient outcomes, a distinction needs to be made between enhancing quality and quantity of life, which begins

with the inclusion of HRQOL indicators. For example, Rumsfeld and Ho (2009) argue for the prioritisation of HRQOL in cardiac research, because for coronary patients, HRQOL outcomes are as important as any potential survival outcomes. Of survival gain, they argue that the benefits are "...limited to specific patient subsets and many patients express a desire for quality of life equal to or greater than their desire for quantity of life" (**82**). The complex relationship between depression, CHD and HRQOL will now be explored in more detail.

1.4. The relationship between depression and mental and physical functioning (HRQOL) in cardiac populations

Traditionally, assessing clinical endpoints such as survival and recurrent CVD events has been considered paramount for monitoring both the recovery of cardiac patients and the effectiveness of rehabilitation interventions, including health coaching and depression management programs. Increasingly, HRQOL outcomes have become of interest in cardiac populations, particularly over the past five years, as evidence has emerged to link clinical and HRQOL outcomes, and to expose the detrimental impact of depression on HRQOL (both in cardiac and other medically ill populations (**83**)). For example, physical parameters such as body mass index (BMI) and obesity, as well as psychological conditions such as depression and anxiety directly relate to HRQOL status in medically ill patients (**84**). In fact, HRQOL has been found to be more strongly and directly related to symptoms of depression than physical components like BMI (**85**). Similarly in cardiac populations, while clinical parameters like heart failure severity have been found to impair the physical domain of HRQOL, depression significantly impairs both the psychological and physical domains of HRQOL (**86, 87**). Additionally, timing of depression onset in relation to a coronary event can impact upon self-rated mental health (See APPENDIX A1). 'Early' depression (assessed at an average of six days post-MI) can impact HRQOL long after a cardiac event (**73**). It has therefore been concluded

that depression is the best predictor of HRQOL in MI populations (**73**), and can remain detrimental to HRQOL for the ensuing year, or even longer (**88**). However, to date, much of the research on the relationship between depression, CVD and HRQOL has been conducted in clinical populations. There is less evidence regarding the current burden of these conditions, and how they interact with each other to impact HRQOL, at the population level. Assessing the burden of co-morbid CVD and depression will be of importance for the subsequent development of prevention and intervention strategies in this population.

1.4.1 The effects of depression treatment on HRQOL of cardiac patients

Few studies have evaluated the impact of depression treatment on HRQOL outcomes of MI patients. Recently, through the implementation of the Bypassing the Blues study (**89**), Rollman and others (2009) developed one of the first studies in this area to use HRQOL as a primary endpoint in their evaluation of a telephone-delivered, stepped, collaborative care program to treat depression in CABG patients. While the results of this study will be described more comprehensively in Chapter 5, briefly, this depression treatment intervention was proven efficacious in improving mental HRQOL outcomes, as measured by SF-36. No significant differences in physical HRQOL were observed between groups.

Given that changes in depression and HRQOL appear to be synchronous (**90, 91**), it may seem intuitive that alterations in depressive symptoms would lead to subsequent improvements in mental HRQOL. However, further research into the role of HRQOL is required in cardiac populations, not only to corroborate the findings of Rollman et al, but to identify a depression treatment program most effective for impacting all areas of HRQOL, including physical functioning. While observational studies (**92**) have demonstrated an association between alterations in depressive symptoms and changes in physical functioning status, this relationship is complex. It appears that the link between improved depression and reduced

functioning may not contain a direct causal link, rather it is more likely to be bi-directional. As previously discussed, depression could either be the cause or the consequence of reduced functioning or disability (**93**).

Further, depressive symptoms such as declining motivation, apathy and hopelessness have been linked to increased risk-factor clustering such as reduced physical activity levels, unhealthy dietary patterns, smoking and alcohol (**45**). These behaviours can debilitate physical functioning and also act as mediators in the onset of other medical conditions. Obesity, hyperlipidaemia, hypertension, diabetes, liver disease and cancers may manifest as a result of risk-factor clustering, or the depression itself. In fact, depression is a modifiable risk factor for diabetes (**94**). This can thereby impact one's physical functioning and level of disability. Physical activity interventions have been found to significantly improve physical HRQOL in medically ill patients, for example, a recent study of cancer survivors evaluated the impact of a strength training program, which demonstrated an effect size of 0.54 on physical HRQOL (**95**). In cardiac patients, physical HRQOL benefits have been observed, attributable to an educational intervention (**96**).

In cardiac patients with depression, the anticipated benefits of combining a lifestyle modification intervention targeting physical functioning with depression treatment that targets mental health functioning become apparent. For patients with both depression and a medical illness, Gaynes et al (2002) recommend "adopting a multidimensional approach to HRQOL rather than treating it unidimensionally" (**83**). To date, the effectiveness of such a program in cardiac populations is unknown. As such, the development and evaluation of this type of program is a research imperative. The benefits of treatment have the potential to go beyond mental and physical functioning to improve other important recovery outcomes, including vocational functioning.

1.5. The relationship between heart disease, depression and vocational functioning

The relationship between depression, heart disease and employment is equally complex. After a cardiac event, depression may act as a barrier to work resumption, or conversely may manifest as a by-product of functional restrictions (e.g. exercise, employment). Specifically, long absences from the workforce after a cardiac event may exacerbate depressive symptoms through feelings of social isolation, reduced productivity or stimulation. Equally, returning to everyday activities like work in the post-MI period may promote feelings of self worth, self esteem, social connectivity and productivity.

Evidence suggests that the majority of patients will resume work after a cardiac event (**97**). However, those experiencing depression will be slower and less likely to return to work (**98**), and more likely to experience social problems than their non depressed peers. These longer absences from the workplace could be further exacerbated by a range of other variables including cognitive factors (e.g. illness perceptions, attitudes to work, values), demographic factors (such as age, location) and environmental factors (e.g. family life, job content and stress (physical and emotional)). The role of depression in work resumption after a cardiac event, however, is more complex than this, when considering that depression appears to be present in a significant proportion of cardiac patients prior to their coronary event. It has been reported in one study that 44% of CAD patients have a prior history of diagnostically defined Major Depression, however the exact figure and the precise sequence of onset of the conditions, remains unclear (**99**). Since authoritative bodies have identified depression and other psychosocial factors (e.g. stress) as risk factors for heart disease, occupational research in chronic disease populations has become of increasing interest (**100**). For example, employment factors such as decision latitude, job strain, high effort-reward imbalance and

psychological demands have all been identified as predicting CHD morbidity and mortality (**101**). In cardiac patients, workplace productivity (including physical, psychological and social functioning of an individual while at work (**102**)) is a useful measure by which a patient's recovery can be determined.

Employment status has also been recognised as an index of the success of rehabilitation efforts (**103**), because both physiological and psychological factors influence vocational outcomes, and both are key components of cardiac rehabilitation. Yet, measuring work resumption alone does not capture productivity once back in the workplace. Post-MI, patients may be prone to absenteeism (work days lost as a result of illness), presenteeism (attending work while sick at reduced productivity), and lower retention rates. Subjectively, almost one third of cardiac patients feel that their MI has decreased their work performance and output one year after the event (**104**). While a recent Australian Institute of Health and Wellbeing (AIHW) report found that CHD and depression were the most common conditions related to unemployment in Australia (**105**), the burden of these conditions when occurring concurrently was not reported. If appropriate treatment strategies are to be developed, further research is required at the population level to assess the burden of this co-morbidity in relation to vocational outcomes.

Of further importance, is identifying the way in which depression can predict the work outcomes of CHD patients. This is of particular relevance as MI survival rates and length of working lives are increasing; indicators of productivity have been identified as "essential in this era of increased attention to resource utilization" (**106**). The association between depression and the work performance of cardiac patients has been of much interest in light of epidemiologic and other studies (**107, 108**); depression has been shown to predict poor work outcomes in other chronic disease cohorts (e.g. diabetes) (**109**). While this finding could be

extrapolated to cardiac patients, the prognostic role of depression on vocational outcomes is yet to be conclusively demonstrated in cardiac populations. The current evidence base indicates that depression, disease severity and age may all act as determinants of work performance (**102**). Epidemiological data has, however, revealed the long term impact of chronic depression on work outcomes; longitudinal (**110**), community (**111**) and primary care (**112**) mental health surveys have reinforced that the presence of chronic depression is correlated with persistent work related impairments. Therefore, there has been much interest in developing efficacious, as well as cost-effective approaches to treating depression in psychiatric populations in order to enhance vocational outcomes.

1.5.1 The impact of depression treatment on vocational outcomes of cardiac patients

Studies evaluating the key work outcomes of depressed, medically healthy patients have provided promising results; strong links have been identified between enhanced wellbeing and work performance. In fact, it has been argued that mood can improve synchronously with work productivity (**113**)(**114**), reduce absenteeism (**115, 116**) and predict sound job performance (**117**).

Others have found no effect; Simon and others (1998) argue that depression treatment does not translate to direct vocational benefits (**93**). The authors did, however, discuss the temporal nature of depression and functioning when discussing this null finding. They propose a possible delay in visible improvements in occupational functioning compared with depressive symptoms, and subsequently, argue that sustained remission of depression may be necessary to achieve good occupational outcome (**93**). In other words, although depression treatment has the potential to improve work outcomes, the relationship does not appear to be immediately synchronous. Rather, programs designed to treat depression with the view to enhance work productivity and performance may require evidence of long term sustainability

if the effect of an intervention is to go beyond altering depression. Of the existing depression treatment programs that have been evaluated in cardiac populations, few, if any, have evaluated the impact on vocational outcomes. Given the relationship between depression, CHD and work, it is likely that treating depression in cardiac patients would improve vocational functioning either directly or as a by product of enhancing mood outcomes. While there is limited evidence from clinical trials to support this, such an intervention could be personally, clinically and economically advantageous.

1.6. Summary

The relationship between depression and CHD is well established. The two conditions often co-exist and there remains compelling evidence that individuals who report this co-morbidity experience a range of poorer outcomes, including worse HRQOL and work outcomes. The biological mechanisms underpinning the relationship between the two conditions were reviewed to provide a context for the role of psychosocial factors, such as HRQOL. While it is clear that key components of HRQOL- mental and physical health functioning- can partially mediate the relationship between depression and CHD, there is much about this relationship that remains unclear. Understanding the burden of co-morbid depression and CVD on HRQOL and work outcomes, as well as the prognostic role of depression after a cardiac event, is crucial for the development of targeted interventions to improve key functioning outcomes of cardiac patients experiencing depression. Evidently, more research regarding suitable treatment approaches is required in this area: "...It would be expected that treating depression and anxiety would lead to improved quality of life and reduction in days of restricted activity and days missed from work [in cardiac patients]. This remains to be demonstrated in a clinical trial, however" (**118**). While the evidence presented in this chapter showed some evidence of depression treatment impacting mental HRQOL and lifestyle

interventions, like exercise, benefiting physical HRQOL few programs have applied a multi-faceted approach to treating co-morbid depression in cardiac populations. Combining a depression management program with a lifestyle intervention using a targeted approach, could result in overall HRQOL benefits and subsequently enhance vocational functioning. By focusing on the fundamental gaps in the literature, this thesis will address three research questions via four hypotheses. In doing so, this thesis aims to provide multidisciplinary, clinically relevant recommendations, with the overall objective of improving the health and wellbeing of people with depression following a cardiac event.

1.7. Research questions & study hypothesis

This thesis addresses the following three research questions.

In individuals with co-morbid depression and cardiovascular disease:

1. *What is the impact of this co-morbidity on mental, physical and vocational functioning?*
2. *What is the effectiveness of depression treatment on mental and physical functioning?*
3. *Can a targeted depression management and CHD secondary prevention program improve mental, physical and vocational functioning?*

These research questions will be addressed via the following hypotheses:

1a. *Individuals with co-morbid CVD and diagnostically-defined, major depressive disorder will demonstrate poorer workforce participation, productivity and absenteeism and lower HRQOL (as measured by the Assessment of Quality of Life), than individuals with one or neither condition (Chapters 2 & 4).*

1b. *Depression recorded after a cardiac event will predict poor 'return to work' outcomes at 6-12 month follow up (Chapter 3).*

2. *Cardiac patients receiving any depression treatment (pharmacologic, psychological, composite approaches) will demonstrate significantly greater improvements in mental and physical HRQOL compared with those assigned to a control condition, at six month follow up (Chapter 5 & 6).*

3. *Compared with those receiving usual medical care, ACS patients participating in a telephone-delivered, depression management and secondary prevention program (MoodCare) will report significantly greater improvements in HRQOL and work outcomes at six month follow up, as measured by the Short Form-12 and absenteeism/presenteeism measures, respectively (Chapters 7 & 8).*

1.8. Figures

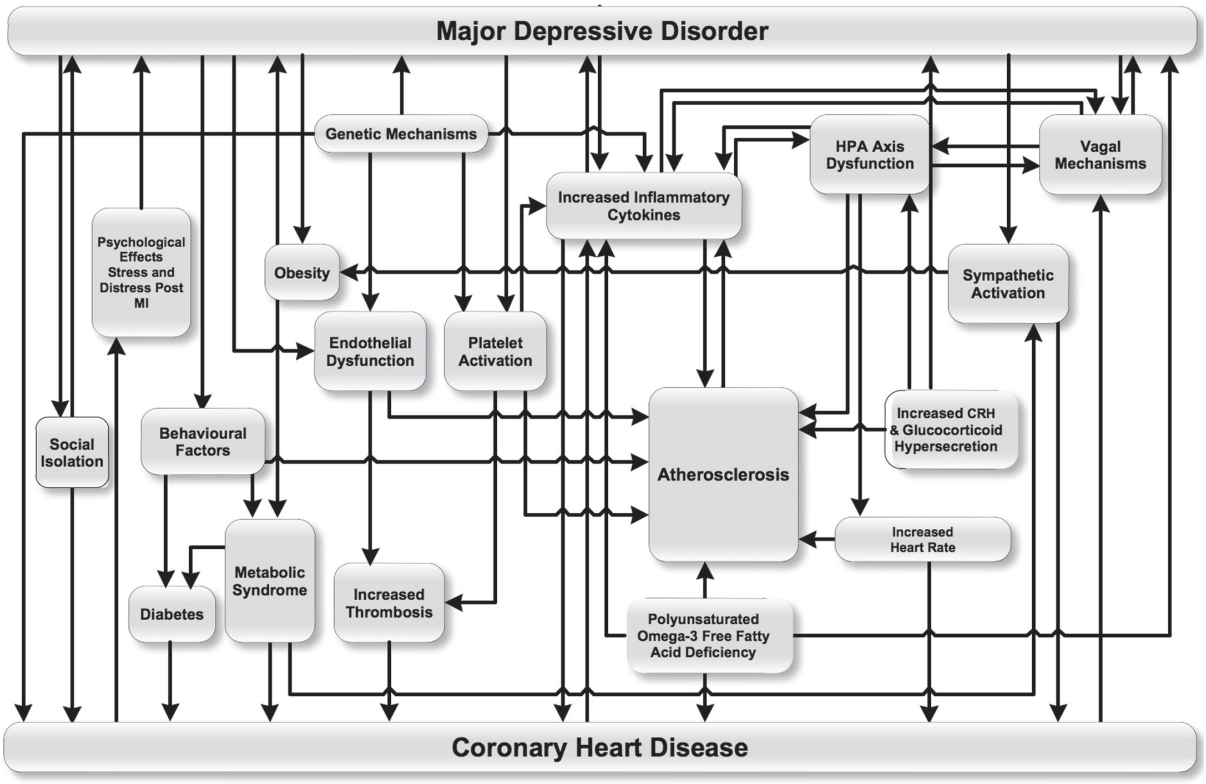

Figure 1.1. The relationship between major depressive disorder and coronary heart disease: a topographical map of the causal network (**119**)

Chapter 2: CO-MORBID DEPRESSION IS ASSOCIATED WITH POOR WORK OUTCOMES IN PERSONS WITH CARDIOVASCULAR DISEASE (CVD): A LARGE, NATIONALLY REPRESENTATIVE SURVEY IN THE AUSTRALIAN POPULATION

Chapter Overview

Having identifying the research gaps and thesis aims, this chapter examines the association of, and interaction between, co-morbid major depressive disorder (MDD) and cardiovascular disease (CVD) on work outcomes in the Australian population. Assessing the burden of this co-morbidity is a research imperative for the subsequent development of specialised treatment programs for those with co-morbid MDD and CVD.

Citation: O'Neil A, Williams ED, Stevenson CE, Oldenburg B, Sanderson K (2012). Co-morbid depression is associated with poor work outcomes in persons with cardiovascular disease (CVD): A large, nationally representative survey in the Australian population. *BMC Public Health.* **12**:47.

2.1. Publication Declaration

Declaration by candidate

In the case of Chapter [2], the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
AO conceptualised and refined the concept of the paper, accessed the data, conducted statistical analysis and interpretation, wrote the original version of the manuscript and submitted the final version.	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Emily Williams	Assisted with statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A
Chris Stevenson	Assisted with statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A
Brian Oldenburg	Refined conceptualization and critically revised the final version of the manuscript.	N/A
Kristy Sanderson	Conceptualized the paper, refined conceptualization, oversaw statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A

Candidate's Signature	**Date: 24.11.10**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Public Health and Preventive Medicine Monash University Alfred Campus

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

			Date
Signature 1	EW	[redacted]	24/11/10
Signature 2	CS		24/11/10
Signature 3	BO		3/12/10
Signature 4	KS		23/11/10

2.2. Abstract

Background: Co-morbid major depressive disorder (MDD) and cardiovascular disease (CVD) is associated with poor clinical and psychological outcomes. However, the full extent of the burden of, and interaction between, this co-morbidity on important vocational outcomes remains less clear, particularly at the population level. We examine the association of co-morbid MDD with work outcomes in persons with and without CVD.

Methods: This study utilised cross-sectional, population-based data from the 2007 Australian National Survey of Mental Health and Wellbeing (n = 8841) to compare work outcomes of individuals with diagnostically-defined MDD and CVD, MDD but not CVD, CVD but not MDD, with a reference group of "healthy" Australians. Workforce participation was defined as being in full- or part-time employment. Work functioning was measured using a WHO Disability Assessment Schedule item. Absenteeism was assessed using the 'days out of role' item.

Results: Of the four groups, those with co-morbid MDD and CVD were least likely to report workforce participation (adj OR:0.4, 95% CI: 0.3–0.6). Those with MDD only (adj OR:0.8, 95% CI:0.7–0.9) and CVD only (adj OR:0.8, 95% CI: 0.6–0.9) also reported significantly reduced odds of participation. Employed individuals with co-morbid MDD and CVD were 8 times as likely to experience impairments in work functioning (adj OR:8.1, 95% CI: 3.8–17.3) compared with the reference group. MDD was associated with a four-fold increase in impaired functioning. Further, individuals with co-morbid MDD and CVD reported greatest likelihood of workplace absenteeism (adj. OR:3.0, 95% CI: 1.4–6.6). Simultaneous exposure to MDD and CVD conferred an even greater likelihood of poorer work functioning.

Conclusions: Co-morbid MDD and CVD is associated with significantly poorer work outcomes. Specifically, the effects of these conditions on work functioning are synergistic. The development of specialised treatment programs for those with co-morbid MDD and CVD is required.

2.3. Background

Depression and cardiovascular disease (CVD) are leading causes of health and economic burden globally (**3**). By 2020, it is predicted that major depressive disorder (MDD) and coronary heart disease (CHD) will be the leading two global causes of disease burden (**1**). A common medical co-morbidity, depression often co-exists with CVD. Depression can manifest before or after CVD onset leading to a range of poorer outcomes including decreased medication adherence, greater suicide risk (**9**), poorer health service utilisation, CHD risk factor profiles, survival (**120**) and some work outcomes (**121**). Co-morbid mental and physical health conditions are highly prevalent in developed countries, such as the United States (US), United Kingdom (UK) and Australia (**122**), therefore the impact of co-morbid MDD and CVD on industry is likely to be great. However, to date, the burden of, and interaction between, these conditions at the societal level remains unclear.

Poor health has been associated with both work absenteeism and presenteeism (attending work while sick). It is also the case that individuals with chronic conditions are less likely to be in full-time employment than those without (**105**). Despite the benefits of active employment such as greater positive affect, less negative affect and fewer somatic complaints (**123**), people with a chronic condition are more likely to leave employment and retire early. Indeed, heart disease and depression have been reported as the two leading chronic diseases that contribute to labour force non-participation in developed countries (**105**). The co-morbid burden of depression and other chronic conditions (e.g. musculoskeletal disorders (**124**)) on workforce participation has already been established; Baune (2007) demonstrated that MDD co-occurring with any medical disorder was strongly associated with lower full-time working status (**125**). However, less is known about the specific burden of co-morbid MDD and CVD and how these two conditions

interact to influence various aspects of working life. Indeed, when the impact of co-morbid MDD and a range of chronic conditions (including CHD) have been explored, co-morbid MDD has been shown to approximately double the likelihood of increased functional disability and work absence (**126**). While elevated functional impairments may result from these conditions interacting rather than acting independently, evidence of such an effect remains inconsistent. Previous studies have shown a synergistic effect of co-morbid MDD and chronic physical conditions (e.g. diabetes) on functioning (**127**), but not on work absenteeism (**126**). Further research is required to determine the nature of the relationship between MDD and CVD on key work outcomes.

The aim of the paper is to examine (i) the association of co-morbid MDD with work outcomes (workforce participation, work functioning and workplace absenteeism) in persons with and without CVD; and (ii) the way in which MDD and CVD interact to impact on work outcomes.

2.4. Methods

2.4.1 Study design and sampling

Cross-sectional, population-based data from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB) were utilised. This methodology has been described in detail elsewhere (**128**), but briefly, the sample was based on a stratified, multistage probability sample of persons aged 16-85 years living in private dwellings in Australia, excluding very remote areas. The overall response rate was 60%, totalling 8841 participants. Non-response (n= 5964) was largely due to refusals (61%), not completing the full survey (21%) or partial or incomplete information (i.e. participants not answering all questions which apply to them) (12%) (**129**). A follow up study of NSMHWB

participation confirmed that non-response was small at the aggregate level (**129**). Data were provided by the Australian Bureau of Statistics (ABS) from a Confidentialised Unit Record File. This dataset is openly available to research institutions via the ABS.

2.4.2 Data collection instruments

Depression and CVD

Respondents with depression in the last 12 months were identified using the Composite International Diagnostic Interview (CIDI 3.0), one of the most widely-used, structured diagnostic interviews for psychiatric disorders in the world. CIDI 3.0 is primarily used for epidemiological research and has demonstrated sound validity and reliability for diagnosing depression; the inter-rater reliability for any depressive disorder has been shown to be high (kappa statistic of 0.95 (**130**)) and moderate to good concordance with the Structured Clinical Interview for DSM-IV (SCID) has been observed (**131**). Diagnostically, MDD is characterised by the presence of severely depressed mood persisting for at least two weeks (**132**). Respondents were identified as having CVD on the basis of their response to the question 'have you had or been treated for a CVD condition (e.g. heart attack, angina, high blood pressure) over the past 12 months?' (research has shown a reasonable correlation between self-reported chronic diseases, such as diabetes, heart disease and asthma and those identified in medical records (**133**)). This process allowed us to classify people as those (1) without MDD or CVD, (2) with MDD but not CVD, (3) with CVD but not MDD, (4) with both MDD and CVD. The time frame of 12 months was selected for each condition to best reflect participants' current disease status.

Work outcomes

Workforce status was assessed using a reduced set of questions from the ABS monthly Labour Force Survey. Individuals reporting participation in the workforce on a full (≥35

hours per week) or part time (less than 35 hours per week) basis (**128**) were categorised as employed, versus those not participating in the labour force at the time of survey completion. Number of hours usually worked by employed participants in one week was recorded. Workplace absenteeism over the past month was assessed using the 'days out of role' item (**128**) (used in previous NSMHWB surveys, e.g Lim et al (**134**)). This entailed participants nominating how many days they were totally unable to work because of their health and if less than 30 days, the number of days they had to cut down on what was done or did not get as much done as usual because of their health. Work functioning was measured using an item on the World Health Organization Disability Assessment Schedule (WHO-DAS) where participants rated their difficulty with day-to-day work as none, mild, moderate, severe or extreme.

Co-variates

Demographic information included age, sex, registered marital status, area socioeconomic disadvantage (Decile 1-10; where 1=most disadvantage and 10=least disadvantage) (**128**), country of birth, main language spoken at home (English, other), physical activity in the past week (number of occasions spent walking for recreation, exercise, etc), rurality (residing in major urban, other urban, other), education (dichotomised into pre and post-graduate attainment), body mass index (BMI) (calculated using the standard equation of weight divided by height squared (**135**)), psychological distress (Kessler-10)) (**136**), social support (frequency of contact with family and friends) and current smoking status (**128**). Participants self-rated their current mental and physical health using validated 5-point scales (excellent to poor), considered valid for measuring general health (**137**).

2.4.3 Data analysis

Estimates and standard errors (SE) were derived using a complex estimation procedure to account for the stratified multistage survey design, oversampling and non-response (**128**), using the Jack-knife delete-2 technique. Probability (sampling) weights were applied to weight the sample back to the population from which the sample was drawn. Re-running the analysis in the same way without weights indicated similar odds ratios to the reported results (data not shown). No age limits were placed upon participant's inclusion, as n=222 participants under the age of 18 years were reported to be in the workforce, as well as n=197 participants over the age of 65 years. For some categorical variables, we retained the additional group of "no response or not applicable" where necessary, to include all respondents in our analyses. Due to a limited number of cases, the work functioning variable was dichotomised into *no difficulty* and *mild to extreme difficulty*. The days out of role variable (workplace absenteeism) was treated as a categorical variable. Previous studies have classified individuals reporting ≥5 days of missed work in the prior month as having significant work disability (**109**), therefore the following categories were applied: 0 days absent per month; 1-4 days absent per month; 5 days absent per month or more (linear regression modelling was not applied because data were not normally distributed).

A multivariate, logistic regression analysis was performed with workforce participation as the dependent variable, to explore differences in workforce participation according to MDD/CVD disease group, using methods described by Hosmer and Lemeshow (2000)(**138**). Post-estimation tests were conducted to assess goodness-of-fit and specificity of the final model. This regression modelling strategy was also used to explore the relationship between disease group and work functioning. To assess the relationship between disease status and absenteeism, ordinal logistic regression was applied using the

proportional odds model (Adjusted Wald statistic); the assumptions of which were met. Only participants indicating that they were participating in the workforce were included in the models assessing work functioning and absenteeism. Synergistic effects of CVD and MDD were assessed by the addition of a CVD/MDD interaction to a model containing separate main effects terms: CVD over the past 12 months (yes/no) and MDD over the past 12 months (yes/no). All measures of magnitude were presented as adjusted Odds Ratios (OR) with Jack-knife SEs and 95% confidence intervals (CIs). Stata 11 (survey procedures) was used for all statistical analyses. STROBE guidelines (**139**) were applied for the reporting of cross-sectional studies.

2.5. Results

Table 2.1 displays the distribution of participants across disease groups, by workforce participation status and hours worked per week. The key characteristics of each group are displayed in Table 2.2. Those with MDD had the youngest mean age (36.7 years) while those with CVD only had the oldest mean age (62.1 years). Those with co-morbid MDD and CVD comprised the lowest proportion of males, followed by the MDD group. The co-morbid MDD and CVD group also reported: lowest proportion of excellent to good self-rated physical and mental health and lowest frequency of physical activity over the previous week, the lowest proportion of participants with a normal BMI, the highest proportion of participants in lower socio-economic deciles and who exhibited moderate to high psychological distress. Those with MDD only comprised the highest proportion of smokers and non-married participants, and individuals with a normal BMI range. This group reported the highest frequency of physical activity in the previous week (Table 2.2). While the gender distribution for the prevalence of depression was relatively equal across the MDD only and MDD/CVD groups, there was a slightly greater proportion of women

reporting MDD. This is consistent with the existing literature suggesting that affective disorders are more common in women than men (**140**).

2.5.1 Relationship between disease status and workforce participation

Multivariate logistic regression, adjusting for sex, age, marital status, rurality, smoking, area social disadvantage, education, country of birth, main language spoken, self-rated physical health and social support, revealed that individuals with co-morbid MDD and CVD were approximately half as likely to be working compared with those without either condition (adj OR 0.4, 95% CI: 0.3–0.6) (Table 3). Those with MDD only (adj OR: 0.8, 95% CI: 0.7- 0.9) and CVD only (adj OR: 0.8, 95% CI: 0.6–0.9) also reported significantly reduced odds of participation. Since age is related to both work participation and disease status, we conducted a sensitivity analysis that stratified by age group. We selected the following age groups on which to base our analysis: under 36 years (the lowest mean age of the 4 groups (MDD only)), 36–65 years (retirement age in Australia at the time of survey), and over 65 years. When we explored the odds of reduced participation for those aged between 36 and 65 years, similar odds ratios were observed; those with co-morbid CVD and MDD reported reduced odds of participation (adj OR: 0.6, 95% CI: 0.4- 0.8). However, for those aged under 36 years, the odds of work participation for those with co-morbid CVD and MDD was more pronounced (adj OR: 0.2, 95% CI: 0.1- 0.9). No significant effects were observed between disease group and work participation for those over 65 years of age (data not shown).

2.5.2 Relationship between disease status and work functioning

Of all the groups, employed individuals with co-morbid CVD and MDD were most likely to experience mild to extreme impairments in work functioning (Table 2.4). Compared with the healthy reference group, this group was 8 times more likely to report impaired

functioning (adj OR: 8.1, 95% CI: 3.8- 17.3), followed by those with MDD alone (adj OR 3.8, 95% CI: 3.0- 4.8), after adjusting for age, sex, country of birth, education, smoking, chronic lifetime physical condition, number of hours worked per week. Compared with the healthy reference group, those with CVD only reported no significant differences in work functioning. Because functioning could be associated with time spent at work, we further stratified work functioning by hours usually worked per week. Those with co-morbid MDD and CVD, again, reported greater odds of poor functioning; those working on a full time basis reported greatest odds (Table 2.5) (large CIs reflect small number of cases).

2.5.3 Relationship between disease status and workplace absenteeism

After adjustments for age, sex, marital status, education, smoking, mental and physical self-rated health and area social disadvantage, those with co-morbid CVD and MDD were three times more likely to belong to a higher category of days absent from work (adj. OR: 3.0, 95% CI: 1.4- 6.6) (Table 2.6). Those with MDD were also significantly more likely to report a higher category of workplace absenteeism (adj. OR: 1.8, 95% CI: 1.4- 2.4). Those with CVD only reported no differences in workplace absenteeism compared with the healthy reference group. Further, we stratified workplace absenteeism by hours usually worked per week (Table 2.7). Those with co-morbid MDD and CVD reported greatest odds of workplace absenteeism for both part time workers (employed less than 35 hours per week) (adj OR 3.6, 95% CI: 1.4- 11.7) and full time workers (employed ≥35 hours per week) (adj OR: 3.0, 95% CI: 1.3- 8.0). Those with MDD only also had increased odds of workplace absenteeism, compared with the healthy reference group for both part time (adj OR: 1.9, 95% CI: 1.3- 2.9) and full time (adj OR: 1.7, 95% CI: 1.2- 2.5) workers.

In addition, we ran all of the models with disease status coded to include those with lifetime CVD and MDD, in order to assess the association between long term disease status

and work outcomes. These analyses yielded similar odds ratios for all outcomes (data not shown).

Finally, we explored the interactive effects of MDD and CVD on all three work outcomes. We found a significant interaction between MDD and CVD on work functioning (p=0.04). The effects of MDD and CVD on workforce participation and absenteeism (for both part and full time workers) were shown to be additive rather than synergistic; interaction terms were non-significant (p>0.05).

2.6. Discussion

Our research findings demonstrate that major depression which co-occurs with CVD is associated with poor work outcomes, including reduced workforce participation and greater work functioning impairments and workplace absenteeism. For all outcomes, those with co-morbid CVD and MDD experienced greater impairment than those with either condition by itself. While no significant interactive effects were found between MDD and CVD on work participation or absenteeism, a synergistic relationship was observed between MDD and CVD on workforce functioning, indicating that the combined effect of these conditions on functioning is greater than the sum of the effects of depression and CVD when they occur independently. To our knowledge, this is the first time the burden of, and interaction between MDD and CVD, specifically, has been explored on work outcomes at the population level.

Our findings are consistent with cross-sectional studies conducted in Europe (**125**), Northern America (**109**) and Australia (**124**) in which other co-morbid populations have also demonstrated poorer work outcomes. For example, Baune (2007) found that MDD co-occurring with any medical disorder was strongly associated with lower full-time working

status and significantly more disability days (**125**). Further, our findings add to others in this field, by confirming a synergistic effect of co-morbid MDD and chronic physical conditions on functioning (**127**), but not work absenteeism (**126**).

The synergistic relationship observed between MDD and CVD on work functioning, but not participation or absenteeism, suggests the negative effects of this co-morbidity are most pronounced for functional outcomes. Previous studies in MDD and diabetes populations (**127**) also support this finding. It would be expected that depression impacts mental functioning and CVD impacts physical functioning, and that cumulatively, the conditions combine to impede overall functioning. However, the interaction we observed between MDD and CVD on functioning may be a result of depressive symptoms exacerbating perceived impairment due to CVD, or may reflect greater physical symptom severity which can impede mental and physical components of functioning; essential for work productivity. That is, those who are depressed may have more severe forms of the disease. Further research is required to disentangle the association between this co-morbidity and mental and physical functioning.

There are several explanations for our finding of poorer work outcomes in those with co-morbid MDD and CVD. While its cross-sectional design precludes us from making causal inferences about the association between co-morbid mental and physical conditions and workforce status, we speculate that employment status may be influenced by both internal and external factors. As depression is a recognised risk factor for CVD (**141**) and stress is a shared risk factor for depression and CVD (**142**), stress may, in fact, act as a mediator in this relationship. Alternatively, risk factor clustering could exacerbate the effects of both CVD and MDD. For example, individuals with MDD may be more likely to report alcohol and tobacco use (**143**) and poor dietary regimes (**144**) and physical activity levels (**145**); many

of which occur simultaneously. Indeed, these behaviours can impede recovery after a CVD event, increase the risk of cardiac events and contribute to the physiology which underlies disease progression.

Moreover, we observed significant age-related effects of this co-morbidity on workforce participation; those under 36 years reported more pronounced reductions in participation than those aged 36-65 years, and no significant reductions were observed for those over 65 years. There are several possible explanations for this finding. For example, individuals who have experienced this co-morbidity at a young age may have: more chronic symptoms with greater severity, greater difficulty managing their conditions due to competing interests (such a child rearing), or different disease management or treatment plans compared with their older counterparts. Further, since depression can manifest either before or after CVD onset, and order of onset has been shown to result in differential outcomes (APPENDIX A1)(**146**), it is possible that the clinical course of MDD and/or CVD and their associated outcomes, differs in younger persons compared with older individuals.

This study has the following strengths. Compared with most other existing studies (**147**), our study used a valid psychiatric diagnostic instrument to assess MDD. While a diagnostic interview is time consuming, it is a more accurate method for the classification of depression than self-report methods. Another strength of our study is its robustness due to the use of a large probability sample from the general population. However, some study limitations should also be acknowledged. Self-report measures were used to define participants' CVD status which may have led to recall bias, misclassification or incorrect identification of CVD. This may have resulted in an under-reporting of CVD and thus a possible dilution of the CVD effect. Similarly, it is possible that MDD may have also been

under-reported; a study of NSMHWB non-responders revealed non-response may be associated with mental illness for younger individuals and males (**129**). However, the representativeness of this sample has been reported previously (**129**). A further limitation of the study is the large CIs and SEs resulting from small numbers of employed participants with both co-morbid depression and CVD.

More research is needed to further understand the inter-relationships and the implications for developing effective prevention and intervention programs for people with co-morbid CVD and MDD. Longitudinal cohort studies have the potential to reveal both the long-term and causal impact of depression and CVD on workforce retention, early retirement and disability, as observed in international studies (**148**). Future longitudinal studies should investigate whether this trend is comparable for individuals with co-morbid MDD and CVD. Further, randomised controlled trials that aim to improve vocational outcomes of individuals with co-morbid depression and CVD are required. To date, existing trials in this area have focused more on clinical outcomes, over psychosocial or functional outcomes such as employment. Several of these trials have, however, demonstrated positive effects of depression management on mental health functioning in those with CVD (**89**). While it is likely that these benefits extend to vocational functioning, there is limited evidence to support this. Several studies in this area are currently exploring the impact of depression management after a cardiac event on work outcomes (**89, 149**). As it is likely that the relationship between disease and employment status is bi-directional, interventions could be of a work-based nature, where occupational programs have the potential to improve disease management, or alternatively, of a psychological nature, where treating depression is likely to enhance both work and psychological outcomes in those with CVD.

2.7. Conclusions

It has been argued that the occupational rehabilitation needs of people with co-morbid depression and chronic conditions are currently being underestimated (**150**). Our findings highlight that those exhibiting co-morbid MDD and CVD are at high risk of functional impairments and work absenteeism. This should be considered by the relevant health professionals working in this field (psychologists, occupational therapists, cardiologists and rehabilitation nurses). The implementation and evaluation of targeted interventions in this population which facilitate work resumption, retention and productivity have the potential to be individually, organisationally and economically advantageous. Given the emergence of co-morbid psychological distress and chronic disease as a growing public health issue affecting workers in Western economies (**151**), mental and physical medical co-morbidities need to be prioritised given their prevalence and subsequent burden.

2.8. Abbreviations

CVD = Cardiovascular disease

MDD = Major Depressive Disorder

CHD = Coronary Heart Disease

NSMHWB = National Survey of Mental Health and Wellbeing

ABS = Australian Bureau of Statistics

CIDI 3.0 = Composite International Diagnostic Interview 3.0

SCID = Structured Clinical Interview for DSM-IV

BMI = Body Mass Index

NHPA = National Health Priority Areas

WHO-DAS = World Health Organization Disability Assessment Schedule

SE = Standard Errors

OR = Odds ratios

CI = Confidence Intervals

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

2.9. Competing Interests

The authors declare that they have no competing interests.

2.10. Author contributions

AO conceptualised the paper, analysed and interpreted data, and wrote the original version of the manuscript. EDW assisted with statistical analysis and interpretation of the data, and contributed to drafts of the manuscript. CEW assisted with statistical analysis and interpretation of the data, and contributed to drafts of the manuscript. BO critically revised the manuscript. KS assisted with conceptualising the paper, statistical analysis and interpretation of the data, and critically revised drafts of the manuscript. All authors read and approved the final version of the manuscript.

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2.12. Tables

Table 2.1. Number and proportion of NSMHWB survey participants, by disease group

	All participants (n=8841)		Employed participants (n=5499)		Working ≥35 hours per week (n=3,499)	
Condition type	n	%	n	%	N	%
Neither CVD nor depression	6,079	68.8	4067	74.0	2,617	74.8
Depression only+	1,326	15.0	909	16.5	564	16.1
CVD only±	1,223	13.8	434	7.9	266	7.6
Co-morbid depression+ and CVD±	213	2.4	89	1.6	52	1.5
Total	8841	100	5,499	100	3499	100

+Major depressive disorder (past 12 months); ± Been told or treated for heart/ circulatory condition (angina, heart attack, high blood pressure) in past 12 months

Table 2.2. Key characteristics of survey participants, by disease group (n=8841)

	(1) Neither MDD nor CVD n=6,079 Mean /Percentage (95% CI)	(2) MDD only n=1326 Mean /Percentage (95% CI)	(3) CVD only n=1,223 Mean /Percentage (95% CI)	(4) Co-morbid MDD & CVD n=213 Mean/Percentage (95% CI)
Age	42.5 (42.2, 42.8)	36.7 (35.7, 37.7)	62.1 (60.9, 63.2)	54.6 (52.1, 57.2)
Sex (male)	50.6 (49.7, 51.6)	45.4 (41.4, 49.4)	51.0 (47.5, 54.4)	40.9 (30.3, 51.5)
Country of birth (Australia)	71.2 (69.3, 73.2)	80.9 (77.6, 84.1)	71.6 (66.6, 76.6)	75.0 (66.1, 83.9)
Main language spoken at home (English)	90.4 (89.1, 91.7)	94.2 (91.6, 96.7)	92.7 (89.4, 95.9)	96.4 (92.5, 100.0)
Registered marital status (not married/single)	46.5 (45.0, 48.0)	64.7 (60.1, 69.3)	28.7 (25.0, 32.5)	41.2 (31.63, 50.7)
Post graduate education (yes)	57.0 (55.6, 58.4)	51.9 (48.3, 55.6)	46.8 (42.5, 51.1)	48.4 (37.7, 59.1)
Level of Area social economic disadvantage (Decile 1-5)+	44.7 (42.5, 46.9)	46.7 (42.3, 51.2)	49.1 (44.3, 54.0)	57.5 (46.3, 68.6)
Self-rated physical health (Excellent-Good)	89.8 (88.7, 90.8)	77.5 (74.8, 80.2)	76.2 (72.6, 79.8)	44.4 (33.5, 55.2)
Self-rated mental health± (Excellent-Good)	96.1 (95.5, 96.8)	72.7 (68.0, 77.3)	92.4 (90.2, 94.5)	53.5 (52.8, 74.2)
Psychological distress (Moderate to high distress)	20.7 (19.2, 22.1)	64.3 (60.7, 67.9)	24.1 (19.8, 28.3)	68.9 (56.9, 81.0)
Smoke (yes)	20.6 (19.1, 22.2)	38.5 (34.4, 42.6)	10.6 (8.1,13.0)	28.0 (16.1, 39.9)
Body Mass Index (% normal)	44.5 (42.6, 46.3)	49.3 (45.5, 53.1)	23.9 (20.1, 27.6)	18.9 (9.6, 28.3)
+Frequency of physical activity in past week	5.2 (4.9, 5.5)	5.6 (4.9, 6.2)	4.3 (3.6, 4.9)	4.2 (2.7, 5.7)

+Most disadvantaged; does ± not include the full 8841 participants due to missing data

Table 2.3. Logistic regression model for the relationship between workforce participation and disease group (n=8841)

Employment status[+]	Unadjusted Odds ratio	Adjusted Odds ratio±	Jack-knife Standard Error	Confidence intervals (95%)
Condition Neither CVD nor MDD	1.0			
MDD only	1.0	0.8*	0.1	0.7, 0.9
CVD only	0.3*	0.8*	0.1	0.6, 0.9
Co-morbid MDD and CVD	0.3*	0.4*	0.1	0.3, 0.6
CVD-MDD interaction		0.7	0.3	0.4, 1.5

[+] 0= Not employed in workforce 1=full or part-time employment in the workforce, where 0 is the reference group; ± = Adjusted for sex, age , marital status, rurality, smoking, area social disadvantage, education, country of birth, main language spoken, self-rated physical health and social support*=p<0.05; Goodness of fit (**152**) and link tests produced non-significant test statistics (p=0.10 and p=0.29 respectively), reflecting goodness of fit and sound model specificity.

Table 2.4. Logistic regression model for the relationship between impaired work functioning and disease group (employed participants) (n=5499)

Amount of difficulty in day to day work[+]	Unadjusted Odds Ratio	Adjusted Odds ratio±	Jack-knife Standard Error	95% Confidence intervals
Condition				
Neither CVD nor MDD	1.0	-	-	-
MDD only	4.3*	3.8*	0.4	3.0, 4.8
CVD only	1.0	0.9	0.2	0.6, 1.4
Co-morbid MDD & CVD	10.7*	8.1*	3.0	3.8, 17.3
CVD-MDD interaction	-	2.4*	1.0	1.01, 5.7

[+] 0=None or not known, 1=Mild- Extreme difficulty, where 0 is the reference group; ±= Adjusted for age, sex, country of birth, education, smoking, chronic lifetime physical condition, number of hours worked per week; Goodness of fit (**152**) and link tests produced non-significant test statistics (p=0.24 and p=0.051 respectively), reflecting goodness of fit and sound model specificity.

Table 2.5. Logistic regression model for the relationship between impaired work functioning and disease group, by hours worked (n=5499)

Amount of difficulty in day to day work+	Unadjusted OR	Adjusted OR ±	Jack-knife Standard Error	Confidence intervals
<35 hours per week				
Neither CVD nor MDD	1.0	1.0		
MDD only	3.1*	3.4*	0.6	2.3, 5.0
CVD only	0.8	0.8	0.3	0.3, 1.6
Co-morbid MDD & CVD	5.9*	4.5*	2.2	1.7, 11.8
≥*35 hours per week*				
MDD only	4.6*	4.0*	0.6	2.9, 5.6
CVD only	1.1	0.9	0.3	0.5, 1.7
Co-morbid MDD & CVD	14.9*	10.6*	5.3	3.9, 29.0

±= Adjusted for age, sex, country of birth, education, smoking, chronic lifetime physical condition

Table 2.6. Ordinal logistic regression model for the relationship between workplace absenteeism and disease group (employed participants) (n=5499)

Category of days unable to work+	Unadjusted Co-efficient	Adjusted Coefficient±	Jack-knife Standard Error	Confidence intervals
Condition				
Neither CVD nor MDD	1.0	1.0	-	-
MDD only	2.7*	1.8*	0.2	1.4, 2.4
CVD only	1.0	1.0	0.2	0.6, 1.6
Co-morbid MDD & CVD	4.5*	3.0*	1.2	1.4, 6.6
CVD-MDD interaction	-	1.8	0.8	0.7, 4.6

+ 0= 0 days per month (reference group), 1=1-4 days; 2=5 days per month or more; ±= Adjusted for: age, sex, marital status, education, smoking, area social disadvantage, self-rated mental and physical health *p<0.05; Post-estimation tests revealed good model specificity (linktest p=0.45), and no violation of proportion odds assumption (p=0.36).

Table 2.7. Ordinal logistic regression model for the relationship between workplace absenteeism and disease group, by hours worked (n=5499)

Number of days unable to work+	Unadjusted OR	Adjusted OR ±	Jack-knife Standard Error	Confidence intervals
<35 hours per week				
Neither CVD nor MDD	1.0	1.0	-	-
MDD only	2.5*	1.9*	0.4	1.3, 2.9
CVD only	1.0	1.1	0.6	0.4, 3.3
Co-morbid MDD & CVD	5.0*	3.6*	2.1	1.4, 11.7
≥*35 hours per week*				
MDD only	2.2*	1.7*	0.3	1.2, 2.5
CVD only	0.7	0.9	0.2	0.5, 1.6
Co-morbid MDD & CVD	3.2*	3.0*	1.5	1.3, 8.0

+ 0= 0 days per month (reference group), 1=1-4 days; 2=5 days per month or more; ±= Adjusted for: age, sex, marital status, education, smoking, area social disadvantage, self-rated mental and physical self-rated health *p<0.05

Chapter 3: DEPRESSION AS A PREDICTOR OF WORK RESUMPTION FOLLOWING MYOCARDIAL INFARCTION (MI): A REVIEW OF THE RESEARCH EVIDENCE

Chapter Overview

Having established the current burden of, and interaction between, CVD and depression on vocational outcomes at the population level, the relationship between depression and employment requires further investigation in clinical populations. Due to inconsistencies in the current literature, this chapter will systematically review the recent research evidence to establish if depression acts as a prognostic indicator of return to work after a cardiac event.

Citation: O'Neil A, Sanderson K, Oldenburg B. (2010). Depression as a predictor of work resumption following myocardial infarction (MI): a review of recent research evidence, *BMC Quality of Life and Health Outcomes.* 8:95. doi:10.1186/1477-7525-8-95

3.1. Publication Declaration

Declaration by candidate

In the case of Chapter [3], the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
AO conceptualised the paper, synthesised, analysed and interpreted data, and wrote the original version of the manuscript.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Kristy Sanderson	KS refined conceptualization, assisted with inclusion/exclusion criteria, coding, synthesis and analysis of data and critically revised drafts of the manuscript.	
Brian Oldenburg	BO refined conceptualization and critically revised drafts of the manuscript.	

Candidate's Signature [redacted] **Date** 24/3/10

Declaration by co-authors

The undersigned hereby certify that:

(7) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(8) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(9) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(10) there are no other authors of the publication according to these criteria;
(11) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(12) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Public Health and Preventive Medicine Monash University Alfred Campus

Signature 1	[redacted]	**Date** 24/03/10
Signature 2		24/3/10

3.2. Abstract

Background: Depression often coexists with myocardial infarction (MI) and has been found to impede recovery through reduced functioning in key areas of life such as work. In an era of improved survival rates and extended working lives, we review whether depression remains a predictor of poorer work outcomes following MI by systematically reviewing literature from the past 15 years.

Methods: Articles were identified using medical, health, occupational and social science databases, including PubMed, OVID, Medline, Proquest, CINAHL plus, CCOHS, SCOPUS, Web of Knowledge, and the following pre-determined criteria were applied: (i) collection of depression measures (as distinct from 'psychological distress') and work status at baseline, (ii) examination and statistical analysis of predictors of work outcomes, (iii) inclusion of cohorts with patients exhibiting symptoms consistent with Acute Coronary Syndrome (ACS), (iv) follow-up of work-specific and depression specific outcomes at minimum 6 months, (v) published in English over the past 15 years. Results from included articles were then evaluated for quality and analysed by comparing effect size.

Results: Of the 12 articles meeting criteria, depression significantly predicted reduced likelihood of return to work (RTW) in the majority of studies (n=7). Further, there was a trend suggesting that increased depression severity was associated with poorer RTW outcomes 6 to 12 months after a cardiac event. Other common significant predictors of RTW were age and patient perceptions of their illness and work performance.

Conclusion: Depression is a predictor of work resumption post-MI. As work is a major component of Quality of Life (QOL), this finding has clinical, social, public health and economic implications in the modern era. Targeted depression interventions could facilitate RTW post-MI.

3.3. Background

3.3.1 Relationship between myocardial infarction, depression and work

Depression is a common and debilitating condition which is often experienced after a heart attack [myocardial infarction (MI)]. It is estimated that approximately 15% of individuals will suffer major depression post-MI, with another 15-20% exhibiting mild to moderate symptoms (**153**). Although depression may be transitory, there is evidence to suggest it can precede a cardiac event. For example, more than half of MI patients experience feelings of fatigue and general malaise in the months before infarction (**154**). Despite its prevalence, depression often remains unrecognised and undiagnosed in this population. This may be due to issues such as brief hospitalisation periods (the average length of stay for MI is now 3-5 days (**155**)) and the fact that symptoms of depression and MI can overlap. Left untreated, co-morbid depression has a significant impact on recovery and functioning and is associated with increased morbidity and mortality, poorer clinical, behavioural and psychological outcomes, and reduced overall quality of life (QOL) (**6**).

Work is a major constituent of QOL. It plays an important role in the recovery and adjustment of patients post-MI, through its related constructs such as satisfaction, social value and productivity. With evidence to suggest survival rates are increasing, indeed many patients will resume work after experiencing a cardiac event; it is currently estimated that 80% of MI patients will return to work (RTW) post infarct within a 12 month period (**97**). However, patients with cardiac depression are slower and less likely to RTW (**98**) than those without. For patients who have not resumed work by 12 weeks, the likelihood of doing so decreases by half (**156**). Depression symptoms- both cognitive and somatic- can inhibit desire to resume employment, resulting in longer absences from the workplace. In patients who RTW, the benefits remain well documented; increased positive affect and fewer cognitive complaints

(**157**). However, those experiencing co-morbid depression are more likely to report poorer vocational functioning, social problems, increased absenteeism, presenteeism or early retirement. Despite this evidence, research investigating depression as a prognostic indicator of RTW post MI has produced inconsistent results in recent years (**158**).

3.3.2 Existing evidence for depression as a predictor of RTW after MI

During the 1970s and 80s, RTW was considered a key indicator of the effectiveness of cardiac rehabilitation and patient recovery. Age, education, socio-economic status, severity of MI, and physical functioning were all implicated as strong moderators of RTW after a cardiac event. The latter was often used as a means by which to measure one's capacity and readiness to RTW (e.g. Dennis, 1988 (**159**)). However, during this time, the prognostic role of depression and psychosocial factors became of interest. Two key studies of this time [Hlatky et al (1986) and MÆland et al (1987)] found that depression recorded in hospitalised cardiac patients predicted poorer RTW outcomes, increased work disability and greater loss of employment (**160, 161**). Patients with co-morbid depression were also found to experience greater difficulties in occupational adjustment and deficits in other outcomes. MÆland et al (1987) further observed a linear relationship between RTW and levels of depression, concluding that increased depression severity was linked to poorer rates of RTW in MI patients (**160**).

More recently, although evidence has emerged that depression is a predictor of employment status up to a year after admission for patients with other cardiovascular (CVD) conditions, such as stroke (**162**), in MI populations it "cannot be assumed that factors identified over 25 years ago as predictors of return to work will be relevant in the modern era"(**121**). There are several reasons for this. Longitudinal trends have indicated that survival rates after MI are increasing (**163, 164**). For example, data from the Atherosclerosis Risk in Communities (ARIC) study [1987 to 1994] indicated a decline in MI severity in the US (**165**). This trend was

further demonstrated for the period 1994-2002 (**164**). Second, advances in procedures for diagnosis and treatment, i.e. imaging stress tests, Percutaneous Coronary Intervention (PCI) and stents, overall rates of revascularization (substantially increasing since 1993 (**166**)), and increased medication prescription [aspirin, Angiotensin-converting enzyme (ACE) inhibitors] (**167**) have led to changes in the management of cardiac patients. Third, trials investigating the role of depression post MI (**81**) have more likely been expressed using clinical and psychological markers over employment outcomes. Fourth, increased awareness about the prevalence of depression in this population has led to further research in this area in recent years. In light of the contemporary management of cardiac patients, and the subsequent implications on rates of discharge and RTW, recent studies need to be drawn on to determine if depression remains a predictor of work outcomes post MI.

The identification of depression as a predictor of work outcomes in MI patients is important. From a clinical perspective, facilitating RTW after MI may significantly reduce emotional distress (**168**). From a societal perspective, shifts in social trends including increased life expectancy and financial instability, translating to longer working lives, require that barriers to workforce participation be identified. From a public health perspective, the increasing burden of coronary heart disease on western society, its augmented risk with age, and increased survival rates (e.g. up to 20 million people survive a heart attack globally each year (**169**)), highlight a need to implicate factors which facilitate workforce participation. From an economic perspective, depression as a sole condition accounts for 13.8 million work days lost in the UK (**170**) and 225 million days lost in the US, annually (**171**). When co-existing with a chronic disease, depression can have even greater economic implications on the workforce.

The aim of our study was to determine whether depression remains a predictor of poorer work outcomes following MI by conducting a review of studies conducted in the past 15 years.

3.4. Methodology

3.4.1 Search Strategy

The literature search aimed to identify articles which assessed work resumption as an outcome measure and depression as a primary prognostic variable in cardiac patients. Studies were identified using databases for medical, health, occupational and social sciences, with the intention to cover concepts identified by the authors in Table 3.1. Databases included PubMed, OVID, Medline, Proquest, CINAHL plus, CCOHS, SCOPUS, Web of Knowledge. Reference lists of relevant studies and reviews (identified using databases such as EBM Reviews, Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED) were also examined. Grey literature and web pages were examined using search engines such as Google Scholar. Previous recommendations for effective strategies in identifying prognostic studies (**172**) were also employed.

3.4.2 Selection of studies

Articles were identified using this search strategy and reviewed for relevance by the first author and an independent reviewer (CR) between March and July, 2009. Abstracts were obtained for articles which potentially included: (i) application of depression measures (as distinct from 'psychological distress') and work status at baseline, (ii) examination and statistical analysis of *predictors* of work outcomes, (iii) cohorts with patients exhibiting symptoms consistent with ACS, (iv) follow up of work-specific and depression specific outcomes at minimum 6 months, (v) those published in English over the past 15 years. Full text articles were obtained for those appearing to meet criteria, where the following information was extracted from each: author, population, design, depression measure, definition of RTW, major findings, effect of depression as a predictor on RTW, other significant predictors of RTW post MI. Data were analysed through synthesis and quality

assessment of this information, as the inconsistencies between study definitions of RTW and variety of instruments used to assess depression precluded formal meta-analysis. Using a framework for assessing internal validity used in other prognostic reviews (**173**), these articles were subject to application of a quality criteria (Table 3.5). Articles were systematically scored in reference to quality, to determine level of evidence. A score of 12 or more was considered high quality, 10-11 was considered moderate quality and nine or less was deemed low quality. The quality of articles was considered not as exclusion criteria but in the analysis of results.

3.5. Results

Initial searches were conducted independently by AO and CR, yielding 1231 results; 309 of these articles were considered for inclusion from an initial review, and their abstracts obtained. After screening using the inclusion criteria, the full text of 31 articles were obtained and details of those appearing to meet criteria were recorded in extraction tables. The first author and reviewer convened to compare the results of their respective searches. After excluding 19 of the 31 studies initially considered to meet criteria, 12 articles were finally agreed upon by the two assessors for inclusion (initial assessor consensus was 93%; where consensus was not reached, the second author was consulted). Reasons for exclusion were: duplicate articles of the same study (n=8), follow up period not long enough (n=2), did not record depression using appropriate assessment techniques (n=2), and did not analyse/present data on predictors of work outcomes (n=7). Figure 3.1 displays the results of the search strategy, in alignment with PRISMA guidelines. Papers included in the review were those published in English between 1994 and July 2009. Each article for final inclusion in the review was subject to assessment using a quality assessment inventory (Table 3.5). Quality assessment ratings are displayed in Table 3.2, where each article was graded using these

criteria. Seven of the 12 articles were considered high quality, four moderate quality and one low quality. Collectively, the most common features of the articles were: well defined inclusion criteria, measurement selection and baseline data collection point, and use of multivariate techniques for data analysis. The least common feature of the articles was the reporting of a representative sample (four articles reported recruiting samples with males only). While measurements used for data collection were clearly documented, in most instances a justification for selection was not given.

3.5.1 Population and design

Articles included a collective total of 2795 participants who were employed at the time of their cardiac event, of working age (18+ [retirement age differed between countries]), recruited from an acute hospital setting with one of the following diagnoses: MI, ACS or CAD (including those undergoing cardiac interventions: Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA)). Data were derived from prospective cohort or longitudinal studies using prognostic variables, with the exception of one randomised controlled trial of a cardiac rehabilitation intervention (**174**). Timing of classification of participant baseline depression ranged from hospital admission, upon stabilising of condition, immediately prior to discharge, pre surgical intervention, beginning of rehabilitation program, three days post discharge, 7-10 days post discharge, 17-21 days post discharge and two months post discharge. It was not possible to determine the average length of time since infarct as a result of this variation. Follow up assessment points used in the studies ranged from six months, eight months and 12 to 13 months.

3.5.2 Depression Measures

Studies recorded depression outcomes using validated instruments. The most commonly used instrument was the Beck Depression Inventory (**97, 121, 174, 175**), followed by the Hospital Anxiety and Depression Scale (HADS) (**158, 176, 177**), Cornell Medical Index (**178**), Subscale of Minnesota Multiphasic Personality Inventory (MMPI) (**179**), Center for Epidemiologic Studies Depression Scale German version (CES-D-ADS) (**180**) and a validated 12 item depression measure (**181**). One study used both HADS and BDI Fast Scale (BDI-FS) (**182**) to assess depression, but after independent analysis of the measures, reported that HADS was superior to the BDI-FS in predicting RTW ($p = 0.026$); the results of the former instrument were included in the review.

3.5.3 Definition of Work

RTW data were collected via self report (participant interview or questionnaire) in all studies to determine work status post MI. One study also used work data from a Social Insurance Institution Registry (**174**) to validate participant self report. Although the data collection method was consistent between studies, there was wide variation regarding the definition of RTW and the subsequent questions asked to participants (Table 3.3). Broadly, work resumption was defined as either a reported date of RTW or a positive response to the question: "Have you returned to work?". Only two studies considered RTW to be defined by a tangible time frame (i.e. "hours per week", returned at 100% of hours pre infarct). In the absence of these data, it was not possible to calculate mean time between cardiac episode and RTW. In a further attempt to ascertain work status, over half of studies (n=7) collected information on work hours (full or part time) and almost one quarter provided estimates of current and pre-infarction activity. Additional information collected included: intent to RTW, disability, profession, early retirement, sick leave, job strain and organizational

characteristics. One study did not provide a sufficient definition of RTW in its methodology but expressed findings as proportions of participants "seeking" and "returning" to work at follow up (**158**).

3.5.4 Impact of Depression on RTW

Depression was a significant predictor of failure or delay in RTW at 6-12 months in 7 of the 12 studies. These studies are outlined in Table 3.4 along with a summary of effect sizes, p values and confidence intervals regarding the likelihood of depressed patients returning to work after MI. Findings are expressed as estimated relative risk and adjusted odds ratios are presented. Potentially confounding variables controlled for in each regression model are detailed (commonly demographic, clinical and other variables previously found to influence RTW rates in these populations or those found to be significant as a result of univariate analysis).

Of the studies to find depression a significant predictor of RTW, Fukuoka et al (2009) (**175**) and Bhattacharyya et al (2007) (**121**) found that depression not only significantly predicts work resumption but that a dose response relationship exists between severity of depression and likelihood of RTW, six to twelve months after a cardiac event. In regards to the impact of past history of depression on RTW, these were the only two studies to record depression which occurred pre-infarct. These studies reported disparate results. Fukuoka et al (2009) (**175**) found a significant difference in those with depressive history who RTW, when compared with those without ($p<0.05$), while Bhattacharyya et al (2007) (**121**) found that depression experienced six month pre-infarct was not related to RTW at 12 months.

In these seven studies, other significant predictors of work resumption included demographic factors (age, education), organizational factors (job strain, decision latitude, social network at

work, profession), clinical factors (recurrent cardiac events, arrhythmia), and individual factors (personality type, expectations, health concerns). Besides depression, age was the only variable to feature as a significant predictor in more than one study (n=4).

Of the studies which failed to find depression a significant predictor of RTW, somatic health (OR 1.08 (CI 1.02-1.14; p= 0.011) and footsteps per day (OR 1.18 (CI 1.01-1.38; p= 0.033) (**177**) were significant predictors at six months. At 12 months, age (OR 1.22 (CI 1.10-1.34), self assessed work capacity at six months (OR 8.5 (CI 2.3-32.0; p=0.003), physician's perception of disability (OR 1.61 (CI 1.16-2.07) (**180**), functional class (OR 6.7 (CI 1.8-24.5), and absence from work ≤ 3months (OR 4.9 (CI 1.2-20.2) (**174**) were all predictors of RTW. The only common predictor was patient perceptions; of health (self perceived disability; OR 3.02 (CI 2.48-3.57)) (**180**) and work (OR 6.4 (CI 1.6-26) (**174**). However, many of these associations yielded wide confidence intervals.

Mayou (2000) found no significant differences in RTW of participants according to HADS score at 12 months (**158**), therefore a regression analysis was not reported for depression and RTW. Of the studies which found depression to be an independent predictor of RTW, five were considered high quality, compared with two of the studies which failed to find an effect.

3.6. Discussion

The aim of the paper was to review whether depression remains a predictor of poorer work outcomes following MI, by reviewing the literature from the past 15 years. Our findings suggest that depression recorded between admission and up to two months post discharge can significantly predict poorer RTW outcomes 6 to 12 months after a cardiac event. There is also some evidence to suggest that increases in severity of depression can reduce likelihood of

RTW. Age and patient perceptions of their illness or work performance were also shown to significantly predict RTW in these populations.

Our first finding is consistent with earlier studies conducted in the 1980s (**160, 161**), which found depression to be a strong determinant of work outcomes. Hlatky et al (1986)(**161**) found depression to predict work disability outcomes (χ^2=20, p< 0.00001), and loss of employment in the year following CAD (p = 0.006). More specifically, MÆland and others (1987)(**160**) found that RTW rates were strongly related to level of depression reported by MI patients at hospitalization (χ2=20.74, p<0.05, *G*= -0.49) and 6 week follow-up (χ2= 11.30 p<0.05), and that this relationship was linear. Although this result appears in alignment with our second finding, it should be noted that a combined depression and anxiety measure was used in the MÆland study. The confounding effects of measuring these conditions using a composite instrument need to be considered.

Interestingly, both studies also found that alongside depression, patient perception was an important determinant of work status after a cardiac event. This was a finding observed in the current review, and elsewhere (Petrie et al, 1996)(**183**). This raises questions about the role of cognition as a mediating factor in the relationship between depression and work.

Overall, commonalities between past and present studies may suggest that while the management of cardiac patients has changed in recent years, the factors influencing recovery and RTW identified over 15 years ago remain relevant. Determining the extent to which depression can predict major QOL outcomes post MI is important due to its clinical applications to rehabilitation. Modern rehabilitation programs should not only ascertain participant intent to resume work, but assess and treat depression in order to facilitate recovery. In depressed populations, patients receiving depression treatment such as anti-depressants or psychotherapy are significantly more likely to maintain paid employment over

a 12-month period than those who do not (**184**). Workplace initiatives targeting depression could potentially improve retention rates for employees exhibiting depression after returning to work post MI. These findings are of further value as it has been argued that identifying depression as a predictor of RTW could "give insight into mechanisms underlying an association between depression and cardiac mortality and morbidity" (**158**).

The review methods that we report on have two significant shortcomings. First, several articles in the review included samples comprising participants either recruited from cardiac rehabilitation or who had received a surgical intervention, post infarct. While it is acknowledged that this reflects modern management of cardiac patients, this may have confounded the representativeness of these samples. Those experiencing co-morbid depression are often less likely to attend rehabilitation programs, and report higher withdrawal rates (**185**). As a result, depression may have been underrepresented in these samples. The inclusion of samples using participants who underwent surgical procedures may also have confounded results. These patients may experience added complications in the post operative period which prevent work resumption, or conversely, these procedures may promote better work outcomes, a finding which has been reported previously (**186**). A further issue related to sampling was the lack of representativeness of female participants (one third of the studies had all male participants). For example, after a cardiac event, men have been found to have a greater likelihood of returning to work in a full time capacity and are less likely to report depression than females (**187**). The inclusion of samples with only male participants may have both overrepresented RTW rates, and underrepresented the presence of depression. Female representation in this area of study is important when considering the proportion of those in paid employment at the time of MI has increased for both genders in recent times. For example in 1985, studies showed 34% of males and 18% of

females were employed at the time of MI (**188**) compared with 65% and 32% respectively in 1999 (**189**), which may reflect demographic changes of workforce participation, or a decrease in the average age of a cardiac event.

If we compare the studies that did and did not find an association between depression and RTW post-MI, while no clear methodological differences were observed, failure to control for gender may have been a potential issue. Of the seven studies reporting depression as a predictor of RTW, one included males only, compared with three of the studies not reporting significant results. In fact, of the studies which failed to show depression as a significant predictor of RTW post-MI, only one controlled for gender (Mayou (**158**)), which may have had an impact upon results.

Second, the wide variation between definitions of RTW and depression measures may have undermined comparability of the studies included in the review. It should be noted that the variance in depression assessment instruments used in these studies also meant inconsistencies in time frames over which participants were asked to report their depression symptoms (for example, the MMPI assesses depression over a 12 month preceding period, while HADS assesses depression over a four week period), which has implications on results. Although not the focus of the review, there is evidence to suggest that depression assessment tools vary in their sensitivity to detect depression as a predictor of RTW (**186**). Future studies in this area should consider this. Despite these limitations, our findings suggest that the majority of articles included in this review remained of moderate to high quality. In order to overcome the methodological limitations observed, we recommend the development and use of a brief, validated work measurement to capture employment outcomes, in order to enhance comparability of studies and allow for appropriate analyses of work outcomes.

While depression was found to be a significant factor influencing RTW at both 6 and 12 months post MI, further research is required to determine the long lasting effects of cardiac depression on job retention. As the studies included in the review did not report assessing clinical depression using diagnostic instruments but rather self-report inventories, it remains unclear whether treating depression would improve vocational outcomes. While there is evidence that treating depression symptoms can improve vocational outcomes in primary care attendees (e.g. Lo Sasso et al (**190**)), this is yet to be demonstrated in CVD populations.

Therefore, we recommend that future clinical trials evaluating the effectiveness of post MI depression treatment use RTW as an endpoint. Furthermore, only two of the studies included in this review examined the impact of pre-existing depression on RTW rates. With evidence suggesting that depression outcomes (persistent major depression, subthreshold depression, or remission) are strongly associated with the probability of maintaining paid employment in depressed populations (**191**), further research is required into how work outcomes may differ according to types of depression in cardiac populations. Distinguishing between transient depressive symptoms following a life threatening cardiac event, (which, in many cases are only captured by self-report inventories), and more stable clinical depression may be useful for anticipating longer term effects on functioning.

3.7. Acknowledgements

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3.8. Figures

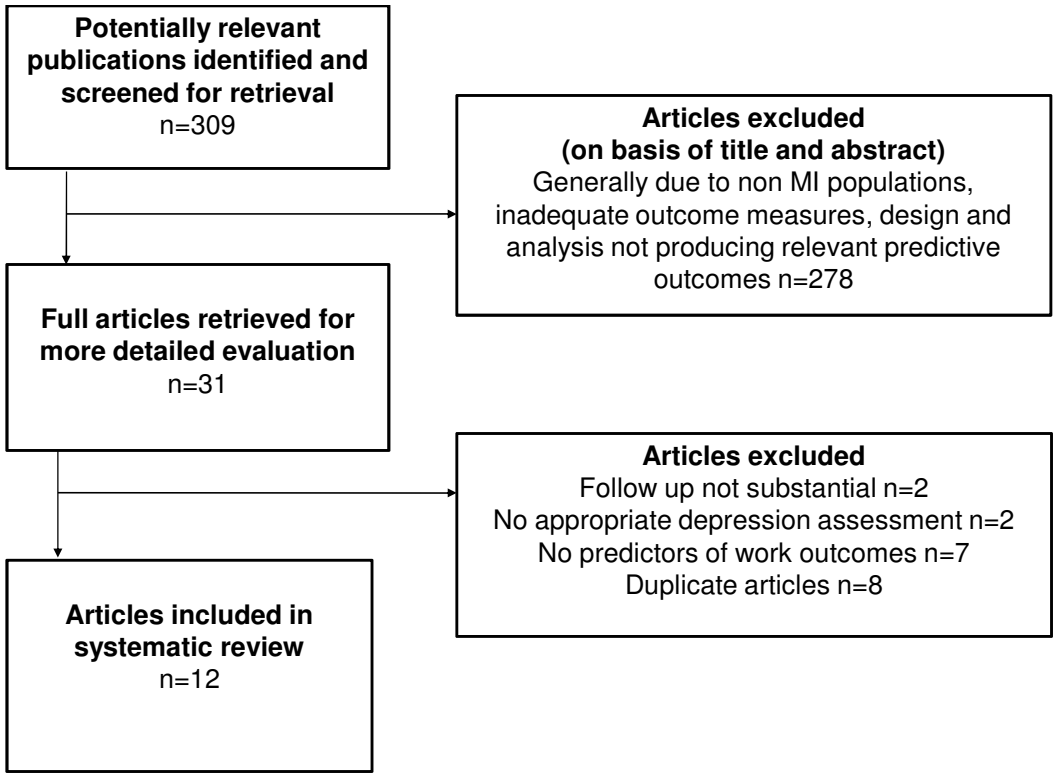

Figure 3.1. Flowchart of articles included in systematic review

3.9. Tables

Table 3.1. Search concepts and terms

Concepts	Terms
Predictors	Determinants, factors, influences, risk, psychological, clinical, social, psycho social
Work resumption	Return to work, loss of work, absenteeism
Recovery	Cardiac rehabilitation, adjustment, lifestyle
Employment	Work, full time, part time, workplace, vocation, job content, work limitations, productivity, work outcomes
Quality of Life	Impairment, functionality, activity
Demographic information	Age, gender, education, socio economic status, income
Chronic disease	Myocardial Infarction, Acute Coronary Syndrome, Cardiovascular disease, Coronary Heart Disease, Coronary Artery Disease, depression, psychological distress, morbidity, co-morbidity

Table 3.2. Quality of articles assessed using a framework for assessing internal validity (**173**)

Author	High 12 or more	Moderate 10-11	Low 9 or less
Bhattacharyya (2007) (**121**)	✓		
Brink (2008) (**177**)	✓		
Fukuoka (2009) (**175**)	✓		
Engblom (1994) (**174**)	✓		
Ladwig (1994) (**181**)			✓
Mayou (2000) (**158**)		✓	
McGee (2006) (**182**)	✓		
Mittag (2001) (**180**)		✓	
Soderman (2003) (**97**)		✓	
Soejima (1999) (**178**)	✓		
Sykes (2000) (**179**)		✓	
Samkange-Zeeb (2006) (**176**)	✓		

Table 3.3. Summary of population, data collection, endpoints of studies included in review

Authors	Population	Assessment points	Depression measure	Definition of Return to Work (RTW)
Bhattacharyya (2007) (**121**)	N=126 ACS patients	7-10 days after admission, 12 months	BDI	Patients were asked when they had started work again and whether they were working full time or part time.
Brink (2008) (**177**)	N=88 MI patients	4-6 months	HADS	Questionnaire about gainful employment, unemployment, early retirement, sick leave before and after MI
Fukuoka (2009) (**175**)	N=198 ACS patients	During hospitalisation, 2 and 6 months after hospital admission	BDI	Questionnaire about work status and the date participants returned to work. RTW was defined as starting back at work for more than 20 hours/week.
Engblom (1994) (**174**)	N=102 CABS male patients	Before CABG, 2 and 8 months after	BDI	Questionnaire, interview about work status (defined as paid employment, full or part time) and check of registry of Social Insurance Institution
Ladwig (1994) (**181**)	N=377 MI male patients	17-21 days after event, 6 months	Validated 12-item version of depression composed of three subscales with rank-ordered ratings from 1 to 3	Patients were asked to complete a questionnaire about vocational and social status at the time of participation. 'Have you returned to work?'
Mayou (2000) (**158**)	N=344 MI patients	3 days after admission, 3 and 12 months	HADS	Insufficient
McGee (2006) (**182**)	N=363 ACS patients	In hospital, 12 months	BDI –FS, HADS-D	Questionnaire about RTW (full or part time employment)
Mittag (2001) (**180**)	N=119 males post MI or CABG patients	During hospitalisation, 12 months	CES-D/ADS Depression	Postal questionnaire, asking whether participants had resumed their occupations, if they were working in their former job or had changed to some other workplace, and if they were working full time or not.
Soderman (2003) (**97**)	N=198 CABG, PCTA patients	"Start of program," end of four week residential stay, 12 months	BDI	RTW was measured in two different ways, (a) RTW at full-time (100% of earlier working hours), and (b) RTW at reduced working hours
Soejima (1999) (**178**)	N=111 married males AMI patients	Average 24.8 days post admission (in hospital) Average 8 months	Cornell Medical Index, 6 item depression index	Three measures of RTW: whether participant had returned to work, interval in days between hospital discharge and resumption of work, and estimates of activity level at work compared with before MI
Sykes (2000) (**179**)	N=149 MI patients	Baseline was pre discharge upon stabilising of condition and again at 12 months	Subscale of MMPI	Employment status was defined as returned to work or not, with information collected on patient occupation, Social Economic Status and work strain
Samkange-Zeeb (2006) (**176**)	N= 620 CHD patients	Beginning of rehab, 6 and 12months post rehab	HADS (adjusted for Germany)	Current working situation and questionnaire on intention to RTW, disability and profession

Table 3.4. Summary of effect of depression predicting likelihood of RTW post-MI at 6-8 and 12-13 months

Author	Finding	Ratio	Depression severity	Estimate of relative risk	CI (95%)	P value	Variables included in multivariate analysis** (bold indicates significance)
DEPRESSION SIGNIFICANTLY PREDICTED RTW							
6-8 MONTHS							
Fukuoka (2009) (**175**)	As a time-dependent covariate, increases in depression score predicted slower RTW at 6 months	Adjusted Hazard ratio*	Moderate depression Severe depression	0.47 0.37	0.31-0.72 0.21-0.66	<0.001 0.001	Age, sex, nationality, education, income, marital status, smoking, hyperlipidemia, Duke activity index score (physical functioning), job strain, **job satisfaction,** job security, **working hours per week, shift work,** social support (from supervisor, co-workers)
Samkange-Zeeb (2006) (**176**)	Level of depression was significant predictor of RTW at 6 months	Adjusted Odds ratio	Borderline depression Clinical depression	0.62 0.28	0.35-1.12 0.14-0.58		**Age,** sex, profession, anxiety, **expectations about work incapacity and desire to RTW**
Soejima (1999) (**178**)	Depressed patients less likely to RTW at 8 months	Adjusted Odds ratio		0.15	0.02–0.87	<0.031	**Age**, education, occupation, **personality type** health locus of control
12-13 MONTHS							
McGee (2006) (**182**)	Baseline depression significantly predicted RTW at 12 months	Adjusted Odds ratio	HADS depression	0.2	0.06–0.6	0.007	Prior ACS, age and sex
Sykes (2000) (**179**)	Depression significant predictor of RTW at 12 months	Wald test		7.335 (df=1)		0.0068	**Decision latitude, work social interaction, age, medical prognosis (Coronary Prognostic Index)**
Samkange-Zeeb (2006) (**176**)	Level of depression was significant predictor of RTW at 12 months	Adjusted Odds ratio	Borderline depression Clinical depression	0.35 0.24	0.18-0.68 0.11-0.49		**Age**, sex**, profession**, anxiety, **expectations about work incapacity and desire to RTW**
Soderman (2003) (**97**)	Clinical depression (BDI >16) predicted RTW at 12 months	Adjusted Odds ratio	Clinical depression Mild depression Clinical depression Mild depression	9.43 (fulltime) 2.89 (fulltime) 5.44 (reduced hours) OR not shown	3.15-28.21 1.08–7.70 1.60-18.53	<0.001 0.0300 <0.0068 0.7848	Gender, **age, education**, exercise capacity
Bhattacharyya	Every increase in BDI	Adjusted		0.90	0.82-0.99	0.032	Age, gender, risk of cardiac event,

(**121**) (2007)	index reduced likelihood of RTW at 12-13 months	Odds ratio					heart failure, antidepressant use, **Arrhythmia during admission, recurrent cardiac events**
DEPRESSION DID NOT SIGNIFICANTLY PREDICT RTW							
6-12 MONTHS		**Significant predictors**					
Brink (**177**)	Somatic health better predictor of RTW than mental health at 6 months	Adjusted Odds ratio	Physical health component score	1.08	1.02-1.14	0.011	**Physical health,** age, **footsteps per day**
			Footsteps per day	1.18	1.01-1.38	0.033	
Ladwig (1994) (**181**)	Depression as a significant predictor of RTW at 6 months (OR: 0.39, Cl 0.18-0.88), was lost after adjustment for age, social class, rehabilitation, recurrent infarction, cardiac events, helplessness (OR: 0.54 CI 0.22-1.31)		-				
Mayou (2000) (**158**)	No significant differences in RTW between distressed and nondistressed at 12 months		-				
Engblom (**174**)	At 12 months, patients' expectations of work, duration of absence from work before CABS and physical capacity of patients after surgery are important determinants of RTW after CABS	Adjusted Odds ratio	Self assessed work capacity at six months (Good vs Poor)	8.5	2.3-32.0	0.003	Type of rehabilitation, previous MI, **expectations regarding work**, physical strain of work, **duration of the preoperative absence from work,** basic education, professional education, socioeconomic status, preoperative BDI score, final work load at exercise test, **functional class, patients' perception of working capacity at 6 months after the CABS**.
			Functional Class (Canadian CVD class I vs II-III)	6.7	1.8-24.5	0.006	
			Patient expectation about work (RTW vs retire)	6.4	1.6-26.0	0.013	
			Absence from work before the CABS (3 months or less)	4.9	1.2-20.2	0.032	
Mittag (**180**)	Three variables predicted RTW at 12 months in 85% of all cases: (1) age, (2) patients' feelings about disability (3) physicians' views on the extent to which vocationally disabled	Adjusted Odds ratio	Age	1.22	1.10-1.34	<0.01	Results of exercise testing, optimistic coping style, family income, negative incentives for RTW, physicians' subjective prognosis as to re-employment, patients' wish to return to work, **age, self perceived vocational disability, physician's perception of patient disability**.
			Self perceived disability	3.02	2.48-3.57	<0.001	
			Physician's view of disability	1.61	1.16-2.07	<0.05	

3.10. Additional Table

Table 3.5. Quality criteria

SAMPLE	
1.	Inclusion criteria defined
2.	Time of baseline data collection clearly stated
3.	Representative sampling
4.	Clinical/Demographic/ other important characteristics described
5.	Study setting and site clearly described
6.	Measures/data collection applied at appropriate assessment points for the research
PROGNOSTIC INDICATORS	
1.	The variables are clearly defined
2.	Measures used are justified
3.	The multifactorial nature of RTW is recognised.
4.	Study uses standardise, valid instruments to take measurements
ANALYSIS	
1.	Multivariate techniques used to adjust for confounding variables
2.	Analysis avoided “overfitting the data”
3.	Prospective validation in another cohort was performed
PATIENT FOLLOW UP	
1.	RTW outcome was defined (or measure of absence)
2.	Duration of follow up greater or equal to 6 months
3.	Complete data on at least 80% of sample (measured at baseline)
4.	Outcome measures were blinded (not revealed to patients)

Chapter 4: THE HEALTH RELATED QUALITY OF LIFE BURDEN OF CO-MORBID CARDIOVASCUALR DISEASE AND MAJOR DEPRESSIVE DISORDER IN AUSTRALIA: FINDINGS FROM A POPULATION-BASED, CROSS-SECTIONAL STUDY

Chapter Overview

Having established the national burden of co-morbid CVD and depression on vocational functioning and the prognostic role of depression on RTW after a cardiac event, the current HRQOL burden of depression and CVD needs to be established if we are to identify effective treatment for improving, not only vocational outcomes, but mental and physical health functioning in this population. This chapter aims to determine the current HRQOL burden of co-morbid CVD and depression in Australia. Here, the synergistic effect of these conditions on HRQOL will be explored as well as potential differences in the dose-response relationship between HRQOL and depression in those with and without CVD.

Citation: O'Neil A, Stevenson CE, Williams ED, Mortimer D, Oldenburg B, Sanderson K. The Health Related Quality of Life burden of co-morbid Cardiovascular Disease and major depressive disorder in Australia. Findings from a population-based, cross-sectional study. *Quality of Life Research*. Accepted, 20 January 2012.

4.1. Publication Declaration

Declaration for Thesis Chapter [4]

Declaration by candidate

In the case of Chapter [4], the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
AO co-conceptualised and refined the concept of the paper, accessed the data, conducted statistical analysis and interpretation, wrote the original version, refined subsequent versions of the manuscript and submitted the final version.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Chris Stevenson	Assisted with statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A
Emily Williams	Assisted with statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A
Duncan Mortimer	Provided expertise on data collection instrument, assisted with statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A
Brian Oldenburg	Critically revised the fi nal version of the script.	N/A
Kristy Sanderson	Conceptualized the paper, refined conceptualization, oversaw statistical analysis and interpretation, critically revised drafts of the manuscript.	N/A

Candidate's Signature	[redacted]	Date: 8.8.2011

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Public Health and Preventive Medicine Monash University Alfred Campus

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

			Date
Signature 1	CS	[redacted]	24/08/20[illegible]
Signature 2	EW		16/08/2011
Signature 3	DM		8/08/2011
Signature 4	BO		8/9/2011
Signature 5	KS		16/08/2011

4.2. Abstract

Purpose: Health Related Quality of Life (HRQOL) can be significantly impaired by the presence of chronic conditions such as cardiovascular disease (CVD) and major depressive disorder (MDD). The aim of this paper was to: (1) identify differences in HRQOL between individuals with CVD, MDD, or both, compared to a healthy reference group, (2) establish whether the influence of co-morbid MDD and CVD on HRQOL is additive or synergistic, (3) determine the way in which depression severity interacts with CVD to influence overall HRQOL.

Methods: Population-based data from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB)(n=8841) were used to compare HRQOL of individuals with MDD and CVD, MDD but not CVD, CVD but not MDD, with a healthy reference group. HRQOL was measured using the Assessment of Quality of Life (AQOL). MDD was identified using the Composite International Diagnostic Interview (CIDI 3.0).

Results: Of all four groups, individuals with co-morbid CVD and depression reported the greatest deficits in AQOL utility scores (Coef:-0.32, 95% CI:-0.40,-0.23), after adjusting for covariates. Those with MDD only (Coef: -0.27, 95% CI: -0.30, -0.24) and CVD only (Coef: -0.08, 95% CI: -0.11, -0.05) also reported reduced AQOL utility scores. Second, the influence of MDD and CVD on HRQOL was shown to be additive, rather than synergistic. Third, a significant dose-response relationship was observed between depression severity and HRQOL. However, CVD and depression severity appeared to act independently of each other in impacting HRQOL.

Conclusions: HRQOL is greatly impaired in individuals with co-morbid MDD and CVD; these conditions appear to influence HRQOL in an additive fashion. HRQOL alters with depression severity, therefore treating depression and improving HRQOL is of clinical importance.

Key words: health related quality of life, depression, cardiovascular disease, dose-response, synergistic

4.3. Introduction

Globally, cardiovascular disease (CVD) is the leading cause of premature death (**2**) and major depressive disorder (MDD) the top-ranking cause of disability (**3**). While individually, the health and economic burden of these conditions is great, it is substantially more pronounced when the two conditions co-occur. For example, patients with CVD such as myocardial infarction (MI) who report MDD are significantly more likely to experience poorer health outcomes including increased morbidity, mortality (including suicide) (**9**) and Coronary Heart Disease (CHD) risk factor profiles, compared with those without depressive symptoms.

4.3.1 Relationship between CVD, depression and Health Related Quality Of Life (HRQOL)

While the relationship between MDD and CVD has been extensively researched over the past 20 years, more recently the role of HRQOL in this relationship has become of interest. Although there are a range of definitions, HRQOL most often comprises key aspects of functioning, including mental, physical and social functioning. For coronary patients, HRQOL outcomes have been shown to be as important as any potential survival outcomes, in some cases, of greater importance. Of survival gain, Rumsfeld and Ho (2009) argue that the benefits are "...limited to specific patient subsets and many patients express a desire for quality of life equal to or greater than their desire for quantity of life" (**82**). There is compelling evidence that depression is the best predictor of HRQOL in MI populations, both in the short (**73**) and long term (**88**). The importance of the role of depression in the HRQOL of CVD patients has been highlighted when the influence of mental health, as distinct from physical health (**77**), has been examined. Findings from the Heart and Soul study identified depression, over physiological factors like left ventricular ejection fraction and ischemia, as having the most

important influence on HRQOL of cardiac patients. In fact, this association is such that a dose-response relationship exists between HRQOL and depression.

4.3.2 Dose-response relationship between HRQOL and depression

Cross-sectional (**77**) and other studies (**192**) indicate that depression severity increases synchronously with HRQOL impairments. This dose-response relationship has been demonstrated in cardiac, as well as other, populations. However, the way in which the relationship between depression and HRQOL is attenuated by the presence of CVD remains less clear. Because HRQOL encompasses both physical and mental health functioning, it would be expected that the presence of co-morbid depression and CVD, compared with the presence of major depression alone, would exacerbate the effect between HRQOL and depression observed in previous studies. However, to our knowledge there is limited evidence to support this assertion. An understanding of the way in which depression severity interacts with CVD to influence overall HRQOL is required to aid our knowledge of the complex relationship between CVD, depression and HRQOL.

4.3.3 The impact of co-morbid depression and CVD on HRQOL: synergistic or additive?

Indeed, the relative impact of chronic medical co-morbidities on HRQOL has been investigated in order to determine whether the impact of disease on HRQOL is synergistic or additive in nature. An additive effect suggests that the combined effect of MDD and CVD on HRQOL would approximate the sum of the independent effect of each of these conditions, whereas a synergistic relationship suggests that the combined effect is "greater than the sum of the independent effect of each of these conditions" (**193**). To date, research exploring the additive and synergistic effects of medical co-morbidities on HRQOL has revealed disparate results, across disease populations. For individuals with diabetes and other chronic medical co-

morbidities, the impact of co-morbid conditions on HRQOL has been shown to be additive, rather than synergistic (**193**). In contrast, research comprising Hepatitis C (**194**) populations has revealed a synergistic influence of MDD and disease on HRQOL. In those with CVD and diabetes specifically, these conditions have been found to significantly interact with one another to result in poorer functioning (**195**).

Previous research conducted in the 1980's suggested that MDD and CVD may have an additive effect on wellbeing and functioning; the combination of heart disease and depression was shown to cause almost twice the social impairment caused by either condition alone (**196**). However, the current understanding of the impact of MDD and CVD on HRQOL using appropriate instruments, specifically designed to detect differences in HRQOL, is limited. Identifying whether a synergistic relationship exists between these two conditions in relation to HRQOL is important for two key reasons. A condition such as MDD may affect a patient's behavior in an adverse manner, thereby impacting negatively on treatment outcomes for CVD (**197**). Alternatively, treating one condition may subsequently impact on the other pre-existing condition, resulting in lower HRQOL than would be expected as a result of the pre-existing condition on its own.

The aim of the paper was to address the current research gaps by using the Assessment of Quality of Life (AQOL) instrument to: (1) identify differences in HRQOL between individuals with CVD, MDD, or both, compared to a healthy reference group, (2) establish whether the influence of co-morbid MDD and CVD on HRQOL is additive or synergistic, (3) determine the way in which depression severity interacts with CVD to influence overall HRQOL.

4.4. Methods

4.4.1 Study design and sampling

Cross-sectional, population-based data from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB) were used. This methodology has been described in detail elsewhere (**128**). Briefly, the sample was based on a stratified, multistage probability sample of persons aged 16-85 years living in private dwellings in Australia, excluding very remote areas. The overall response rate was 60%, totalling 8841 participants. AQOL utility scores were available for 8820 participants.

4.4.2 Participants

Respondents with depression in the last 12 months were identified using the Composite International Diagnostic Interview (CIDI 3.0)(**198**), one of the most widely-used, structured diagnostic interviews for psychiatric disorders in the world. Diagnostically, MDD is characterised by the presence of severely depressed mood persisting for at least two weeks (**132**). Respondents were identified as having CVD on the basis of their response to the question 'have you had or been treated for a (new or recurrent) CVD condition (e.g. heart attack, angina, high blood pressure) over the past 12 months?' Research has shown a good correlation between self-reported chronic diseases, such as diabetes, heart disease and asthma and those identified in medical records (e.g. Kappa=0.85 for diabetes mellitus (**133**)). This process allowed us to classify people as those (1) without MDD or CVD, (2) with MDD but not CVD, (3) with CVD but not MDD, (4) with both MDD and CVD.

4.4.3 Data collection instruments

Depression and CVD

Between August and December 2007, specially-trained ABS interviewers carried out the assessments at participants' private dwellings. All interviews were conducted using a computer assisted interview which involved the use of a notebook computer to record, store, and transmit the collected data. The CIDI 3.0 was administered to diagnose depression. Information was collected to differentiate between three types of depressive episodes, based on the number of symptoms experienced by the participant: Severe Depressive Episode (depressed mood; loss of interest in activities; lack of energy or increased fatigue; and additional symptoms (to total at least eight symptoms)); Moderate Depressive Episode (at least two of the first three symptoms given above and additional symptoms (to total at least six symptoms)); Mild Depressive Episode (at least two of the first three symptoms from the above list and additional symptoms (to total at least four symptoms)(**128**). The time frame of 12 months was selected for each condition to best reflect participants' current disease status.

Health Related Quality Of Life

The Assessment of Quality of Life (AQOL-4D) instrument (**199**) was used to assess HRQOL. It was originally developed to increase the sensitivity of multi-attribute utility measurement and has the ability to detect nuanced differences in HRQOL- including mental health (**200**). The AQOL-4D was the first HRQOL instrument to independently model all the sub-dimensions of health (independent living, social relationships, physical senses, psychological well-being, and illness) and combine sub-models to obtain a multi-attribute utility score (**200**). Scores from the first 4 dimensions form the multi-attribute utility score. Each individual dimension is weighted to produce a dimension score between 'dimension worst' (0.0) and 'dimension best' (1.0) health states. Dimension scores are then combined to obtain an overall utility score ranging from worst possible HRQOL state (–0.04) to death (0.00) to full HRQOL (1.00). The AQOL-4D measure has maintained structural independence between health dimensions while

simultaneously obtaining a high degree of descriptive sensitivity (**200**). Based on Receiver Operator Characteristic (ROC) curve analyses and relative efficiency estimates, Osborne (2003) concluded that this is a sensitive and responsive HRQOL measure (**201**). Because of its robust psychometric properties and the brevity of the scale, the AQOL-4D is considered a suitable instrument for epidemiologic studies where HRQOL and utility data are required. The AQOL-4D has also been used in mental health (**202**) and cardiac populations (**203**).

Co-variates

Demographic information included age, sex, registered marital status, area socioeconomic disadvantage (Decile 1-10; where 1=most disadvantage and 10=least disadvantage)) (**128**), country of birth, main language spoken at home (English, other), rurality (residing in major urban, other urban, other) (**128**), education (dichotomised into pre- and post-graduate attainment) (**128**). Data were also collected to measure participants' body mass index (BMI) (calculated using the standard equation of weight divided by height squared (**135**)), psychological distress (Kessler-10)) (**136**) and current smoking status (**128**). Social support was measured according to frequency of social networking with friends and family (nearly every day, 3-4 days a week, 1-2 days a week, 1-3 days a month, less than once a month; or never). Physical activity in the past week (number of times spent walking for recreation, exercise or gain) was measured using a widely used and validated instrument (**128, 204**).

4.4.4 Data analysis

Data were provided by the Australian Bureau of Statistics from a Confidentialized Unit Record File. Estimates and standard errors (SE) were derived using a complex estimation procedure to account for the stratified multistage survey design, oversampling and non-response (**128**), using the Jackknife delete-2 technique. The use of Jackknife techniques is commonly used for the analysis of complex survey data. It involves deleting one sample primary sampling unit

(PSU) at a time to form replicates, and reweighting every replicate as necessary in order to make inference to the population represented by the full sample. Using these replicates, it is possible to calculate the standard error, using the delete-a-group Jackknife standard error estimator (**205**). Probability (sampling) weights were applied to weight the sample back to the population from which the sample was drawn.

Using methods described by Hosmer and Lemeshow (2000), linear regression was performed to assess differences in AQOL utility scores across disease groups, the synergistic effect of disease on HRQOL, and dose-response effects between AQOL utility scores and recent depression severity over the past 12 months. Algorithms for AQOL scoring were obtained from http://www.aqol.com.au/scoring-algorithms.html. Where negatively skewed (AQOL utility scores), data were transformed using the appropriate log transformations ($\log_e$ transformation^3). Post-estimation tests were conducted for final regression models. Measures of magnitude were presented as adjusted Coefficients with Jackknife SEs and 95% confidence intervals (CIs). Synergistic effects of CVD and MDD were assessed by the addition of a CVD/MDD interaction to a model containing separate main effects terms: CVD over the past 12 months (yes/no) and MDD over the past 12 months (yes/no). Stata 11 (survey procedures) was used for all statistical analyses. STROBE guidelines (20) were applied for the reporting of cross-sectional studies.

4.5. Results

The key characteristics for all survey participants are displayed in Table 1, by disease status (n=8841). Those belonging to the healthy reference group comprised the greatest proportion of individuals with a post-graduate education and non English speaking individuals. Those with co-morbid CVD and MDD had the highest proportion of individuals belonging to a lower socio-economic bracket, reporting lowest physical activity frequency, and highest

psychological distress and BMI. Those with MDD only reported the youngest mean age. Of those belonging to this sub-group, almost two thirds were single/not married. This sub-group comprised the greatest proportion of smokers and the most frequent physical activity over the previous week. Those with CVD only were least likely to be single, reported the highest mean age of CVD onset and mean age. Approximately 10% of the overall sample (10.3%, 95% CI: 9.6, 11.1) reported having ever received helpful or effective treatment for depressive symptoms (sadness/lack of interest); 28.3% (95% CI: 20.4, 36.2) of the MDD and CVD group and 30.7% (95% CI 27.6, 33.9) of the MDD only group.

AQOL utility scores were available for 8820 participants. Of those respondents for whom AQOL utility scores were not available (n=21), none belonged to the co-morbid CVD/MDD group; 13 belonged to the reference group, three were from the MDD only group and five were from the CVD only group. Overall, they were older, comprised more males, belonged to a lower socio-economic bracket and reported higher psychological distress, when compared with those for whom full data were available. After controlling for sex, age, marital status, education, area disadvantage, rurality, smoking, social support, BMI, employment status, a multivariate linear regression model revealed significant impairments in AQOL utility scores in all three disease groups, compared with a healthy reference group (Table 2). Of all the groups, individuals with co-morbid depression and CVD reported the lowest AQOL utility scores (Coef: -0.32, 95% CI: -0.40, -0.23). Those with MDD only (Coef: -0.27, 95% CI: -0.30, -0.24) and CVD only (Coef: -0.08, 95% CI: -0.11, -0.05) also reported reduced AQOL utility scores. In addition to exploring the impact of disease on overall AQOL utility score, we re-ran these analyses for each AQOL dimension (independent living, social relationships, physical senses, mental health). We observed similar trends in impairment by disease group for each dimension of HRQOL (data not shown).

To explore whether the impact of this co-morbidity was additive or synergistic, we undertook another multivariate linear regression analysis. After adjusting for sex, age, marital status, education, area disadvantage, rurality, smoking, social support, BMI and employment status, the model revealed a non-significant interaction between CVD and MDD (Adjusted Coefficient: 0.03, 95% CI: -0.06, 0.12; p=0.52), suggesting the relationship may be additive, rather than synergistic.

Next, we explored whether a dose-response relationship exists between MDD severity and HRQOL. After adjusting for sex, age, marital status, smoking, social support, BMI, employment status and CVD-MDD severity interaction, a regression model revealed a significant relationship between MDD severity and HRQOL (Mild; Coef: -0.16, 95% CI: -0.20, -0.12, Moderate; Coef: -0.28, 95% CI: -0.32, -0.24, Severe; Coef: -0.47, 95% CI: -0.51, -0.43) (Table 3). This relationship is displayed in Figure 4.1, where an increase in depression severity is shown to be associated with greater deficits in AQOL utility score. We then entered CVD and MDD severity into the model as an interaction term. The interaction failed to reach significance, suggesting that CVD and depression severity may act independently to impact HRQOL, rather than synergistically.

4.6. Discussion

Our finding that impairments in HRQOL are greatest for those with co-morbid MDD and CVD, is consistent with studies of clinical populations which have demonstrated the magnified effects of this co-morbidity on HRQOL (**73**). These results add to the literature by providing robust evidence of these disease related impairments at the population level. Our findings are potentially more representative than other studies, where estimates derived from clinical populations may be skewed towards more severe health states. While our second finding, that the influence of MDD and CVD on HRQOL is additive, rather than synergistic, is consistent

with some studies of other medical co-morbidities on HRQOL (**193**), to our knowledge, ours is the first to attempt to disentangle the independent effects of CVD and MDD on HRQOL, using a measure of HRQOL which specifically detects nuanced differences in HRQOL (**200**). Third, our finding of a significant dose-response relationship between depression severity and HRQOL, while consistent with studies comprising Coronary Artery Disease populations (**77**), adds to the existing literature because, to our knowledge, this is also the first time this has been demonstrated in those with CVD, at the population level. We chose to compare our findings with those of clinical populations as we would expect those studies comprising MI patient samples to show a more pronounced dose-response effect between depression and HRQOL because of the recency of the cardiac event and the likelihood of depression occurring in the first six months, post-MI (**206**). Our study provides a broader view of the relationship between depression and HRQOL in a wide sample of individuals affected by a range of CVD, not restricted only to those hospitalized as a result of MI. Thus, our results are potentially more generalizable to the wider CVD population, in addition to those experiencing post-MI depression.

Indeed, our findings highlight the influence of co-morbid depression (particularly of increasing severity) and CVD on HRQOL status. There are a range of explanations regarding the mechanisms which link MDD and CVD to HRQOL. The observed deficits in HRQOL for those with co-morbid CVD and MDD may reflect physical illness of greater severity which subsequently intensifies depression severity. Conversely, increasing depression severity may exacerbate an individuals' perception of their functional impairments. Indeed, our findings suggest that depression severity is a stronger contributor to HRQOL impairments than CVD; the presence of CVD does not appear to attenuate the dose-response effects previously observed between depression and HRQOL (**77**). Depression management has been shown to

improve HRQOL in patients with depression (**207**). However, in co-morbid populations, given that the effects of MDD and CVD appear to act independently of each other, we recommend that cardiac rehabilitation programs which address lifestyle factors be incorporated into depression treatment programs if overall HRQOL status (particularly physical functioning) is to be improved. We further recommend that randomised controlled trials which evaluate the benefits of combined depression treatment and lifestyle modification programs in CVD patients exhibiting depression be undertaken, with the inclusion of HRQOL endpoints. Furthermore, the cost-effectiveness of such a program should be evaluated from the perspective of each of the responsible fund-holders (e.g. hospital cost-centers, hospital/health network, state/federal health budgets) to determine the possible business case for wide scale implementation (**149**). Where routine depression treatment is seldom available after a cardiac event, and participation in cardiac rehabilitation programs is often low, offering alternative approaches to treatment after a cardiac event could potentially reduce the HRQOL burden. Contemporary approaches to treatment using tele-health or web-based interventions could promote uptake and adherence to rehabilitation, where various logistic and other barriers (including depressive symptoms) have been shown to impede participation (**208**).

A strength of this study was the administration of a diagnostic interview to assess MDD and the use of the AQOL instrument and the utility scores it generates. A further advantage of this study was its robustness and representativeness due to the use of a large, probability sample from the general population. Third, the use of the AQOL instrument to measure HRQOL is advantageous; it has been shown to have sound instrument sensitivity where other HRQOL instrument sensitivity is questionable (**209**). However, several limitations were observed. The cross-sectional design of the study precludes us from determining causality, or the long term impact of co-morbid depression and CVD on HRQOL in this population. Additional research

could use longitudinal or panel studies to explore HRQOL trajectory and associated costs over time. Secondly, in the absence of objective data, CVD status was determined by self report. Further, CVD was defined as "any heart or circulatory condition". These measures may have led to recall bias, misclassification or incorrect identification of CVD and possible dilution of the CVD effect.

4.7. Conclusions

Our assessment of the impact of co-morbid MDD and CVD on HRQOL at the population level, as distinct from clinical populations, provides an important snapshot of the current burden of, and interaction between, CVD and a high prevalence mental health disorder like depression in the general population. Due to their increasing prevalence in ageing Western populations, minimising the burden of their consequences at the population level through prevention and appropriate management remains paramount.

4.8. Abbreviations

CVD = Cardiovascular disease

MDD = Major Depressive Disorder

MI= Myocardial Infarction

CHD = Coronary Heart Disease

HRQOL = Health Related Quality of Life

NSMHWB = National Survey of Mental Health and Wellbeing

CIDI 3.0 = Composite International Diagnostic Interview 3.0

AQOL-4D = Assessment of Quality of Life

BMI = Body Mass Index

SE = Standard Errors

CI = Confidence Intervals

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

4.9. Competing Interests

The authors have no competing interests to declare.

4.10. Acknowledgements & Funding

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4.11. Figures

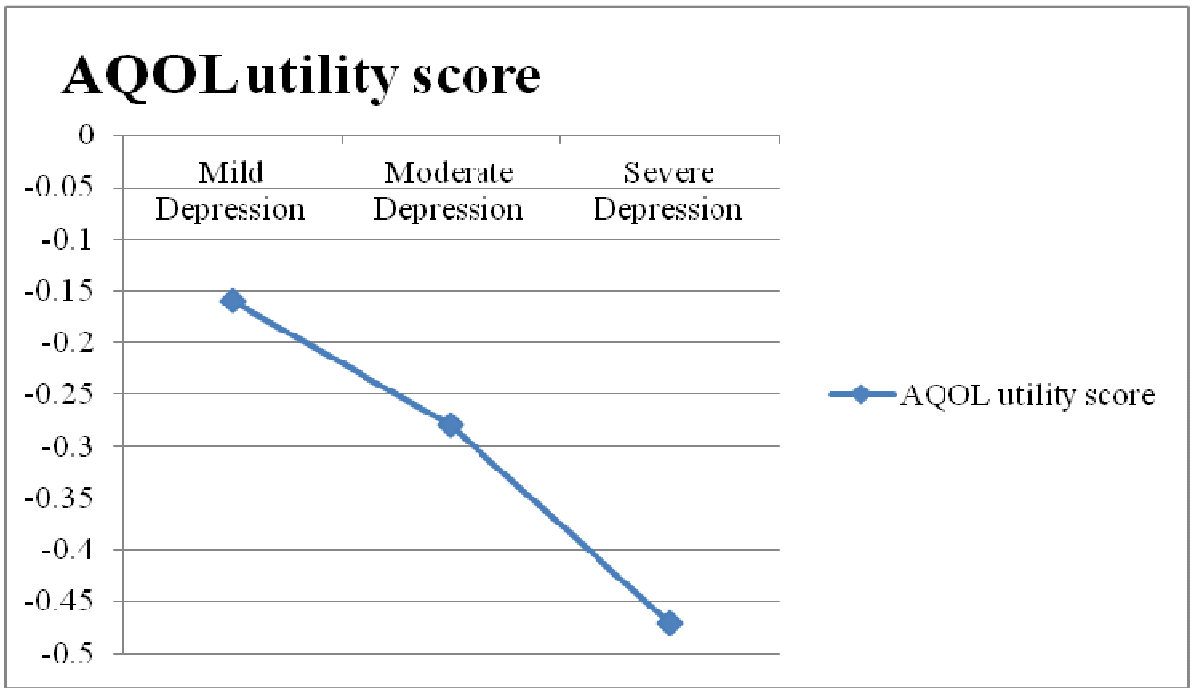

Figure 4.1. Dose-reponse relationship between AQOL utility score and depression severity

4.12. Tables

Table 4.1. Key characteristics of all survey participants, by disease group (n=8841)[a]

	(1) Neither MDD nor CVD n=6,079 Mean /Percentage (95% CI)	(2) MDD only n=1326 Mean /Percentage (95% CI)	(3) CVD only n=1,223 Mean /Percentage (95% CI)	(4) Co-morbid MDD & CVD n=213 Mean /Percentage (95% CI)
Age	42.50 (42.17, 42.81)	36.68 (35.71, 37.64)	62.06 (60.86, 63.25)	54.63 (52.08, 57.18)
Sex (male)	50.62 % (49.70, 51.56)	45.44% (41.44, 49.43)	51.00 (47.46, 54.44)	40.89 (30.32, 51.46)
AQOL utility score[b]	0.87 (0.87, 0.88)[d]	0.69 (0.67, 0.71)	0.78 (0.76, 0.80)	0.57 (0.51, 0.64)
Country of birth				
Australia	71.24 (69.31, 73.16)	80.86 (77.60, 84.12)	71.64 (66.62, 76.65)	75.00 (66.09, 83.90)
Other English speaking country	11.20 (10.15, 12.26)	9.74 (7.71, 11.76)	13.52 (10.84, 16.19)	13.25 (6.67, 19.83)
Non English speaking country	17.56 (15.83, 19.28)	9.40 (7.17, 11.64)	14.84 (10.64, 19.04)	11.75 (6.24, 17.26)
Main language spoken at home				
English	90.40 (89.15, 91.66)	94.17 (91.62, 96.73)	92.69 (89.45, 95.94)	96.37 (92.54, 100)
Registered marital status (single)	46.51 (44.97, 48.05)	64.71 (60.15, 69.26)	28.73 (25.00, 32.46)	41.16 (31.63, 50.69)
Post graduate qualifications (yes)	57.03 (55.64, 58.43)	51.94 (48.28, 55.60)	46.82 (42.50, 51.14)	48.44 (37.75, 59.13)
Level of Area social economic disadvantage (Decile 1-5)[c]	44.68 (42.48, 46.88)	46.74 (42.31, 51.18)	49.15 (44.30, 54.00)	57.48 (46.35, 68.60)
Psychological distress (Moderate to high distress)	20.67 (19.23, 22.11)	64.31 (60.74, 67.87)	24.08 (19.81, 28.35)	68.95 (56.89, 81.20)
Smoke (yes)	20.59 (19.02, 22.17)	38.46 (34.36, 42.56)	10.60 (8.15, 13.04)	28.00 (16.07, 39.93)
Body Mass Index[b]	26.02 (25.83, 26.21)	25.88 (25.46, 26.30)	28.60 (28.14, 29.06)	30.37 (28.38, 32.36)
Age of first CVD event	-	-	50.81 (49.54, 52.09)	45.71 (43.22, 48.20)
Frequency of physical activity in past week[b]	5.21 (4.87, 5.54)	5.56 (4.95, 6.18)	4.27 (3.59, 4.94)	4.17 (2.66, 5.68)
Depression severity (n %)				
None	6079 (100%)	-	1223 (100%)	
Mild	-	465 (35%)	-	69 (33%)
Moderate	-	473 (36%)	-	88 (41%)
Severe	-	388 (29%)	-	56 (26%)

[a] Person weighted, survey corrected means and 95% confidence intervals; [b]does not include all participants due to missing data; [c]Most disadvantaged; [d]The population norm for the AQOL utility score is 0.83 (SD 0.20) (**210**).

Table 4.2. Linear regression model for the relationship between log-transformed AQOL utility scores and disease status (n=8820)

Disease group	Univariate Co-efficient	Adjusted Co-efficient[a]	p	95% CI[a]	
Neither CVD nor MDD	1.0	1.0			
MDD only	-0.27	-0.27	<0.00	-0.30	-0.24
CVD only	-0.15	-0.08	<0.00	-0.11	-0.05
Co-morbid MDD and CVD	-0.40	-0.32	<0.00	-0.40	-0.23

[a]Adjusted for sex, age, marital status, education, area disadvantage, rurality, smoking, social support, BMI, employment status

Table 4.3. Linear regression model assessing dose-response relationship between depression severity and AQOL utility scores (n=8820)

Depression severity	Univariate Co-efficient	Adjusted Co-efficient[a]	p	95% CI
Mild	-0.14	-0.16	<0.00	-0.20, -0.12
Moderate	-0.29	-0.28	<0.00	-0.32, -0.24
Severe	-0.50	-0.47	<0.00	-0.51, -0.43
CVD-Mild depression Interaction	0.05	0.06	0.47	-0.11, 0.23
CVD-Moderate depression Interaction	-0.03	-0.01	0.73	-0.09 0.07
CVD-Severe depression Interaction	0.05	0.04	0.26	-0.03 0.12

[a]Adjusted for sex, age, marital status, smoking, social support, BMI, employment status, CVD-MDD severity interaction

Chapter 5: EVALUATING DEPRESSION TREATMENT INTERVENTIONS IN CORONARY HEART DISEASE POPULATIONS

Chapter Overview

Having highlighted the significant role of depression in predicting work outcomes after a cardiac event, the magnitude of the burden of co-morbid MDD and CVD on work and HRQOL outcomes has also been established. With the view to reduce this burden and enhance these outcomes, targeted approaches to depression management for cardiac patients are required. This chapter will provide a review of the programs which have been evaluated, to date. Their effectiveness will be explored in the context of improving depression outcomes, with the view that these programs could potentially improve HRQOL and other functional outcomes, including vocational outcomes.

5.1. Background to the development of depression management interventions for cardiac patients

The 1970s and 1980's saw the introduction of intervention trials that evaluated psychosocial management as a constituent of rehabilitation after a cardiac event. The inclusion of educational counselling (**211**), as well as exercise and psychological counselling programs (**212**) into rehabilitation was found to improve psychological and lifestyle functioning, compared with usual care (UC). Prominent authors in this area (e.g. Mayou) have argued that cardiac rehabilitation should comprise "simple, flexible, and cost effective care that is (both) psychologically and cardiologically informed"(**213**).

More recently, authoritative bodies such as the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand have formally recognised depression and other psychosocial factors such, as stress, as risk factors for cardiac events (**214**). The American Heart Association Taskforce has further identified the management of psychosocial factors as a key component of patient recovery after a cardiac event (**215**). These recommendations have prompted further research into the impact of depression treatment on the health outcomes of cardiac patients. Although, to date, there remains little evidence that treating depression in cardiac populations improves survival (**81**), depression management can promote important secondary prevention behaviours and impact positively on other clinical outcomes, such as re-hospitalisation (**216**). Due to the complexity of this co-morbidity however, what constitutes best practice for treating depression after myocardial infarction (MI) in real world settings, is currently unclear.

There are several reasons for this. Firstly, sub-types of depressive symptoms may differ for those with and without cardiovascular disease (CVD) (**217**). Thus, it is possible that cardiac

patients may differ from other medical populations in their responsiveness to depression treatment. Secondly, identifying the best approach to treatment is further complicated by the fact that: (i) different clusters of psychological symptoms can lead to different patient outcomes in cardiac populations; for example, anhedonia (loss of pleasure) has been associated with recurrent cardiac events and mortality (**218**), (ii) different approaches to depression treatment may result in differential patient outcomes; for example depression treatment can reduce re-hospitalisation but does not appear to impact CVD status of cardiac patients, (iii) only half of cardiac physicians report treating depression in the belief that depression will spontaneously remit after the stress of an acute cardiac event has subsided (**219**), and (iv) anti-depressant treatment may not, in fact, influence the psycho-physiological pathways thought to underpin the relationship between CVD and depression (see Chapter 1) (**220**). A number of large scale studies have been enacted over the past 10 years to develop the evidence-base. These studies have rigorously evaluated the effectiveness of both pharmacologic and psychological approaches to treatment under controlled conditions, many of which have yielded significant reductions in depressive symptoms. These trials will now be reviewed, with key characteristics displayed in Table 5.1.

5.2. Pharmacologic approaches to depression treatment in cardiac populations

The efficacy of anti-depressant medication for the management of depression in cardiac populations has been investigated in various large scale trials. Key studies include: the Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART), The Canadian Cardiac Randomized Evaluation of Anti-depressant and Psychotherapy Efficacy Trial (CREATE), and The Myocardial Infarction and Depression Intervention Trial (MIND-IT).

These are all placebo-controlled, randomised trials that have evaluated pharmacologic approaches to depression treatment (e.g. selective serotonin reuptake inhibitors (SSRIs) [sertraline hydrochloride, citalopram hydrobromide], and a serotonin-norepinephrine reuptake inhibitor [mirtazapine]), on depression and other outcomes of Coronary Heart Disease (CHD) patients.

The SADHART trial (**221**)(**222**) was one of the first major trials to provide evidence for the efficacy of SSRIs in cardiac populations. This study saw 369 ACS patients with major depressive disorder (MDD) recruited and assigned either an anti-depressant treatment (sertaline) or a placebo. Results indicated that sertraline was significantly superior to placebo on the Clinical Global Impression Improvement (CGI-I) depression scale measured over 24 weeks (responder rates for the intervention group were 67% vs 53% for placebo). However, this effect was not observed using the Hamilton Depression Rating Scale (HAM-D) scale, measured at 16 weeks. Sertraline was also found to be efficacious in patients experiencing recurrent depression, as measured by both the CGI-I and HAM-D. Therefore, the authors concluded that sertraline is an efficacious way to treat depression in acute MI patients with depression. While this effect was statistically significant, the clinical relevance of these findings has been considered modest.

The CREATE study (**223**) also investigated the use of SSRIs in CAD patients reporting clinical depression, this time assessing its efficacy through the combined use of citalopram and interpersonal therapy (IPT). Previously, citalopram has been found to be particularly effective when evaluated in depressed populations (e.g. the STAR*D trial (**224**)). Two hundred and eighty four CAD patients diagnosed with MDD were recruited from nine Canadian academic centres, with participants undergoing two separate randomisations: (1) to receive 12 weekly sessions of IPT plus clinical management or clinical management

only and (2) to receive 12 weeks of citalopram, 20 to 40 mg/d or placebo. Results indicated that citalopram (and clinical management) was efficacious in reducing HAM-D depressive symptoms when compared with a placebo (effect size 0.33; p=.005). IPT was found to be less efficacious than clinical management (effect size, 0.23; p=.06). Based on these and other findings from SADHART, the authors concluded that citalopram or setraline should be used in the treatment of cardiac depression, but found no evidence of added value of IPT over clinical management. Similarly to the SADHART study, the effect of this pharmacologic intervention has been considered small to modest (**225**).

The MIND-IT Trial (**226**), randomly assigned 331 MI patients reporting MDD to an intervention of serotonin norepinephrine reuptake inhibitor or a placebo arm, and assessed depression outcomes at 3, 12 and 18 months. First-choice treatment consisted of placebo-controlled treatment with mirtazapine. In case of refusal or non-response, alternative open treatment with citalopram was offered. Using the Beck Depression Inventory (BDI), the authors observed no significant differences in depression levels between the intervention and placebo arms at 18 months. Additionally, no intervention effects were observed on cardiac prognosis. While participants receiving the intervention demonstrated reductions in depressive symptoms, similar trajectories were observed in the control group. This finding has led some to reject the value of treating post MI depression if symptoms seemingly spontaneously remit. However, others have argued that "regardless of whether depression impacts on cardiac outcomes directly or indirectly, the need to screen and treat depression is imperative"(**215**).

The administration of anti-depressant medications to cardiac patients needs to be carefully considered. For example, tricyclics have been associated with adverse cardiac effects (**227**); in particular, orthostatic hypotension and cardiac conduction disturbances. Using an

administrative database to study the risk of MI for users of all antidepressants, Cohen et al. (2000) found that this class of anti-depressant more than doubles the risk of MI (**228**). A review by Alvarez and Pickworth (2003) further suggests that, compared with tricyclics, other anti-depressant medications such as SSRIs can produce a superior cardiovascular profile (**229**). Sertraline, in particular, has been demonstrated to reduce rates of re-infarction and mortality in cardiac patients, and has demonstrated greater tolerability (**230**). The SADHART investigators demonstrated the safety of SSRIs by change in left ventricular ejection fraction and concluded that SSRIs are safe for use in this population (**222**). However, recently, there have been concerns regarding the use of citalopram and escitalopram in cardiac populations. In view of recent evidence that their effect on the QT-interval (time between the beginning of the Q wave and the completion of the T wave in the heart's electrical cycle) are dose dependent, new daily dosage restrictions have been published (**231**).

While data from these key studies provide some promising results regarding the efficacy of pharmacologic approaches to treating cardiac depression, in most instances, effect sizes have been small to modest. The effects of anti-depressants, more generally, may be even less pronounced in light of evidence to suggest that publication bias has overstated their effects (**232**). While review papers from authoritative taskforces do not advocate the use of one particular anti-depressant medication for the management of depression in MI patients, the effectiveness of their prescription is endorsed based on this and other evidence. For patients who cannot tolerate anti-depressants or prefer a non pharmacologic approach to treatment, several well-designed trials have been enacted to evaluate the use of psychological approaches to treatment.

5.3. Psychological approaches to depression treatment in cardiac populations

5.3.1 Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) aims to help patients identify and challenge self-critical or defeatist thoughts that may induce or perpetuate depression (**233**). This type of therapy is considered one of the most effective ways to treat depression (arguably, not all types of depression) in both psychiatric (**234, 235**) and medical populations (e.g. chronic pain (**236**) and chronic fatigue (**237**)). The use of CBT is considered appropriate for application in cardiac populations for a number of reasons. CBT can not only reduce depression, but can maximise cardiac functioning through the teaching of techniques such as relaxation, mental focusing and imagery, health related behaviour change, stress relief and problem solving. Indeed, CBT has been endorsed by authoritative taskforces like the American Heart Association (AHA) as "an alternative for cardiac patients who cannot tolerate antidepressants or who may prefer a non-pharmacological or counseling approach to treatment" (**215**), because of promising findings emerging from several studies.

The Enhancing Recovery in Coronary Heart Disease patients (ENRICHD) study (**81**) is the largest international trial, to date, to investigate the impact of depression treatment on cardiac patients using a CBT approach for patients who were either depressed and/or experienced low social support. The study enrolled 2481 patients after admission for MI to one of 73 US hospitals. Eligible participants were randomly assigned to UC or a psychological intervention. The latter comprised a 6-month course of weekly CBT (with adjunct anti-depressant treatment where necessary). At six month follow up, this study successfully demonstrated significant, albeit modest, reductions in depressive symptoms between the treatment and UC groups (3 points on BDI scores, $p < 0.001$; 2 points on the

HAM-D, $p < 0.001$) and increased perceived social support (**81**). However, the study failed to report any benefits in event-free survival at (average) 29 month follow up, as a result of the intervention.

The effectiveness of CBT has further been demonstrated for Coronary Artery Bypass Surgery (CABS) patients. Freedland et al (2009) recruited 123 patients exhibiting major or minor depression 12 months post CABS, randomly assigning participants to one of three conditions; UC, CBT (weekly, 50-60 minute sessions delivered by a trained mental health clinician with experience and training in CBT over 12 weeks) or supportive stress management (weekly, 50-60 minute sessions delivered by a trained mental health clinician, over 12 weeks). After three months, greater reductions were observed in depression scores for the CBT and supportive stress-management arms than the UC group (**238**). Results also indicated that CBT was superior to UC on anxiety, hopelessness and stress measures. At 9 month follow up, CBT was also the most effective form of treatment for patient remission rates. The authors concluded that of the two interventions proving efficacious, CBT displayed "greater and more durable effects than supportive stress management on depression and several secondary psychological outcomes" (**238**).

In Australia, the feasibility of using CBT to treat depression in CHD populations has been explored, albeit on a smaller scale. The BRAVEHEART study, an Australian-based pilot study evaluated the effects of a 6-week, group-based, CBT intervention for the treatment of persistent depression in 39 CAD patients, post cardiac rehabilitation. For the 30 who completed the BRAVEHEART program, (mean number of face to face sessions attended = 5.3), significant reductions in depressive symptoms on the BDI and Hospital Anxiety and Depression Scale (HADS) (**239**) were observed at six month follow up. While these changes

were considered of moderate to large effect, the small number of study participants and the absence of a control condition are recognised weaknesses of the study.

In conclusion, these studies suggest that CBT-based treatment of depression in cardiac populations can lead to modest reductions in depression when delivered in either group-based or individually-based settings. To address some of the limitations observed in these studies, others have employed non-traditional approaches to delivering psychological therapy to cardiac patients.

5.3.2 Telephone-delivered therapy

Psychological and pharmacologic approaches to depression management are not without limitation. While psychological therapies can effectively reduce symptoms of depression and anxiety when delivered in face to face (**240**) and group settings (**241**), therapeutic programs have been criticised for being labour intensive and resource laden. Further, the effectiveness of anti-depressant treatments can be limited by reach and compliance. For example:

- On a population level in the U.S, only 25- 30% of those with depressive disorders receive an effective level of either psychotherapy or pharmacologic treatment (**242**)
- For patients who begin taking anti-depressants, adherence is poor; 40% discontinue within a month and only a quarter receive minimum follow up (**243**)
- Only one third of patients with depressive disorders receive psychotherapeutic treatment (**242**). Of those beginning psychotherapy, one quarter attend only one session and only half attend four or more sessions (**244**).

Recent reviews have provided some support for the application of tele-health programs in the management of chronic disease, particularly in relation to reducing the cost of service

delivery (**245**). Tele-health programs have been applied in depressed populations, not only to provide cost-effective care management, but in order to overcome some of the aforementioned barriers to patient participation. In addition to issues related to compliance, logistic factors can preclude the delivery of effective depression treatment. According to Mohr, et al (2008), "one reason for [the] discrepancy between interest and failure to initiate or follow through with psychotherapy is that there are considerable barriers for many patients, including time constraints, transportation problems, care-giving responsibilities, stigma concerns, disability, or living in a rural area that lacks adequate mental health services" (**246**). Thus, the authors conclude that "many of these barriers could potentially be mitigated through the use of the telephone in administering psychotherapy" (**246**).

Although the practical advantages of telephone therapy are apparent, the fidelity (i.e. strategies used to monitor and enhance the validity and reliability of behavioural interventions (**247**)) of delivering depression treatment has been questioned, along with its overall effectiveness. However, according to a meta-analysis (**246**) and other studies of medical populations (**248**), telephone-delivered interventions for distressed patients are particularly well-received, can reduce depressive symptoms and improve attrition rates when compared with similar face-to-face interventions. In fact, these studies have demonstrated markedly lower attrition rates and improved maintenance of remission of depression symptoms as a result of telephone-administered psychotherapy in comparison to face-to-face therapy (**246**).

The extent to which telephone therapy is effective in reducing clinical depression in cardiac populations remains less clear. A recent meta-analysis indicated that tele-health interventions can be effective in modifying important cardiovascular risk factors for

secondary prevention of adverse events in cardiac patients such as total cholesterol (weighted mean difference =0.37 mmol/l, 95% CI=0.19-0.56) and systolic blood pressure (weighted mean difference =4.69 mmHg, 95% CI=2.91-6.47) (**249**). However, the feasibility of using the telephone to deliver a psychotherapeutic program for depression and an intervention which modifies CHD risk factors is less clear. The evaluation of teletherapy delivered both in primary care (e.g. Simon (**250**), Hunkeler (**251**)) and specialist settings (**252**) has yielded promising results, and has subsequently been employed for use in cardiac populations. For example, Bambauer et al (2005)(**253**) examined the impact of a telephone-based, brief psychosocial intervention on depression outcomes of patients already attending cardiac rehabilitation. The study recruited 79 ACS patients with depression and assigned them to UC or an intervention condition; six 30-minute telephone-counselling sessions delivered by doctoral level, mental health clinicians addressing specific issues including fears, loss of control and self-image, dependency, stigma, abandonment, anger, isolation, and fear of death. While the generalisability of these results is limited due to the small numbers of participants enrolled in the trial, findings demonstrate that this telephone-based, psychosocial intervention can improve psychological distress. The authors concluded that such a program can be conducted in conjunction with cardiac rehabilitation.

In summary, this evidence provides support for the application and feasibility of telephone-based therapy for the management of depression after a cardiac event. Others have continued to build on this evidence-base by using the telephone to deliver collaborative- and stepped-care models of disease management.

5.3.3 Collaborative- and stepped-care approaches

Collaborative care has been described as a multidisciplinary plan of care that is decided upon by a collaboration of members of the health care team, the patient and their family. Such an approach has been used previously for the management of co-morbid depression in diabetes patients (**254**). Recently, Huffman et al (2011) adapted this approach for use in cardiac patients. The authors conducted a prospective, randomised trial of a low intensity, collaborative care approach to depression management for ACS patients using the telephone. This study comprised 175 depressed patients hospitalised for ACS (including arrhythmia, or heart failure) and compared a 12 week depression management program to usual medical care. Collaborative care subjects (n=90) reported significantly greater improvements on all mental health outcomes at 6 and 12 weeks, including rates of depression response and anxiety, but no differences were observed at 6 months (**255**).

The Bypassing the Blues intervention trial (**89**) also evaluated an 8 month telephone-delivered, collaborative-care model of disease management which incorporated stepped care. Stepped care models of chronic disease management comprise the provision of low-intensity treatment to all patients in the first instance, and through systematic monitoring of treatment results, progression to a higher-intensity treatment, as necessary. Originally based on that of the IMPACT program developed for the management of late-life depression in primary care (**256**), these models have been adapted for use in a range of patient populations (**257**), including CABG patients (**89**). The Bypassing the Blues intervention comprised: (i) initiation/adjustment of anti-depressant pharmacotherapy prescribed under patients' primary care physician, (ii) watchful waiting for mild to moderate mood symptoms, or (iii) referral to a local mental health specialist such as a psychiatrist or psychologist. A workbook promoting participant self care behaviours was

also provided. Post-intervention, those assigned to the intervention condition (n=150) reported greater improvements (all p<0.01) in mood (HAM-D: effect size: 0.36), and cardiac functioning compared with UC (n=152).

The Coronary Psychosocial Evaluation Studies (COPES) study employed a similar approach for treating depression in ACS patients (**258**), using the IMPACT model of stepped-care. Using a cut off score of ≥10 on the BDI indicating at least mild depression, patients were eligible for participation in the COPES trial if depressive symptoms were evident within a week of hospitalisation for the index event and subsequently at 3-months. Two hundred ACS patients meeting depression symptom eligibility criteria were randomised to either a six month intervention or UC condition at the completion of an observation period. The intervention comprised the five key elements of the IMPACT study: (1) care management delivered by a nurse specialist, psychologist, social worker, and/or psychiatrist; (2) individual choice of psychotherapy and/or pharmacotherapy; (3) problem-solving therapy; (4) a review of symptom severity, with treatment augmented accordingly; and (5) a standardised depression screening instrument. At the completion of the intervention period, those participating in the program reported greater reductions in depression scores (change: –5.7) compared with UC patients (change: –1.9) (n=80 intervention, n=77 UC). However, the primary endpoint for this study was participant satisfaction, not depression.

While these studies demonstrate some of the benefits of stepped- and collaborative-care models, these approaches to care management have been criticised for being resource intensive, especially when delivered in co-morbid populations like those with depression and CVD. For example, engaging physicians from both acute and primary care settings to ensure continuity of care after discharge may be problematic when implementing

collaborative care models for cardiac patients exhibiting depression. Tully (2010) argues that, in the Australian context, this approach may not be feasible: "Cardiology departments would probably require staff with specialist training in psychiatry, psychology and cardiology to balance the clinical and cost-effectiveness of such a collaborative care package" (**259**). Further, he identified cultural and other practical barriers, such as organisation culture and workplace roles, practitioner resistance, mental health services costs, and overlap with cardiac rehabilitation services as potential barriers to translating this type of program into clinical care (**259**).

Overall, the approaches to cardiac depression treatment outlined in this chapter are not without limitation. First, the appropriateness of the timing of the intervention has been a topic of conjecture. Goldston and Baillie (2008) (**260**) argue that the trajectory of depressive symptoms exhibited after a cardiac event should be considered more carefully when designing depression management interventions. The authors maintain that patients with co-morbid depression may display different responsiveness to treatment at different times throughout the post MI period. They recommend that future studies determine which patients are most likely to respond to a particular intervention at a particular time point in the disease trajectory (**260**). Second, elevated attrition rates were observed in many of these trials. For example, Burg (2008) (**261**) argues that in the ENRICHD study, only half (54%) of patients randomised to the intervention received the complete course of treatment due to missed appointments and treatment dropout, potentially diluting intervention effects. Third, evidence from both MIND-IT and ENRICHD suggest that a proportion of patients will have depressive symptoms spontaneously remit in the post discharge period, even in the absence of an intervention.

As a result of these and other limitations, there remains conjecture regarding the advantages of treatment. Some have argued that future research evaluating psychological interventions in this population is not warranted because these programs offer little objective benefit to MI patients (**25, 262**) specifically related to survival. It seems possible, however, that benefits related to survival do exist but may have remained undetected due to inadequate follow up periods over which time improvements in survival and other cardiac outcomes are unlikely to be observable. In any case, the benefits of depression treatment on key psychological outcomes have highlighted the way in which these programs can improve patient wellbeing, despite having no effect on clinical markers: "We should not lose sight of the fact that an intervention that improves well-being, but fails to change survival, is still a very valuable treatment" (**263**). Depression interventions continue to be developed and evaluated across cardiac populations as promising findings emerge regarding their effectiveness. In fact, recent evidence has emerged that psychological therapy can extend survival in CVD populations without depression (**264**). Indeed, it stands to reason that the benefits of psychological treatments may go beyond that of mood, to act as a catalyst in the promotion of other behaviours essential for secondary CHD prevention, every day functioning and health related quality of life (HRQOL) in this population. Given the synchronous relationship between depression and HRQOL, and the increasing interest in improving HRQOL as an important clinical endpoint, the benefits of psychological interventions on HRQOL requires further investigation.

5.4. Summary

As the role of depression and other psychosocial factors have become increasingly well-documented in the onset and management of heart disease, various approaches to depression treatment have been evaluated in cardiac populations. Pharmacologic

approaches, predominantly using SSRIs, as well as psychological approaches using CBT and collaborative- and stepped-care programs have all been advocated. The use of CBT specifically, has been recommended because of its durability. Ultimately, whether the benefits of depression treatment can go beyond psychological outcomes to impact HRQOL remains undetermined and requires further investigation.

5.5. Tables

Table 5.1. Characteristics of randomised controlled trials (RCT) evaluating depression treatment interventions in cardiac populations

Author	Population	Study Design	Assessment points	Depression measure	Key findings
PHARMACOLOGIC					
Glassman (**221**) (SADHART)	N=347 ACS (MI, angina) with major depressive disorder according to DSM-IV and BDI>10	2 arm, 24 wk, double blind, randomised clinical trial of antidepressant treatment (50-200 mg Setraline) versus placebo	Baseline, 6, 16, 24 wks	HAM-D CGI-I	Little difference in depression status between groups after 24 weeks of treatment. Effects were greater for severe and recurrent depression
Lespérance (**223**) (CREATE)	N=284 CAD patients with SCID defined MDD (n=142 intervention; 142 placebo)	2x2 factorial design with four groups: 12 wk IPT plus pill-placebo, IPT plus 20 to 40 mg citalopram per day, 12 wk CM plus pill-placebo, and CM plus citalopram.	Baseline, 12 wks	HAM-D BDI II	Citalopram was superior to placebo in reducing 12-weeks HAM-D scores. No evidence of a benefit of IPT over clinical management
Van Melle (**226**) (MIND-IT)	N=331 MI patients reporting ICD–10 clinical depression (intervention *n*=209 or care as usual *n*=122).	Multicentre, 24-week, double-blind, placebo-controlled trial of serotonin norepinephrine reuptake inhibitor versus placebo	Baseline, 3, 12 and 18 mo	BDI	No differences in depression levels or cardiac prognosis between groups at 18 mo.
PSYCHOLOGICAL					
Freedland (**238**)*	N=81 Acute coronary bypass surgery (undertaken in past year) with depression measured by DISH	3 arm, 12 wk, randomised, single-blind clinical trial of Supportive Stress Management, Cognitive Behavior Therapy and UC (antidepressant use recorded but not administered)	Baseline, 3,6,9 mo	HAM-D BDI	Higher % of remission of depression at 3mo for CBT (71%) and stress-management (57%) arms than in UC. CBT greater and more durable effects than supportive stress management
Berkman (ENRICHD) (**81**)	N=2481 post-MI patients diagnosed with major or minor depression or low perceived social support	RCT of intervention comprising a 6-month course of weekly CBT, group therapy when feasible (with adjunct anti-depressant treatment where necessary)	Baseline, 6 mo	BDI HAM-D	Significant yet modest, reductions in depressive symptoms between groups (3 points on BDI, 2 points on HAM-D), increased perceived social support. No benefits in event-free survival at 29 mo
Bambauer (**253**)*	N=79 ACS with HADS indicating mild to severe depression and/or anxiety at 1-2 weeks postdischarge	Prospective, 2 arm, randomised, controlled trial of 8 wk telephone counselling versus UC	Baseline, 2, 3, 6 mo	HADS, CGI-I measure of self-rated health	Statistically and clinically significant improvement in CGI-I scores of intervention group compared with UC at 2 mo

STEPPED/COLLABORATIVE CARE					
Huffman (**255**)*	175 depressed patients hospitalised for ACS (including arrhythmia, or heart failure).	Prospective, randomised trial of a 12-week collaborative care program versus UC	Baseline, 6wk, 12 wk and 6mo	PHQ-9	Intervention associated with significantly greater improvements on rates of depression response and anxiety at 6 and 12 wk. No differences at 6 mo
Davidson (**258**) (COPES)	200 ACS patients with BDI depressive symptoms ≥10, evident within a week of hospitalisation and at 3 mo	Multi centre RCT of patient preference for problem-solving therapy and/or pharmacotherapy, then a stepped-care approach.	Baseline, 6mo	BDI	Intervention group reported greater reductions in depression scores (change:–5.7) compared with UC patients (change:–1.9)
Rollman (**89**) (Bypassing the Blues)*	N=302 post CABG patients reporting depression at 2 weeks post discharge as measured by initial PHQ2 then PHQ9	Multisite, 3 arm, randomised controlled trial of 8-mo nurse led, telephone-delivered collaborative care (therapy and adjunct antidepressant treatment where required) versus UC for depression	Baseline, 8 mo	PHQ9 HAM-D	The intervention yielded greater improvements in mood symptoms on HRS-D at 8 mo

Abbreviations: DISH, Depression Interview and Structured Hamilton; HAM-D/HRS-D, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory ; CGI-I , Clinical Global Impression Improvement Scale; PHQ-9, Patient Health Questionnaire 9; PHQ2, Patient Health Questionnaire 2; CABG, Coronary Artery Bypass Grafting; ACS, Acute Coronary Syndrome; MI, Myocardial Infarction; IPT, Interpersonal therapy; CBT, Cognitive Behaviour Therapy; MDD, Major depressive disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV;, ICD, International Classification of Diseases; UC, Usual Care; RCT, Randomised controlled trial; DASI, Disability Assessment Structured Interview; MIND-IT, the Myocardial INfarction and *Depression*-Intervention Trial; SADHART, Sertraline Anti Depressant Heart Attack Randomized Trial; ENRICHD, Enhancing Recovery in Coronary Heart Disease; *COPES,* Coronary Psychosocial Evaluation Studies; *=telephone delivered intervention

Chapter 6: THE IMPACT OF DEPRESSION TREATMENT ON MENTAL AND PHYSICAL HEALTH RELATED QUALITY OF LIFE: A META-ANALYSIS

Chapter Overview

Having detailed the efficacy and effectiveness of psychological, pharmacologic and other approaches to managing depression after a cardiac event, the impact of such programs on HRQOL outcomes needs to be ascertained, as the negative effects of depression on HRQOL become clear. In order to address current inconsistencies in the literature, this chapter will present a meta-analytic review to assess and measure whether the potential benefits of depression treatment go beyond depression outcomes to impact HRQOL outcomes of cardiac patients.

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6.1. Publication Declaration

Declaration by candidate

In the case of Chapter [6], the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
AO conceptualised the paper, synthesised, analysed and interpreted data, and wrote the original version of the manuscript.	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Kristy Sanderson	KS refined conceptualization, assisted with inclusion/exclusion criteria and statistical analysis of data and critically revised drafts of the manuscript.	
Brian Oldenburg	BO refined conceptualization and critically revised drafts of the manuscript.	
C Barr Taylor	CBT refined conceptualization and critically revised drafts of the manuscript.	

Candidate's Signature  **Date** 24/3/10

Declaration by co-authors

The undersigned hereby certify that:

(7) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(8) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(9) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(10) there are no other authors of the publication according to these criteria;
(11) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(12) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Public Health and Preventive Medicine Monash University Alfred Campus

Signature 1	[redacted]		**Date** 24/03/10
Signature 2			24/3/10
Signature 3			3/20/10

6.2. Abstract

Purpose: To conduct a meta-analysis evaluating the effectiveness of depression treatment on mental and physical health-related quality of life (HRQOL) of cardiac patients.

Methods: Studies were identified using medical, health, psychiatry, psychology, and social sciences databases. Inclusion criteria were: (1) ≥1 control condition, (2) random assignment to condition after admission for myocardial infarction (MI)/acute coronary syndrome (ACS), after recording positive results on a depression screener, (3) documentation of depression symptoms at baseline, (4) depression management as a component of the rehabilitation/intervention, (5) validated measure of HRQOL as an outcome, at minimum 6-month follow-up. For meta-analysis, mental and physical HRQOL were the end points studied, using standardized mean differences for continuous outcome measures, with 95% confidence intervals. Heterogeneity was explored by calculating I^2 statistic.

Results: Five randomized controlled trials (RCTs) included in the analysis represented 2105 participants (1058 intervention versus 1047 comparator). Compared with a comparator group at 6-months, a test for overall effect demonstrated statistically significant improvements in mental HRQOL in favor of the intervention [SMD= -0.29 (-0.38, -0.20), (P<.00001); I^2= 0%]. Depression treatment had a modest yet significant impact on physical HRQOL [SMD= -0.14 (-0.24, -0.04) (P=.009); I^2= 15%].

Conclusion: While the impact of post-MI depression interventions on physical HRQOL is modest, treatment can improve mental HRQOL in a significant way. Future research is required to develop and evaluate a program which can achieve vital improvements in overall HRQOL, and potentially cardiovascular outcomes, of cardiac patients.

6.3. Background

Health-related quality-of-life (HRQOL) has been defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient (**265**). HRQOL has emerged as an important construct for measuring self-rated health in chronic disease cohorts. In cardiac patients, HRQOL is an indicator of recovery and primary outcome of rehabilitation programs (**266**).

Depression is common among cardiovascular disease patients; approximately 15-20% report mild depression after myocardial infarction (MI). A similar proportion experience major depressive disorder. Prospective (**267**) and narrative reviews (**192**) identify depression as the most important independent predictor of HRQOL in this population. Depression further reduces psychologic and physical functioning post-MI (**268, 269**), impacting poorly on cardiovascular outcomes. While randomized controlled trials (RCTs) have demonstrated the effectiveness of depression treatment on specific psychological outcomes in this population (**223**) (ie, reducing depressive symptoms and psychological distress), this has failed to translate to improved morbidity and mortality, and the effect upon broader functioning outcomes (ie, mental and physical HRQOL), as distinct from psychological outcomes, remains less clear.

Traditionally, a major aim of cardiac rehabilitation has been to improve HRQOL of patients; indeed low HRQOL at baseline is linked to survival disadvantage (**270**). Rehabilitation programs can significantly impact HRQOL outcomes (**271**), cognitive functioning (**272**), and key cardiac outcomes (**273**). However, when cardiac patients experience depression they are less likely to attend rehabilitation programs (**274**), or report improved psychosocial outcomes, including HRQOL. Interestingly, there is little evidence that rehabilitation with a

specific depression treatment component directly improves HRQOL, or effects cardiac outcomes (**275**). Systematic reviews have focussed on other elements of rehabilitation (**276-279**) impacting on mortality outcomes and HRQOL as a secondary outcome (**25**). Narrative reviews have provided evidence that depression treatment may improve HRQOL in select cardiac populations (**192**), a finding consistent with recommendations from the American Heart Association (**215**), and in other disease cohorts (**280**). Despite this, conclusive evidence that depression treatment significantly improves physical and mental HRQOL in cardiac patients with depression is yet to be demonstrated.

Preliminary research suggests different components of cardiac rehabilitation impact upon different elements of HRQOL; mental and physical health related functioning. For example, lifestyle and stress management programs can improve physical HRQOL (**281**). Nonrandomised, observational studies have indicated that depression treatment may improve mental HRQOL (**282**). However, few RCTs evaluating outcomes of depressed cardiac patients have significantly impacted both components of HRQOL. Gottlieb et al (**283**) found pharmacologic treatment for depressed heart failure patients significantly improved mental, not physical HRQOL. In MI patients, the impact of depression treatment on components of HRQOL remains unclear; few studies in this area have (a) simultaneously examined depression and HRQOL (**284**) and/or (b) included/published HRQOL outcomes. Recently, there remained "..little evidence to support the suggestion that treating depression will improve quality of life in patients with coronary disease" (**80**). To our knowledge, a meta-analytic review in this area, which evaluates randomized controlled trials has not been conducted.

This article aims to investigate the effectiveness of depression treatment on mental and physical HRQOL of cardiac patients, by systematically reviewing eligible RCTs. Pooled effect

sizes from meta-analyses will determine if the impact of depression treatment is statistically significant.

6.4. Methods

The literature search identified articles measuring the effectiveness of depression treatment in depressed MI populations which included HRQOL outcomes. Studies were identified using the following databases: Cochrane Central Register of Controlled Trials, PubMed, OVID, Medline, Proquest, CINAHL plus, SCOPUS, Web of Knowledge. Reference lists of relevant studies and reviews were manually examined. Grey literature was examined using search engines (eg, Google Scholar). Studies were limited to those published in English, without limits on year of publication.

6.4.1 Selection criteria

Included articles required: (1) ≥1 control condition, (2) random assignment to treatment condition post-admission for MI/acute coronary syndrome (excluding heart failure) and after recording positive on a depression screener (3) documentation of depression symptoms at baseline (as inclusion criterion), (4) depression treatment (ie, pharmaceuticals, psychotherapy, combinations) as a component of the rehabilitation/intervention, (5) validated measure of HRQOL/self-rated health as an outcome at minimum 6-month follow-up.

6.4.2 Data extraction and validity assessment

Data were extracted from articles by a single investigator and collated in a table for review by a second investigator to avoid coder bias, and included study: author, population, design, assessment points, depression measure, HRQOL measure and clinical indicators. The methodological quality of each trial was assessed as per Cochrane Collaboration recommendations on evaluating validity: randomization; allocation concealment; blinding;

completeness of follow-up; and intention-to-treat analysis. Where a study was considered low quality, it was agreed the meta-analysis would be re-run using a sensitivity analysis which excluded the results of that study to determine its weight on the overall pooled effect size. The authors agreed data would be calculated using standardized mean differences (SMD). Variables were coded accordingly. Mental and physical HRQOL variables and commonly measured variables between studies were also coded. Where means and standard deviations were unavailable, standard equations for converting confidence intervals and standard error were used (**285**) to calculate SMD.

6.4.3 Statistical analysis

The primary meta-analysis used mental and physical HRQOL outcomes at 6-month follow-up. Using Review-Manager 5 (RevMan), meta-analyses were performed using SMD for continuous outcome measures (based on post-post means), with 95% confidence intervals, using Hedges' adjusted *g* to adjust for small sample bias. With 1 exception (**253**), all studies reported HRQOL scores whereby higher scores indicated better HRQOL. To adjust for this in RevMan, where higher continuous variables reflect poorer outcomes, data were multiplied by –1. Heterogeneity was explored by calculating I^2 statistic. Where high heterogeneity was observed, a sensitivity analysis identified studies with potential bias or low quality characteristics. To address differences in study characteristics, direct comparisons were made using a random-effect model between trials. *A priori* subgroup analysis estimated the effects of depression treatment on HRQOL by instrument, comparator group and cardiac condition, and explored the effects of different types of depression treatment on HRQOL.

6.5. Results

The search was conducted between June-September 2009. The search strategy, using the terms heart disease *or* myocardial infarction *or* coronary disease *or* acute coronary syndrome, *and* depression treatment *or* depression therapy *or* depression management (explode to include all of its narrower terms including: Serotonin Uptake Inhibitors or Adult or Antidepressant Agents Depression or Psychotherapy or Treatment Outcome) *and* Quality-of-Life, revealed 600 articles using OVID Medline. Once limited to Clinical Trials or Randomized Controlled Trial, 151 articles remained. After reviewing abstracts for relevance, 147 did not meet inclusion criteria. Where uncertainty occurred, authors reached consensus. A similar strategy was used to search Cochrane Central Register of Controlled Trials. The terms "Depress* treatment *and* Quality-of-Life *and* Myocardial Infarction *or* Acute Coronary Syndrome *or* Coronary Heart Disease" yielded 28 results; 4 were considered potentially eligible. These 4 overlapped with those identified by the Medline Search. To search grey literature, Google Scholar was searched using: "Depression Treatment" "Quality-of-life" "Acute coronary syndrome" "myocardial infarction" "randomized controlled trial," revealing 37 articles, 4 of which met criteria. Three of these overlapped with those previously identified, revealing 1 new article. Reasons for exclusion are listed in Figure 6.1. Reference lists of relevant reviews were manually scanned, revealing 1 potentially relevant article. Other generic search engines were used to identify grey literature, using the terms "Cardiac depression", "heart disease", "therapy", "quality-of-life." Of the 714 results, 2 previously unidentified abstracts were revealed. To assess eligibility for inclusion, the primary authors of these abstracts were contacted via email and asked specific methodological questions about follow up period and for publications details of full study results. Correspondence with authors of both studies revealed neither fulfilled inclusion criteria; these studies were excluded. After completing this process, 5 articles were included in the review. Study selection

and extraction process are outlined in Figure 6.1, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**286**).

6.5.1 Study characteristics

Key characteristics are displayed in Table 6.1. The 5 trials included in the review were published between 2003-2009. Studies were conducted in North America (including 1 across 7 countries), and defined participants in their samples as those diagnosed with MI/unstable angina. Two studies comprised participants undergoing bypass surgery (**89, 238**).

6.5.2 Criteria for depression

Studies included samples comprising MI patients reporting depression at the time of recruitment. There was distinction between studies including participants with diagnostically defined depression, using diagnostic instruments, and those identified through self-report. Of the former studies, variations of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) were most commonly used (n=3)(**222, 287**)(**237**), often in conjunction with another scale. Of the latter studies (n=2), the Patient Health Questionnaire-2 (**89**), and the Hospital Anxiety and Depression Scale (**253**) determined depression.

6.5.3 Timing of depression diagnosis

There was wide variation between studies regarding administration of depression screening. One study conducted an initial depression screen when participants were hospitalised for surgical intervention (**89**). Another contacted potential participants postdischarge (1-2 weeks) for depression assessment, after eligible patients were identified in-hospital (**253**). ENRICHD and SADHART administered a modified DSM-IV to MI patients 28 and 30 days postdischarge, respectively. In 1 study (**238**), it was unclear when depression screening was administered, therefore we were unable to calculate an average timeframe for screening. Two

studies used a 2-step process to confirm participant depression status, to differentiate between patients with persistent and transient depression. Swenson et al (**222**) readministered Diagnostic Statistics Manual-IV immediately before randomization to confirm depression diagnosis. Rollman et al (**89**) followed the initial Patient Health Questionnaire-2 screening with the Patient Health Questionnaire-9 two-weeks postdischarge for bypass surgery.

6.5.4 Types of interventions

Broadly, the depression treatments evaluated in the 5 studies were pharmacologic, psychotherapeutic, or composite treatments (details reported in Table 6.1). All studies reported comparator groups; 'Usual Care' for depression or placebo group. Patients assigned to Usual Care received either educational materials (eg, Bambauer et al (**253**)), or normal medical care only (eg, Freedland et al (**238**)).

6.5.5 Definition of HRQOL

The most commonly used HRQOL assessment instrument was SF-36 (**89, 238**) (**222**) and variations (SF-12) (**287**). Means and standard deviations were presented most commonly as 'component' scores. Mental Health Component score comprises vitality, mental health, social functioning, and role emotional. Physical Health Component score comprises physical functioning, role physical, bodily pain, and general health. The other instrument used was the Overall Clinical Global Impressions Scale Score (**253**). Of the papers which included >1 HRQOL measures (**222, 287**), we decided those included in the review should be most comparable to other HRQOL instruments used in the remaining trials (commonly, the SF measures of HRQOL).

6.5.6 Quantitative data synthesis

The studies included in the review were of sound methodological quality (Table 6.2), despite variance in key characteristics. Data were synthesized and converted where necessary for comparability to impute appropriate data required for meta-analyses. Decisions about comparability and quality were reached through discussions between the present study authors. With the exception of 1 study (**89**), 6-month follow-up data were presented in all papers. The landmark assessment point for this trial was 8-months, which the investigators decided was comparable.

Data were extracted from 5 studies (Table 6.3) considered comparable for meta-analysis. Of these, 4 presented baseline HRQOL scores. HRQOL was not presented at baseline for ENRICHD participants (**287**) but data from the trial were included because the assumption of no baseline differences is made for all post-post calculations of Cohen's d/Hedge's g. Further, the assumption of no baseline differences is strongest with random allocation to groups. For trials using a study design with multiple conditions, data were derived from participants assigned to the arm considered most comparable to others in the analysis; eg in the Freedland et al (**238**) study, data from participants receiving a cognitive behavioral intervention were included in the model over a Supportive Stress Management intervention because the former was considered more comparable to the other studies. With 1 exception (**253**), studies presented mean summary scores of mental and physical HRQOL for intervention and comparator groups. Scores for derivatives of SF-36 were considered comparable for analysis as no differences have been reported in standardized response means between SF-12 and SF-36 scales (including mental health components) (**288**).

Where required data could not be extracted, standard deviations were converted from data presented (eg, standard error (**89, 238**) confidence intervals (**287**)) using the appropriate

statistical equations. In the absence of this data (eg Swenson et al (**222**)), descriptive data of SF-36 summary score norms for MI populations were substituted (**288**). After synthesis, data were converted to standardized means in RevMan to account for these variations, and a random-effects model applied.

6.5.7 Effect of depression treatment on mental and physical HRQOL outcomes

A meta-analysis of 5 studies revealed that depression treatment had a statistically significant impact on mental and physical HRQOL outcomes of depressed cardiac patients. Compared with a comparator group (n=1047) at 6-months, a test for overall effect demonstrated significant improvements in mental HRQOL in favor of the intervention condition (n=1058) [SMD=-0.29 (-0.38,-0.20), (*P*<.00001); I^2=0%] (Figure 6.2). This effect remained statistically significant after conducting a sensitivity analysis to exclude the Bambauer et al study (**252**) [SMD=-0.30 (-0.39,-0.20),(*P*<.00001); I^2=8%]; a multipurpose analysis to exclude the only study measuring self-rated health, the only study not to report timing of participant depression assessment and pool the remaining studies which measured HRQOL with the same instrument (ie, derivatives of the SF measures of HRQOL). This result also remained after adjusting for those undergoing surgical intervention (**89, 238**).

Depression treatment was found to have a significant, yet modest, impact on physical HRQOL (Figure 6.3) when intervention (n=1058) and comparator groups (n=1047) were compared at 6-months [SMD=-0.14 (-0.24, -0.04), (*P*=.009); I^2= 15%]. After adjusting for surgical intervention, this effect remained. Depression treatment appeared to have little impact on physical HRQOL of surgical intervention patients (**89, 238**). *A priori* subgroup analysis was performed to adjust for differences in HRQOL between comparator groups. We conducted a sensitivity analysis (n=4), excluding the SADHART study (**222**) which used a placebo group, to examine the effects of depression treatment on mental HRQOL of patients receiving

depression treatment compared with those receiving Usual Care. A test for overall effect size revealed a significant difference in mental HRQOL between groups, attributable to the intervention (*P*<.0001). Rerunning the analysis in the same way for physical HRQOL had an impact on the initial results; the overall effect size failed to reach significance (*P*<.14). We further performed a sensitivity analysis to determine the effects of psychological depression treatment (n=2) (**238, 253**) and combined approaches to treatment (n=2) (**89, 287**) on HRQOL. Both psychological [SMD= -0.44 (-0.77, -0.11)(I^2=10%) (*P*=.01)] and combined approaches to depression treatment [SMD= -0.26 (-0.35, -0.16) (I^2=0%) (*P*<.00001)] had a statistically significant effect on mental HRQOL. Neither treatment type had a statistically significant impact on physical HRQOL.

Three papers included depression outcomes; others reported depression in separate papers so were not included in the analyses. A subanalysis of three studies indicated that depression treatment significantly improved depression in favor of the intervention group [SMD= -0.24 (-0.38, -0.09)(I^2=0%) (*P*<.002)].

6.6. Discussion

This paper investigated the effectiveness of depression treatment on mental and physical HRQOL of cardiac patients by systematically reviewing relevant RCTs, meeting predetermined selection criteria. Depression treatment was effective in improving mental HRQOL, and this effect remained regardless of comparator group or HRQOL instrument used. Significant yet modest effects were observed for physical HRQOL. Treatment had little impact upon physical HRQOL of patients undergoing surgical interventions. While few studies were included in subanalysis of treatment type, psychological approaches appeared to be particularly effective in improving mental HRQOL.

To our knowledge, this is the first meta-analysis to systematically demonstrate that depression treatment significantly improves HRQOL of depressed cardiac patients. Our findings are consistent with studies in heart failure patients, demonstrating that depression treatment has a more significant impact on mental HRQOL compared with physical HRQOL (**283**). These findings have important implications for future research and clinical practice. Our data suggest that depression treatment programs need to include broader attention to other outcomes. Tailoring a program for cardiac patients that includes a composite approach to depression and lifestyle management (risk factor reduction related activities: exercise, stress management) may achieve vital improvements in overall HRQOL-related outcomes, of equal effect size. While depression treatment may effectively impact upon mental HRQOL like social functioning and vitality, risk factor reduction may have a positive impact upon physical HRQOL such as general health and physical functioning. Importantly, elevated physical HRQOL could lead to better cardiac functioning, reduced hospital admissions and mortality benefits. For example, lifestyle interventions like exercise have reduced mortality in depressed MI patients at high risk of adverse effects (**289**). RCTs using composite interventions should be evaluated.

It is likely that a contributor to improvements in HRQOL status was adjustments in mood and depressive symptoms. Depression symptoms have been shown to account for 49% of variance in HRQOL scores in cardiac populations (**290**). As only half of the studies included in the review presented depression outcomes, the small sample size precluded a moderator analysis to determine this. Future studies featuring larger sample sizes should determine how depression acts as a moderator in this relationship.

That depression treatment results in significant improvements in HRQOL may be of clinical significance. Using Cohen's interpretation of effect (.20 for small effects, .50 for moderate

effects, and .80 for large effects) (**225**) and more specifically, using other studies of HRQOL change to define clinical importance (ie, an effect size of .20 has been considered an appropriate definition of a minimal clinically important difference in HRQOL (**291**)), our results suggest that depression treatment has a clinically meaningful impact on mental HRQOL of cardiac patients. HRQOL may be pivotal in assessing functional response to depression treatment in a clinical setting.

Several limitations were observed while undertaking this meta-analysis. First, because of the fundamental design of meta-analyses, which sees data combined from independent studies for analysis, we recommend data be interpreted with caution, because of variances which may be unaccounted for (eg, method of depression assessments, patient baseline characteristics). Well-designed and enacted studies in the future could overcome these issues. Second, the small number of studies included may have introduced bias such as the file drawer effect whereby studies published display inflated effect sizes, and those yielding negative results remain unpublished and not included in reviews. While funnel plots could provide an indication of publication bias, they were not displayed in this paper as it has been reported that ten estimates are required to reliably judge funnel plots (**292**). Small sample size further precluded extensive sub-analyses of the data, due to limited power. Future research using more studies could add to our findings by isolating the most effective components of depression treatment for cardiac patients. Alternatively, future studies could apply recently developed statistical techniques, eg, mixed-treatment comparison approach, to identify these factors (**277**).

6.7. Acknowledgements

The authors wish to thank Prof Michael Abramson.

6.8. Figures

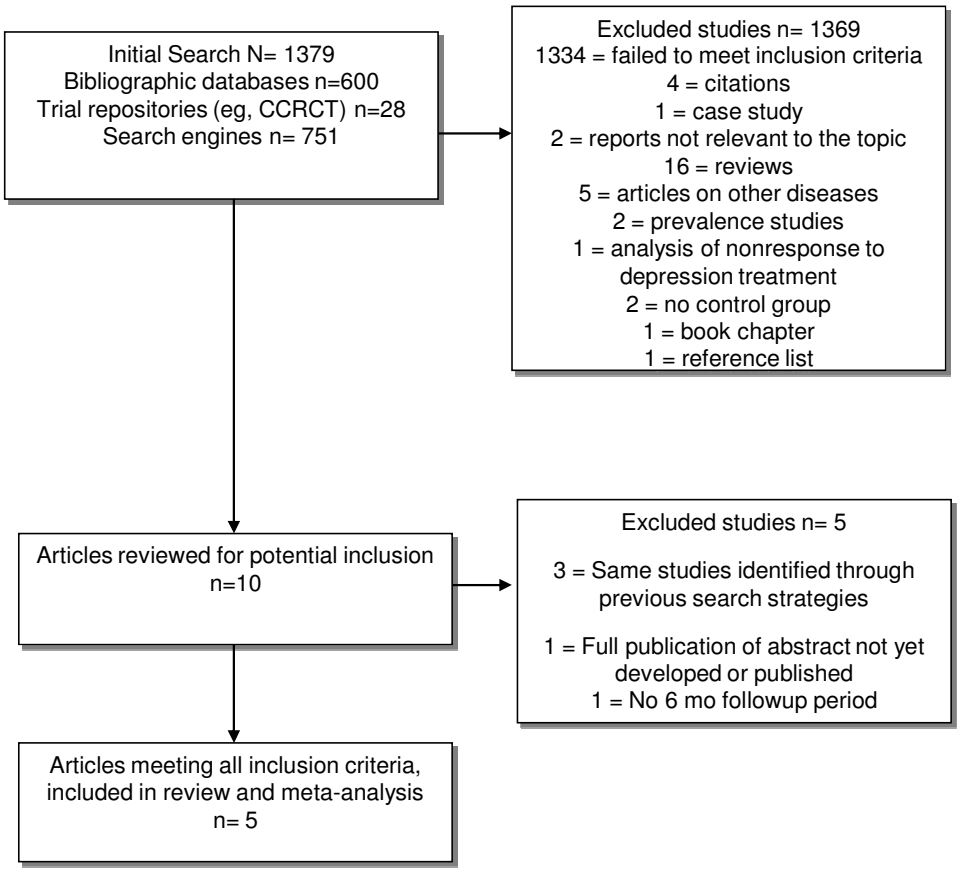


Figure 6.1. Study extraction and selection process

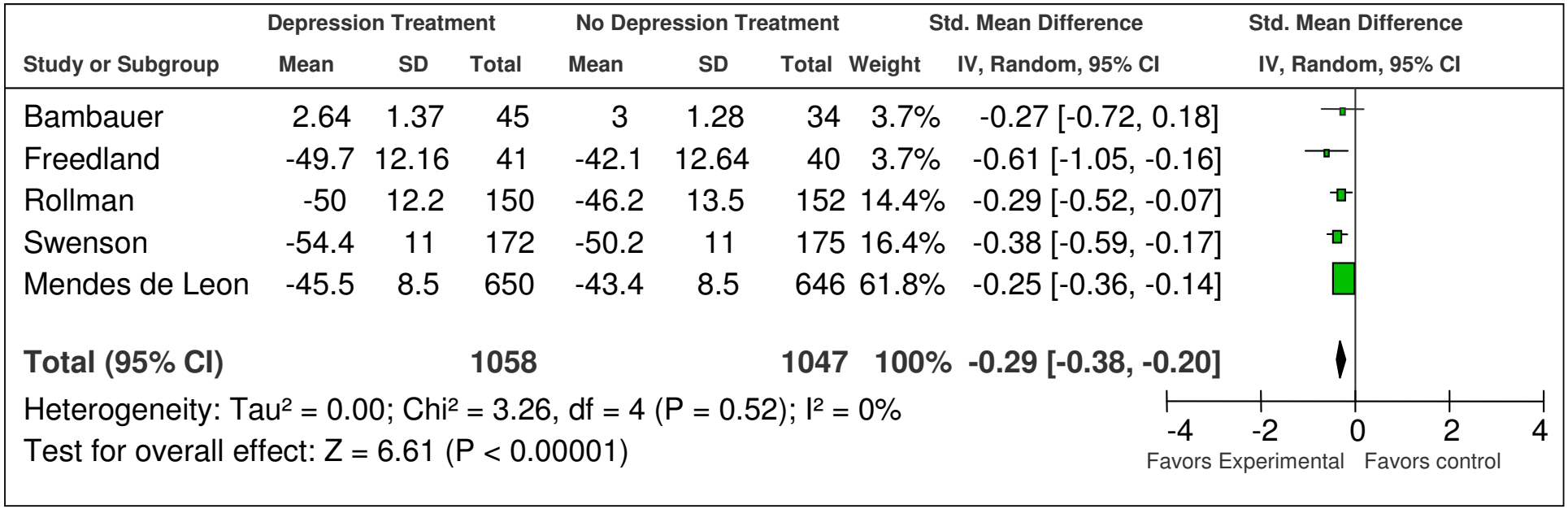


Figure 6.2. Effect of depression treatment on mental Health Related Quality Of Life of cardiac patients at 6 months

	Depression Treatment			No Depression Treatment				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bambauer	2.64	1.37	45	3	1.28	34	5.2%	-0.27 [-0.72, 0.18]	
Freedland	-36.2	9.6	41	-37.3	9.45	40	5.4%	0.11 [-0.32, 0.55]	
Rollman	-44	9.7	150	-41.4	9.8	152	17.9%	-0.27 [-0.49, -0.04]	
Swenson	-46.6	11	172	-44.1	11	175	20.2%	-0.23 [-0.44, -0.02]	
Mendes de Leon	-39.4	10.6	650	-38.6	10.6	646	51.3%	-0.08 [-0.18, 0.03]	
Total (95% CI)			**1058**			**1047**	**100%**	**-0.14 [-0.24, -0.04]**	

Heterogeneity: Tau² = 0.00; Chi² = 4.72, df = 4 (P = 0.32); I² = 15%

Test for overall effect: Z = 2.63 (P = 0.009)

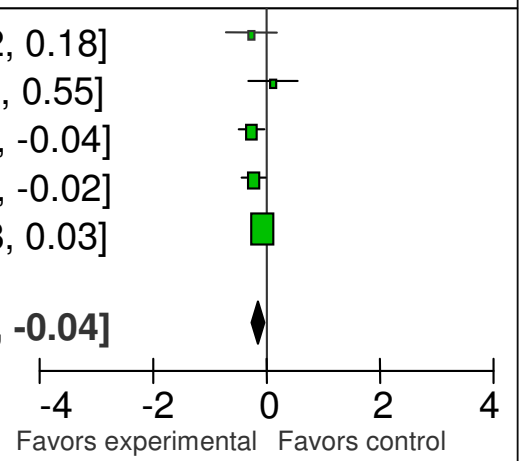


Figure 6.3. Effect of depression treatment on physical Health Related Quality Of Life of cardiac patients at 6 months

6.9. Tables

Table 6.1. Characteristics of included studies in review

Author	Population	Design	Assessment points for HQOL	Depression measure	HRQOL measure	Clinical indicators
Freedland (**238**)	N=81 Acute coronary bypass surgery (undertaken in past year) with depression measured by DISH	3 arm, 12 wk, randomized, single-blind clinical trial of Supportive Stress Management, Cognitive Behavior Therapy and Usual Care (antidepressant use recorded but not administered)	Baseline, 3,6,9 mo	HAM-D BDI	SF-36	Heart surgery Questionnaire (psych impact of CABG)
Swenson (**222**) (SADHART)	N=347 ACS (MI, angina) with major depressive disorder according to DSM-IV and BDI>10	2 arm, 24 wk, double blind, randomized clinical trial of antidepressant treatment (50-200 mg Setraline) versus placebo	Baseline, 6, 16, 24 wks	HAM-D CGI-I	SF-36 Q-LES-Q	Ejection fraction, prior episode, diagnosis Killip class (as predictors of HRQOL)
Mendes de Leon (ENRICHD)(**287**)	N=1296 postMI, met criteria for depression and/or low social support according to DISH and HAM-D	Multisite, 2 arm, randomized controlled clinical trial of 6 mo, individual Cognitive Behavior Therapy program (and adjunct anti-depressant treatment where required) versus Usual Care	Only posttreatment, 6 mo after enrolment	HAM-D BDI	SF-12 Life Satisfaction scale Ladder of Life	n/a
Bambauer (**253**)	N=79 ACS with HADS indicating mild to severe depression and/or anxiety at 1-2 weeks postdischarge	Prospective, 2 arm, randomized, controlled trial of 8 wk telephone counselling versus Usual Care	Baseline, 2, 3, 6 mo	HADS	CGI-I measure of self-rated health	n/a
Rollman (**89**) (Bypassing the Blues)	N=302 postCABG patients reporting depression at 2 weeks postdischarge as measured by initial PHQ2 then PHQ9	Multisite, 3 arm, randomized controlled trial of 8-mo nurse led, telephone-delivered collaborative care (therapy and adjunct antidepressant treatment where required) versus Usual Care for depression	Baseline, 8 mo	PHQ9	SF-36	Cardiac related physical functioning (DASI)

Table 6.2. Methodological quality of included studies in review

Author	Interventionists	Randomization and concealment	Quality of analysis
Freedland (**238**)	Social workers, psychologists	Computer program was used to generate random allocation sequence with block sizes of 3 and 6. Group assignments concealed in sealed envelopes and revealed to study co-ordinator immediately after participant completed all baseline assessments; Outcome assessors masked to participant group assignment	- ITT identified - x^2 test with 2 df used to determine difference among groups - Missing data 7%,8% and 10% at 3,6,9 mo, respectively
Swenson (**222**) (SADHART)	N/A	Assignment carried out with use of computer generated permuted blocks of four, stratified by site and time of onset of depression	- Allocation concealment unclear - Full ITT as well as recurrent depression subanalysis - Two way ANOVA: Effects for treatment group, study center and treatment-by-center - <10% loss to follow-up
Mendes de Leon (**287**) (ENRICHD)	Clinicians with advanced graduate training in clinical or counselling psychology, clinical social work, clinical psychiatry, or psychiatric nursing, clinical experience with Cognitive Behavior Therapy	Randomization stratified by clinical center and used a permuted block algorithm with blocks of varying sizes 2, 4, and 6. Following eligibility determination, study coordinators obtained treatment allocation using an automated telephone randomization system maintained at a Coordinating Center. Although participants and interventionists were aware of the patient treatment assignment, all staff who collected, verified, or classified end point data or follow-up assessments were masked	- ITT analysis identified in previous study paper - Allocation concealment not detailed but has been discussed in previous papers - No data collected preintervention to record loss to followup, and some participants still undergoing treatment at time of completing HRQOL assessment
Bambauer (**253**)	Doctoral level clinicians (psychologists, psychiatrists, interns)	Randomization by coin flip conducted by Study Coordinator, who went on to inform participants of the condition to which they were assigned.	- Not central randomization, no concealment allocation mentioned, coin toss used as method of randomization - ITT mentioned in earlier paper - Mixed effects analysis - 21% attrition (8/53 intervention; 13/47 control)
Rollman (**89**) (Bypassing the Blues)	Nurse or other nonphysician allied health professional "care manager"	Occurred in 1:1 ratio according to a statistician-prepared computer generated random assignment sequence stratified by hospital site Project Manager was blinded to allocation until 2 wks after 2 wk phone call to patients to confirm depression status	- ITT used - Mixed effects analysis - Attrition rate 13% at 8 month

Abbreviations: ITT, Intention to Treat; ANOVA, Analysis of Variance; HRQOL, Health Related Quality of Life; SADHART, Sertraline AntiDepressant Heart Attack Randomized Trial; ENRICHD, Enhancing Recovery in Coronary Heart Disease; CGI-I, Clinical Global Impressions-Improvement

Table 6.3. Summary of results of studies included in meta-analysis

Author	Key mental HRQOL findings	Key physical HRQOL findings	Other findings
Freedland (**238**)	Cognitive Behavior Therapy had significant impact on MCS of HRQOL at 6 mo	Intervention had no effect on physical HRQOL at 6 mo	Intervention superior to Usual Care on depression, anxiety, hopelessness, and stress at 6-mo
Swenson (**222**) (SADHART)	Pharmacologic treatment (Setraline) associated with clinically meaningful improvements in MCS of HRQOL at 6 mo	Pharmacologic treatment (Setraline) associated with clinically meaningful improvements in Physical Component Score of HRQOL at 6 mo	No significant differences in depression, life enjoyment or satisfaction or cardiac event outcomes between Intervention and Usual Care. Those with recurrent depression likely to benefit from intervention on HRQOL and depression outcomes
Mendes de Leon (**287**) (ENRICHD)	Cognitive Behavior Therapy had significant impact on mental HRQOL at 6 mo	No significant differences between Intervention and Usual Care groups on physical HRQOL at 6 mo	Intervention group showed higher life satisfaction scores. Early treatment effect for Cognitive Behavior Therapy on reducing depression; similar for both groups*
Bambauer (**253**)	No significant improvements in self-rated health observed as result of psychotherapeutic intervention at 6 mo	No significant improvements in self-rated health as result of psychotherapeutic intervention at 6 mo	Significantly greater improvements in depression and anxiety for intervention participants*
Rollman (**89**) (Bypassing the Blues)	Stepped care treatment significantly improved mental HRQOL at 8-mo followup	No significant differences between Intervention and Usual Care groups in physical HRQOL at 8 mo	Intervention group reported greater improvements in mood and cardiac functioning indicators at 8-mo followup. Males particularly likely to benefit from the intervention

Abbreviations: MCS, Mental Component Score, HRQOL, Health Related Quality of Life; SADHART, Sertraline AntiDepressant Heart Attack Randomized Trial; ENRICHD, Enhancing Recovery in Coronary Heart Disease. *Results displayed in papers not included in this review

Chapter 7: A RANDOMISED, FEASIBILITY TRIAL OF A TELE-HEALTH INTERVENTION FOR ACUTE CORONARY SYNDROME PATIENTS WITH DEPRESSION ('MoodCare): A STUDY PROTOCOL

Chapter Overview

Having confirmed the benefits of depression treatment in cardiac populations, particularly in relation to mental HRQOL, it is possible that combining a targeted, depression management program with a lifestyle modification intervention could alter overall HRQOL and, as a consequence, vocational functioning, of patients experiencing depression after a cardiac event. Further, given the promising evidence for the use of tele-health in depressed populations, using this mode of delivery for such a program could be advantageous. This chapter will present the methodology of a telephone-delivered, combined depression treatment and CHD secondary prevention program for cardiac patients with depression.

Citation: O'Neil A, Hawkes AL, Chan B, Sanderson K, Forbes A, Hollingsworth B, Atherton J, Hare DL, Jelinek M, Eadie K, Taylor CB, Oldenburg B (2011). A randomised, feasibility trial of a tele-health intervention for Acute Coronary Syndrome patients with depression ('MoodCare'): study protocol. *BMC Cardiovascular Disorders*. 2011, 11:8.

7.1. Publication Declaration

Declaration by candidate

In the case of Chapter [7], the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
AO co-developed the original study design, implemented the study protocol, advanced the original version of the manuscript, coordinated author feedback and submitted the final version of the paper.	50%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Anna L Hawke	Developed the study concept and aims, co-developed study protocol, drafted the study manuscript, and contributed to the final version of the manuscript.	N/A
Bianca Chan	Co-wrote the study protocol, implemented the study protocol and oversaw the collection of data	N/A
Kristy Sanderson	Developed the study concept and aims, co-wrote the study protocol, implemented the study protocol and oversaw the collection of data	N/A
Andrew Forbes	Performed the sample size calculations and randomisation schedule, contributed to the study protocol, is overseeing data analysis, contributed to the final manuscript.	N/A
Bruce Hollingsworth	Developed the study concept and aims, contributed to the study protocol, contributed to the final manuscript.	N/A
John Atherton	Developed the study concept and aims, implemented the study protocol, contributed to the final manuscript.	N/A
David L Hare	Developed the study concept and aims, implemented the study protocol, contributed to the final manuscript.	N/A
Michael Jelinek	Developed the study concept and aims, implemented the study protocol, contributed to the final manuscript.	N/A
Kathy Eadie	Co-wrote the study protocol, implemented the study protocol, contributed to the final manuscript.	N/A

C Barr Taylor	Developed the study concept and aims, contributed to the study protocol, implemented the study protocol and oversaw the collection of data, contributed to the final manuscript.	N/A
Brian Oldenburg	Developed the study concept and aims, co-wrote the study protocol, implemented the study protocol and oversaw the collection of data, contributed to the final manuscript.	N/A

Candidate's Signature		**Date:** 15.2.11

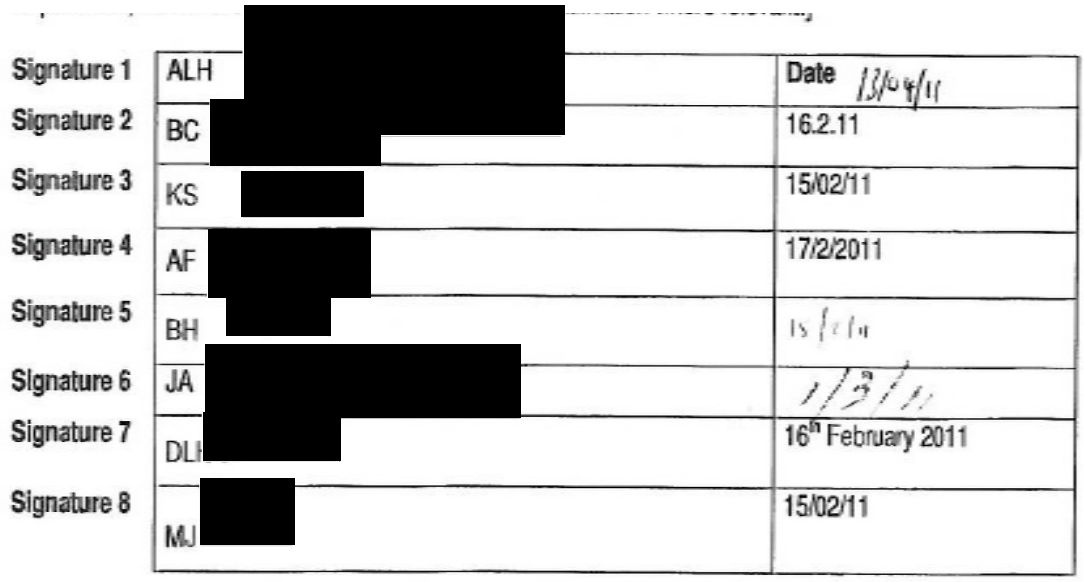
Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Public Health and Preventive Medicine Monash University Alfred Campus

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]



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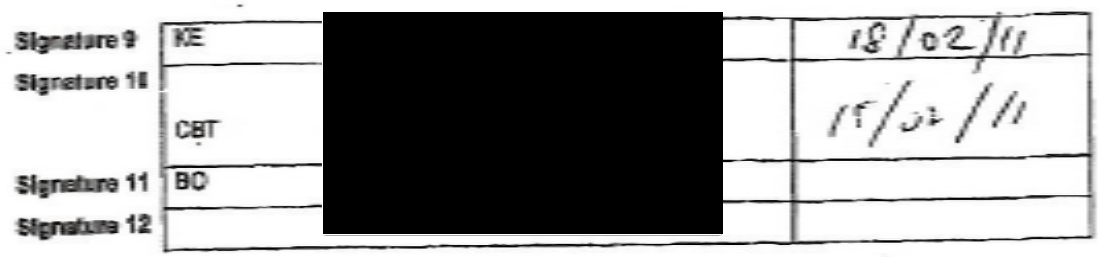

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7.2. Abstract

Background: Coronary heart disease (CHD) and depression are leading causes of disease burden globally, and the two often co-exist. Depression is common after Myocardial Infarction (MI) and it has been estimated that 15-35% of patients experience depressive symptoms. Co-morbid depression can impair health related quality of life (HRQOL), decrease medication adherence and appropriate utilisation of health services, lead to increased morbidity and suicide risk, and is associated with poorer CHD risk factor profiles and reduced survival. We aim to determine the feasibility of conducting a randomised, multi-centre trial designed to compare a tele-health program (MoodCare) for depression and CHD secondary prevention, with Usual Care (UC).

Methods: Over 1600 patients admitted after index admission for Acute Coronary Syndrome (ACS) are being screened for depression at six metropolitan hospitals in the states of Victoria and Queensland, Australia**.** Consenting participants are then contacted at two weeks post-discharge for baseline assessment. One hundred eligible participants are to be randomised to an intervention or a usual medical care control group (50 per group). The intervention consists of up to 10 x 30-40 minute structured telephone sessions, delivered by registered psychologists, commencing within two weeks of baseline screening. The intervention focuses on depression management, lifestyle factors (physical activity, healthy eating, smoking cessation, alcohol intake), medication adherence and managing co-morbidities. Data collection occurs at baseline (Time 1), 6 months (post-intervention) (Time 2), 12 months (Time 3) and 24 months follow-up for longer term effects (Time 4). We are comparing depression (Cardiac Depression Scale [CDS]) and HRQOL (Short Form-12 [SF-12]) scores between treatment and UC groups, assessing the feasibility of the program through patient acceptability and exploring long term maintenance effects. A cost-effectiveness analysis of the

costs and outcomes for patients in the intervention and control groups is being conducted from the perspective of health care costs to the government.

Discussion: This manuscript presents the protocol for a randomised, multi-centre trial to evaluate the feasibility of a tele-based depression management and CHD secondary prevention program for ACS patients. The results of this trial will provide valuable new information about potential psychological and wellbeing benefits, cost-effectiveness and acceptability of an innovative tele-based depression management and secondary prevention program for CHD patients experiencing depression.

Trial Registration Number: ACTRN12609000386235

7.3. Background

Coronary Heart Disease (CHD) and depression are currently two of the most important causes of disability in high-income countries and it is projected that the same will apply to low and middle income countries by 2030 (**1**). These conditions often co-exist with approximately 15% of Myocardial Infarction (MI) patients experiencing major depressive disorder (MDD) and another 15-20% exhibiting mild to moderate depression (**98**). Patients with post-MI depression are more likely to report impaired health related quality of life (HRQOL) (**293**), poorer medication adherence (**55**) and utilisation of health services, increased morbidity (**10**) and suicide risk (**9**), and poorer CHD risk factor profiles, work outcomes (**121**) and survival (**6**). In particular, depression results in poor uptake and completion of CHD secondary prevention or cardiac rehabilitation programs (**274**), which have been shown to play a pivotal role in improving CHD risk factor profiles and other clinical outcomes. Indeed, compared with non-depressed patients, depressed patients are three times less likely to be compliant with medical treatment recommendations (**294**). The clinical benefits of CHD secondary prevention programs are well documented and include decreased risk of fatal and non fatal recurrent MI and CVD (**264**), improved HRQOL, and lower rates of rehospitalisation (**295, 296**). However, despite the high prevalence of depression following a diagnosis of CHD and the poor outcomes associated with the group (**6**), depression remains poorly recognised and managed in CHD patients.

Traditionally, CHD secondary prevention programs are delivered face-to-face in clinic- or hospital-based settings; however, they suffer from low participation rates due to a range of barriers including poor accessibility (**297**). Symptoms of depression following Acute Coronary Syndrome (ACS), including hopelessness, helplessness, and apathy, can further impede participation in secondary prevention programs. Contemporary approaches to CHD

secondary prevention may help to overcome this treatment gap. A recent meta-analysis demonstrated that innovative, tele-based CHD secondary prevention programs may transcend some of the barriers to participation in traditional rehabilitation programs, and they are effective in improving behavioural and clinical outcomes for cardiac patients (**249**). Further, telephone-delivered therapy has proven effective for patients with depression (**250**) and more recently, for those with co-morbid depression following a cardiac event. For example, a tele-health, nurse-delivered, collaborative care intervention for coronary artery bypass graft surgery patients suffering from depression significantly improved depression outcomes, mental health components of HRQOL and disease specific physical functioning (**89**).

Psychological based therapies (**238, 253**), pharmacologic approaches (namely Selective Serotonin Reuptake Inhibitors) (**223**), and composite approaches to treatment (**81**) (**258**) have all demonstrated improvements in depression for CHD patients, especially for those with recurrent depression (**221**). While pharmacologic and psychological approaches have yielded comparable effect sizes in reducing depression (**298**), Cognitive Behaviour Therapy (CBT) has been shown to be particularly favourable for improving depression outcomes for cardiac patients, with an American Heart Association report endorsing its use (**215**). Evidence from a number of well designed trials also demonstrate its effectiveness in reducing depression in cardiac patients when compared with other approaches. For example, compared to usual care (UC), Freedland and colleagues (2007) demonstrated that CBT displayed greater and more durable effects than the other approaches (**238**). However, relatively little is known about its effectiveness under 'real world' delivery conditions, particularly using a tele-based approach. The feasibility of combining a tele-health, depression management program using CBT with a CHD secondary prevention program for ACS patients is yet to be established in the 'real world' setting. The effects of such a program could go beyond treating depression to improve all

aspects of HRQOL and CHD risk factors, and demonstrate significant economic advantages over more traditional modes of delivery. This paper presents the study protocol for a randomised, multi-centre, feasibility trial of a tele-health intervention for ACS patients with depression ('MoodCare'). We hypothesize that the trial will demonstrate the feasibility of the MoodCare intervention through improving key depression and HRQOL outcomes at 6 months, with increased participant satisfaction, and will be cost-effective compared with UC.

7.4. Methods

We are currently enrolling 100 ACS patients in a prospective, multi-centre, feasibility trial with patients randomised to either the intervention or UC control group. Participants in both groups complete assessments at baseline (Time 1), post-intervention or 6 months follow-up (Time 2), as well as at 12 months (Time 3), and 24 months (Time 4) for longer term effects.

7.4.1 Study Aims

Primary Aim: To investigate the feasibility of a telephone-delivered, depression management and CHD secondary prevention intervention for ACS patients over 6 months. Prospective outcomes include: changes in depression using the Cardiac Depression Scale (CDS) and changes in HRQOL using the Short Form-12 (SF-12), cost-effectiveness and participant acceptability compared with UC.

Secondary Aims: (i) To investigate the longer term feasibility of implementing the MoodCare program at 12 and 24 months follow-up.

7.4.2 Study Sample

Eligibility Criteria

Eligibility criteria includes: a clinical diagnosis consistent with that of ACS (MI [STEMI or non STEMI] or unstable angina confirmed by angiogram), aged 21-85 years, fluency in English, availability via the telephone for the duration of the study, and a Patient Health Questionnaire (PHQ9) score of 5-19. Patients are excluded if they are: participating in regular psychological therapy with a mental health professional at the time of admission for ACS, diagnosed with a psychiatric condition which may impact on involvement (including bipolar illness, psychotic illness of any type, dementia, acute suicidality, severe personality disorder), cognitively impaired impacting on their ability to participate in the study, diagnosed with a terminal illness, or unable to participate in a tele-based unsupervised mood and lifestyle intervention as confirmed by the treating clinician.

Sample Recruitment Procedures

We are screening more than 1600 patients over approximately 15 months from six metropolitan hospitals in Victoria and Queensland, Australia. Recruitment commenced in December 2009. All consenting patients are assessed for depression prior to hospital discharge using a psychometrically robust and valid instrument (PHQ9) (**299**). Patients with a PHQ9 score of 5-19 are eligible to participate. This scoring range was selected due to its high sensitivity and specificity, as opposed to the commonly used cut off of ≥10, which has comparable specificity (92% and 90%, respectively), but poorer sensitivity (39% and 54%, respectively) (**300**). Patients with a PHQ9 score <5 are provided with relevant feedback, reassurance and advice. Any persons indicating suicidal thoughts on PHQ9 and/or those with severe depression, as indicated by PHQ9 scores of 20-27, are referred for further assessment by a mental health professional and possible study exclusion. Algorithms are in place for patients assigned to the intervention whose condition deteriorates throughout the program, and who are no longer eligible or lost to follow up throughout the course of the trial.

Eligible participants are subsequently contacted by the research team via telephone within 1-2 weeks of discharge to complete Time 1 data collection. This includes a secondary assessment of depression in order to determine severity. Participants initially respond to a two item screening tool which has a positive endorsement of the first two PHQ items (**300**), before undertaking the full Composite International Diagnostic Interview (CIDI) assessment.

Sample Size Calculations

Anticipating an attrition rate of 20% throughout the study, n=125 participants are required to achieve a final sample size of n=100. Sample size analysis indicated that 50 subjects per group (intervention and control) or a total of 100 are required to complete the study in order to detect an absolute intervention effect with 80% power and type I error of 5% (two-tailed). Sample size was calculated based on an overall difference between participants in the intervention and control groups in the primary outcome measure of depression scores at 6 months, where a sample size of n=100 was sufficient to detect a difference in mean CDS scores of 6.8, assuming a between-patient SD of 12 (**301**). Assuming persistence of effect to 12 months and a conservative correlation of 0.30 between baseline, 6 months and 12 months CDS scores, a pooled analysis at 6 and 12 months will have 80% power to detect a difference of 5.1 units (a change score of 5 on the CDS is considered clinically meaningful).

7.4.3 Ethics Approval

Ethics approval was received from Human Research Ethics Committees of St Vincent's Hospital, The Austin Hospital, The Royal Melbourne Hospital, The Geelong Hospital, The Prince Charles Hospital, The Royal Brisbane and Women's Hospital, and Monash University (APPENDIX B).

7.4.4 Study conditions

Both control and intervention participants receive a brief National Heart Foundation of Australia education pamphlet on MI recovery and a biennial study newsletter based on existing educational materials to enhance study retention. On enrolment, a letter is sent to all participants' primary care provider/s informing them of the aims of the study, the group to which the patient has been randomised and other relevant information that may be required from the participant and the care provider at follow-up.

Control: Control participants continue to receive their usual medical care through their health care providers.

Intervention: The intervention commences within two weeks of baseline screening and is delivered by qualified psychologists ('counsellors') from Monash University. The intervention aims to manage depression as well as CHD risk factor behaviours using a tele-based care management model (**251**) incorporating CBT counselling (**233**). Two psychologists with at least 2 years of relevant clinical experience with CBT are delivering the intervention. The counsellors provide information to patients via the telephone during structured counselling sessions and assist participants to set and attain specific short and long term goals and a plan of action to improve their mental health and CHD risk factor profiles. Cognitive restructuring, behavioural activation, goal setting and motivational interviewing techniques are utilised. Participants are encouraged to seek appropriate treatment and attend follow-up with their usual health care providers as necessary, in addition to activating social/family support and community and environmental linkages (e.g. employment, housing support). The intervention comprises up to 10 x 30-40 minute sessions over a six month period as CBT has been found to effectively reduce depressive symptoms over this time frame (**81**). The sessions are most intensive over the first three months when depressive symptoms are most likely to affect

patients following ACS (**158**) and to impact on their HRQOL and adoption of positive CHD risk factor behaviours. More frequent sessions may be scheduled during the treatment phase based on a patient's needs and interest but the intervention is limited to up to 10 sessions in total.

Intervention participants receive a handbook containing both project specific and general health resources. For example, the handbook contains monitoring forms and recording sheets to be used during and in between sessions for tracking the participant's mood, session activities, the participant's thoughts, CHD risk factor goals and changes. It provides additional information and details on the nature and treatment of depression, as well as the CBT model. More generally, supplementary materials including a list of health related resources are provided in the handbook.

7.4.5 Study Integrity

The study design is guided by the CONSORT statement (**302**), and randomisation to study group occurs following the completion of Time 1 data collection. Project staff who are collecting data are blinded to participants' study group. Participants are asked not to reveal the group to which they have been randomised when completing data assessments. Stratified randomisation occurs using a separate block randomisation list that has been generated for each study group or strata. Randomisation is integrated into the web-based database and automatically generated following the conclusion of baseline assessment. The process is concealed from investigators. The schedule is stratified by severity of depression assessed by the CIDI (i.e. those meeting current diagnosis for depression versus those who do not). The intervention protocol is detailed in a manual. In addition to internal peer review, all intervention calls are audio-taped with a proportion reviewed by a senior clinical psychiatric consultant, using a standardised inventory in order to ensure clinicians'

adherence to the delivery of the intervention protocol and treatment integrity. To assess the quality of the delivery of the intervention, a separate inventory based on the Cognitive Therapy Scale (**303**) has been developed for the MoodCare intervention. All data analyses are conducted on the basis of intention to treat.

7.4.6 Data collection and outcome measures

Clinical and anthropometric data are collected at the time of the participant's initial screening, from hospital medical records (blood pressure, cholesterol level, haemoglobin A1C (HbA1c), family history of heart disease, height, weight, waist circumference, body mass index (BMI), procedures performed or scheduled, General Practitioner (GP) details, cardiologist details, whether patient was transferred from another hospital, details of initial admitting hospital, admission and expected discharge date). At follow-up, participants are requested to collect medical information (blood pressure, cholesterol level, HbA1c, weight, waist circumference) from their primary care provider/s medical records prior to Computer Assisted Telephone Interview (CATI). Self-report and CIDI interview data are collected, at Time 1, Time 2, Time 3 and Time 4 by CATI. Additional outcome data are collected via postal survey to minimise participant burden (see Table 7.1). The feasibility of the trial will be determined by the following outcome measures:

Changes in key depression and HRQOL outcomes

The two primary outcomes are changes in depression and HRQOL which are assessed using the CDS (**304**) and SF-12 (**305**), respectively. The CDS was originally designed to measure depressed mood over the full range generally seen in cardiac patients, combining excellent test-retest reproducibility with responsiveness to change over time (**306**). In addition, it also has excellent sensitivity (97%) at appropriate specificity (85%) for the categorical diagnosis of major depression (**301**). Other outcome variables include: physical activity (**307**),

saturated fat intake (**308**), smoking, alcohol intake (**309**), anxiety (**310**), social support, employment, lipid profile, blood pressure, BMI, waist circumference, diabetes management (HbA1c), and pharmacological management (self report, health care utilisation data). Six month follow up will be the primary assessment point. The measures for each of these outcome variables are summarised in Table 7.1.

Cost-Effectiveness Analyses

A cost-effectiveness analysis (CEA) of the costs and outcomes for patients in the intervention and control groups will be undertaken. Detailed data on costs of Health Care Utilisation (HCU), access to community and other resources, and medication are being collected from both the intervention and 'usual care' control groups. All resources utilised are costed using nationally applicable cost data (e.g. Diagnostic Related Groups costs for hospital admissions). Total medication costs are taken from patient contributions and estimated total Pharmaceutical Benefits Scheme benefits paid by the Health Insurance Commission. For HCU, data linkage with Medicare Australia's database allows the collection of health care utilisation data for use of items under Medicare and Pharmaceutical Benefits Scheme (PBS). Participants are requested to record current medications and number of general practitioner visits prior to Time 3 and Time 4 follow-up assessments.

The expected cost of readmission for ACS is also calculated using hospital-based costs and patient-specific probabilities of readmission for ACS computed using APACHE III (Acute Physiology And Chronic Health Evaluation III). The primary health outcome for the CEA is quality-adjusted life years (QALYs). These are calculated for both arms using HRQOL scores collected in the trial using the SF-6D, a derivative of the SF-12. The SF-12 instrument is widely used internationally, and has been recommended as appropriate and sensitive to change for CHD patients and in depression treatment (**311**). For all economic analyses,

detailed probabilistic sensitivity analysis will be undertaken for all projections and parameters with uncertainty and/or variability.

Intervention Implementation and Acceptability

To assess program implementation, participant acceptability is measured by a self-administered questionnaire at Time 2. Self-administered satisfaction questions include: 'how would you rate the MoodCare Participant Handbook' (*excellent* to *poor*); 'how would you rate your sessions with the Counsellor (*very useful* to *not useful at all)*; 'did you get what you expected from the program' (*yes definitely* to *no definitely not)*; 'to what extent has the program met your needs' (*almost all of my needs have been met* to *none of my needs have been met);* 'has the program helped you to deal more effectively with your health issues' (*yes it helped a great deal* to *no it seemed to make things worse)*; 'in general how satisfied are you with the program (*very satisfied* to *very dissatisfied)*; 'were you satisfied with the length of the counselling sessions' (*yes, no)*; 'were you satisfied with the number of counselling sessions' (*yes, no)*; and 'were you satisfied with the length of the program overall' (*yes, no)*. Participants are also asked to highlight the strengths and weaknesses of the program in two open-ended questions. Participant adherence to the intervention is assessed by: the proportion of sessions completed during the intervention period; the topics covered in each session; and the total length (minutes) of intervention exposure during the six month period.

Long term maintenance and sustainability

The RE-AIM framework has been developed to evaluate the strengths and weaknesses of different approaches to chronic disease management (**312**). This framework will be applied to further assess the feasibility of the MoodCare program. For example, we will evaluate the *Reach,* or representativeness of the sample by assessing the characteristics of eligible, enrolled and randomised participants. Similarly, to assess *Adoption,* characteristics on

program uptake and adherence will be provided. The long term *Maintenance* of the program will be assessed by evaluating participant outcomes beyond six month follow up (e.g. 12, 24 months).

7.4.7 Data Analyses

Baseline characteristics will be compared across intervention arms using summary statistics. Principal analyses will involve comparison of CDS and HRQOL outcomes at each time point between intervention arms using the baseline of the outcome as a covariate where relevant. Pooled analyses across all time points will employ linear mixed models. This will assess comparative rates of change over time, variability between rates of individuals, and allows for incomplete data due to a process of missingness where systematic dependence is upon observed covariates or outcomes, the so called "missing at random" assumption. Results will be expressed as estimated mean changes in CDS depression measures and HRQOL, as an overall mean excess intervention over usual care effect, all with corresponding 95% confidence intervals.

7.5. Discussion

Depression often remains unrecognised and untreated in cardiac patients, despite increasing the risk of poor patient outcomes such as reduced HRQOL and increased mortality (including suicide). For the first time, this study will evaluate the feasibility, efficacy and cost-effectiveness of a state-of-the-art, tele-based depression management and CHD secondary prevention program for depressed ACS patients. If feasible, and successful in promoting depression and HRQOL benefits, the intervention could provide an alternative for those who cannot tolerate or would prefer a non-pharmacological alternative to depression treatment. Further, this contemporary tele-health approach to management may help overcome some of

the barriers to participation that are associated with face to face rehabilitation programs, including distance, cost and time. The intervention could be translated into clinical practice through community-based telephone helplines widely used in Australia and internationally, or through acute clinical care settings.

7.6. Competing interests

The authors declare that they have no competing interests.

7.7. Authors' contributions

ALH, CBT, KS, DLH, BH, JA, MJ and BO developed the study concept and aims. BC, AO, BO, KE and ALH co-wrote the study protocol. BC, AO, CBT, KS, ALH and BO are implementing the study protocol and overseeing the collection of data. AF performed the sample size calculations and randomisation schedule and will oversee data analysis. AO and ALH drafted the study manuscript and all authors contributed to, read and approved the final manuscript.

7.8. Acknowledgements

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7.9 Tables

Table 7.1. Measurement of outcome variables at baseline (Time 1), post-intervention (Time 2), 12 months (Time 3), 24 months follow-up (Time 4)

Variable	Measurement tool	Inpatient Screening	1-2 weeks post discharge TIME 1	6 Months TIME 2	12 Months TIME 3	24 months TIME 4	Type of administration
Depression	Patient Health Questionnaire 9	✓	✓	✓	✓	✓	CATI+
	Two item screener		✓				CATI
	Cardiac Depression Scale		✓	✓	✓	✓	CATI
	Composite International Diagnostic Interview		✓		✓	✓	CATI
HRQOL	Short Form 12		✓	✓	✓	✓	CATI
Physical activity	Active Australia Survey		✓	✓	✓	✓	Postal survey*
Saturated Fat Intake	Short Fat questionnaire		✓	✓	✓	✓	Postal survey*
Social Support	ENRICHD Social Support Inventory		✓	✓	✓	✓	CATI
Smoking	Cancer Council Food Frequency Questionnaire		✓	✓	✓	✓	Postal survey*
Alcohol	Cancer Council Food Frequency Questionnaire		✓	✓	✓	✓	Postal survey*
Medication	Self report/General Practitioner/data linkage		✓	✓	✓	✓	Postal survey,* medical records
Anxiety	General Anxiety Disorder-7		✓	✓	✓	✓	CATI
Medical co-morbidities			✓	✓	✓	✓	CATI
Biomedical and anthropometric measurements	Weight, height, waist circumference, Blood Pressure, lipids, fasting capillary blood glucose	✓			✓	✓	Medical records
Employment	Employment status, absenteeism/productivity		✓	✓	✓	✓	CATI

CATI = Computer Assisted Telephone Interview; *An envelope containing self administered paper copies of each instrument is posted to the participant prior to their baseline telephone interview. The survey is to be completed on approximately the same day as baseline CATI interview to ensure consistency of information, and returned to the Project Manager. +In patient screening conducted face to face by nurses, using the PHQ9. Follow up PHQ9 administration conducted using CATI at all assessment points thereafter

Chapter 8: EFFECTIVENESS OF A COMBINED DEPRESSION MANAGEMENT AND CORONARY HEART DISEASE SECONDARY PREVENTION PROGRAM ('MoodCare') ON MENTAL, PHYSICAL AND VOCATIONAL FUNCTIONING OF ACUTE CORONARY SYNDROME PATIENTS: PRELIMINARY FINDINGS

Chapter Overview

Having detailed the methodology of the MoodCare study, the aim of this chapter was to present the preliminary results of the MoodCare program in relation to HRQOL and vocational functioning at 6 months, compared with usual medical care.

8.1. Abstract

Objective: In cardiac populations, treating depression can improve mood but benefits have not always extended to physical health functioning. Even less is known about its impact on vocational functioning. Combining depression management with a lifestyle modification program could improve mental, physical and vocational functioning. Further, using telephone delivery may facilitate uptake and improve study attrition rates. The aim of this chapter was to determine whether such a program ('MoodCare') can improve mental and physical components of health related quality of life (HRQOL) and vocational functioning of Acute Coronary Syndrome (ACS) patients after 6 months. A secondary aim was to identify predictors of study drop out between baseline and six months.

Methods: Preliminary data from the main trial (refer to protocol in Chapter 7) were utilised. The study methodology, including details of recruitment, has been described previously. Complete baseline and six month follow up data were available for 61 participants (n=32 intervention, n=29 Usual Care (UC)). One-way Analysis of Variance (ANOVA) for Independent Samples were conducted to assess group changes in SF-12 mental (MCS) and physical component summary (PCS) scores, between baseline and follow up. Logistic regression was used to assess group differences in the odds of return to work (RTW), workplace absenteeism and presenteeism, and to identify predictors of study drop out.

Results: The study attrition rate was 12.8% (n=9/70). Attrition was not significantly associated with any of the baseline characteristics investigated. Compared with UC, the intervention yielded statistically significant improvements in PCS scores at follow-up (mean difference=6.7; 95% CI: 1.1, 12.3). A similar pattern was observed for mental HRQOL but was not statistically significant. For those with a previous episode of Major Depressive Disorder (MDD) across the lifetime, intervention effects were most pronounced for MCS (mean

difference: 9.1, 95% CI: 0.02, 18.1, p=0.05). In this sub-group, exposure to the intervention (average length of telephone sessions, in minutes) was significantly associated with improved PCS scores (p=0.03). Overall, significant interactions between the number of General Practitioner visits at baseline and the intervention were found to improve PCS scores (p=0.02). Mean depression levels of each group followed a similar trajectory between hospital screening, baseline and six months, and did not differ significantly at any time. No significant differences in odds of RTW, workplace absenteeism or presenteeism were observed between groups at follow up.

Conclusions: Preliminary findings suggest that the MoodCare program has the potential to improve physical HRQOL outcomes of ACS patients. The program also appears to be particularly effective for improving the mental health functioning of those with a history of MDD. Further research comprising the complete sample is required to confirm these effects, particularly in relation to vocational outcomes where cases were limited. Overall, these findings provide preliminary support for the application of a combined approach to care management using tele-health in depressed cardiac populations.

8.2. Introduction

In recent decades, there has been an increasing interest in the relationship between cardiovascular disease (CVD) and depression. This has led to the development and evaluation of a range of depression management interventions for cardiac patients. However, to date, much of the research in this area has focussed predominantly on survival as well as CVD- and depression-related outcomes as indicators of program success (**223**). While other outcomes have been evaluated (e.g. social support (**81**), cardiac functioning (**89**)), the impact of depression treatment on key functional outcomes such as mental, physical and vocational functioning, has remained neglected by comparison.

Of the existing evidence, depression management has been shown to have a greater effect on mental, as opposed to physical, health functioning of cardiac patients. For example, Rollman et al (2009) found that a telephone-delivered, stepped, collaborative care model for depression management ("Bypassing the Blues") improved mental but not physical HRQOL of Coronary Artery Bypass Grafting (CABG) patients after 8 months (**89**). A recent meta-analysis further confirmed that the benefits of depression treatment in cardiac populations largely relate to mental HRQOL (Chapter 6) (**313**). After pooling findings from the few studies in this area to include HRQOL as an endpoint, intervention effects were shown to be significant but of a lesser magnitude for physical HRQOL, at six month follow up (**313**).

Similarly, CVD-related lifestyle modification programs and cardiac rehabilitation have been shown to effectively improve physical HRQOL, amongst other outcomes. Smith et al (2004) found a home based rehabilitation program for CABG patients to be associated with enhanced physical HRQOL after 12 months (**314**). Developing a similar program which includes a targeted depression management component may have the potential to impact both

components of HRQOL to ultimately optimise the functional outcomes of cardiac patients with co-morbid depression.

An evaluation of the impact of such a program on the vocational outcomes of cardiac patients is also required, where evidence is currently lacking. In one of the first trials of its kind, Rost et al (2004) found that primary care based depression management enhanced work productivity and absenteeism of depressed patients over two years (**315**). In contrast, Simon and others (1998) found no benefits of a pharmacological and collaborative care model on vocational outcomes of depressed primary care patients (**93**). Few, if any, trials of this nature have been conducted in cardiac populations using these endpoints. In fact, these research gaps have been highlighted in the literature: "..It would be expected that treating depression and anxiety [in cardiac patients] would lead to improved quality of life and reduction in days of restricted activity and days missed from work. This remains to be demonstrated in a clinical trial, however" (**118**).

The most effective mode by which to deliver such an intervention also remains unclear. Psychological therapy delivered over the telephone has been shown to effectively reduce depression (**246**). Importantly, this mode of delivery often yields low attrition rates (**246**). Previous studies have also highlighted the benefits of using a tele-health approach with CABG patients who report depression (**89, 238**). These include enhanced uptake, adherence, flexibility and reach. As evidence suggests that uptake of structured rehabilitation programs is often poor after a cardiac event (**316**), particularly for those with depression, the National Heart Foundation of Australia has endorsed the use of "flexible secondary prevention service options that are tailored to the needs of populations and individuals, appropriate to various stages of CVD management" (**317**). Providing a tele-health approach to rehabilitation which combines secondary prevention and depression management may overcome some of the

logistical barriers to poor uptake (**297**) in order to facilitate attendance and improve study attrition rates.

The aim of this chapter was to determine whether the 'MoodCare' program can improve HRQOL and vocational functioning of ACS patients after 6 months. A secondary aim was to identify predictors of study drop out between baseline and six months.

8.3. Methods

The study methodology, including recruitment strategy, of the MoodCare trial has been described previously. This chapter utilises preliminary data of 61 participants collected as part of the main trial described in Chapter 7 (available as at December 2011). The effects of the intervention will be measured using data from two assessment points only (i.e. pre-intervention [baseline] and post-intervention [6 month follow up]).

8.3.1 Statistical analysis

Differences in the baseline characteristics of intervention and UC participants were identified using independent sample t-tests for continuous variables and Fisher's exact tests for dichotomous variables. One-way Analysis of Variance for Independent Samples (ANOVA) were conducted to assess differences in SF-12 MCS and PCS change scores between baseline and follow up, across intervention and UC groups. Results were expressed using estimated mean changes in outcomes by group, all with corresponding 95% confidence intervals (CI). Interaction terms were included in a separate analysis to explore potential effect modification between treatment group and the following variables: medication usage, age of depression onset, recency of depressive episode, baseline enrolment in cardiac rehabilitation and health service utilisation. Participants' level of exposure to the intervention was assessed by recording: (i) the number of intervention sessions completed by the participant (range 0-10)

and (ii) the average time (in minutes) each individual spent participating in the intervention. Content and quality of the intervention sessions were assessed by an independent reviewer. When each participant commenced the intervention, two sessions were randomly selected for independent review using the quality assurance methods described in the previous chapter. For the purpose of this preliminary analysis, the assessments for ~20% of participants (6/32) were selected. These data were used to provide an estimate about the type of content (mood versus lifestyle modification) and the therapeutic approaches most commonly used (behavioural activation versus cognitive therapy) throughout the course of the intervention.

For return to work (RTW), absenteeism and presenteeism variables, only those participants indicating that they were employed (full or part time, casual or work without pay) at 6 months were included in the analysis (n=26; with n=20 providing complete information at follow up). Data were clustered around zero for both absenteeism and presenteeism variables. Therefore, logistic regression modelling was used to assess group differences in all three outcomes of interest. The limited number of cases precluded ordinal regression therefore each variable was treated dichotomously (attended work while sick in the past 4 weeks [yes/no]; stayed away from work due to sickness in the past 4 weeks [yes/no]. Baseline RTW, absenteeism and presenteeism were included as co-variates for the respective models. Measures of magnitude were presented as Odds ratios (ORs), with accompanying 95% CIs. In order to assess differential sub-group effects, a sub-group analysis was conducted comprising only those reporting a history of major depressive disorder (MDD) over the lifetime. The randomisation schedule was stratified by CIDI assessment (MDD versus No MDD) to ensure that the distribution of MDD cases between groups was even. Only individuals with complete data were included in the analyses. Logistic regression modelling was used to identify predictors of drop out between baseline and six months. All participants

were analysed according to their random allocation to group. All statistical analyses were conducted using Stata Version 11.0.

8.4. Results

The flowchart in Figure 8.1 displays the recruitment numbers for the study. Initially, 1242 hospitalised ACS patients were identified as being potentially eligible for the study by recruitment staff. 339 patients completed informed consent and were administered the PHQ9; 158 of these recorded PHQ9 scores between 5 and 19. Of these, 104 participants were randomised (n=48 UC; n=56 intervention). At the time of conducting this analysis, 70 randomised participants had been contacted for scheduled 6 month data assessment. Nine participants (n=4 UC; n=5 intervention) did not complete assessment (lost to follow up/withdrew from the study). Therefore, data from the 61 participants completing both baseline and 6 month follow up assessments were utilised in this preliminary analysis (n=29 UC; n=32 intervention).

Table 8.1 shows the key characteristics of these participants. No statistically significant differences were observed between intervention and UC groups for these key characteristics, but nevertheless some difference estimates were large (e.g. diabetes status, cardiac rehabilitation enrolment). The low SF-12 scores for both groups, indicating serious impairment for both physical and mental health functioning in this sample, were comparable to those of other studies (**89**).

In-hospital PHQ9 depression scores were comparable between groups, although slightly higher for UC participants (mean 10.8, 95% CI: 9.15, 12.5; indicating moderate depression) compared with intervention participants (mean 9.4, 95% CI: 7.9, 10.8; indicating mild depression). For those indicating prior depressive episodes, the average age of depression

onset across the lifetime for UC and intervention participants was also comparable (mean=34.8 and 31.4 years of age, respectively). UC participants reported a more recent depressive episode (mean= 3.7 years ago) compared with intervention participants (mean=6.5 years ago). Those belonging to the UC group reported a higher prevalence of MDD history (52.8% versus 47.2%).

More than half (53%) of the participants assigned to the Moodcare intervention participated in at least 5-10 sessions throughout the intervention period. The median number of sessions was 9 (range 0 - 10). The average length of the telephone calls was 48 minutes (Standard Deviation: 18.2). In relation to intervention content, mood (either anxiety or depression) was addressed on 100% of reviewed calls: anxiety (identifying or managing related behaviour, thinking or body signals) was addressed in 83% of sessions while depression (identifying related feelings, thoughts and behaviours) was addressed in 66% of sessions. Lifestyle modification (setting goals in areas of diet, physical activity, smoking, alcohol, weight management and medication taking) was addressed in all participant sessions, with one exception (83%). Therapists provided participants with 'useful skills' (tips for better sleeping, relaxation, goal setting) in 66% of reviewed sessions. In regards to the type of therapeutic technique applied, cognitive therapy was utilised on 83% of occasions, compared with behavioural activation (50%).

8.4.1 Analysis of main effects

At follow-up, there was a statistically significant, greater improvement in SF-12 PCS scores for the intervention group compared with those receiving UC (mean difference: 6.7, 95% CI: 1.1, 12.3). Similarly, the intervention group reported greater improvement in SF-12 MCS scores, however this failed to reach statistical significance (Table 8.2). In order to explore the interactive effects of other relevant variables on PCS and MCS scores, a series of linear

regression models were created, with each interaction term individually included with the main effects terms. While baseline anti-depressant use, enrolment in cardiac rehabilitation, recency of depressive episode and age of depression onset did not interact with treatment condition to influence either component of SF-12, number of General Practitioner (GP) visits at baseline significantly interacted with the intervention to improve SF-12 PCS scores (p=0.02).

Table 2 displays the mean changes in each outcome by group; the intervention was not associated with improvements in either depression or anxiety. Overall, however, reductions in depression and anxiety were observed for both groups. Figure 8.2 shows a similar trajectory of PHQ9 scores in each group at in-hospital screening, baseline and follow up.

For participants with a history of MDD (n=26), the intervention was associated with statistically significant improvements in SF-12 MCS (mean difference: 9.1, 95% CI: 0.02, 18.1). Although improvements were observed in SF-12 PCS scores, these differences were not significant (mean difference: 4.8, 95% CI: -3.4, 12.8) (Table 8.3). PCS scores were, however, significantly associated with length of exposure to the intervention (average length of participants' telephone sessions, in minutes)(mean difference: 0.4, 95% CI: 0.04, 0.8, p=0.03). The number of intervention sessions delivered to participants was not related to changes in either PCS or MCS scores. Small reductions in PHQ9 scores were observed in favour of the intervention group however, no statistically significant differences for anxiety (GAD-7) or depression (PHQ-9) were observed between groups. Interestingly, improvements in CDS depression scores (the outcome on which the larger trial was powered) at follow up favoured the UC condition (Table 8.3). However, these differences were not significant.

A logistic regression model revealed no statistically significant differences in the odds of return to work (RTW) at follow up (OR: 1.0, 95% CI: 0.2, 5.1). Similarly, no significant

differences in the odds of workplace presenteeism were observed between groups at six months, after controlling for baseline presenteeism (OR: 1.2, 95% CI: 0.1, 10.5; where UC is the reference group). Wide CIs reflect the small number of cases. A separate model was constructed to assess absenteeism. This revealed no statistically significant differences in workplace absenteeism at follow up (OR: 0.2, 95% CI: 0.0, 2.4; where UC is the reference group).

8.4.2 Predictors of study drop out

To identify predictors of drop out between baseline and six months, the following baseline characteristics were individually included in separate logistic regression models: Treatment condition, age, gender, employment status, education, country of birth, language spoken, income, private health insurance, CDS and PHQ9 depression score, age of depression onset, recency of depressive episode, GAD-7 anxiety score, SF-12 scores (MCS and PCS), doctor-defined diabetes diagnosis, high blood pressure, high cholesterol and social support score. No variable was found to significantly predict study drop out.

8.5. Discussion

The primary aim of this chapter was to determine whether a targeted depression management and Coronary Heart Disease secondary prevention program ('MoodCare') improved mental and physical HRQOL and vocational functioning of ACS patients. At six months, the intervention was associated with statistically significant improvements in physical HRQOL. A similar effect was found for mental HRQOL, but failed to reach significance. An interaction between baseline health care utilisation and treatment condition was observed for physical HRQOL. For those with a history of MDD, significant intervention effects were observed for MCS. While no significant differences were observed for PCS in this group, the

amount of time the individual spent participating in the intervention significantly predicted improved PCS scores. No differences in RTW or vocational functioning (presenteeism or absenteeism) were observed. No significant predictors of study dropout were identified between baseline and follow up.

The first finding adds to those of other studies that have used a telephone-delivered approach to deliver depression treatment to CABG patients; Rollman et al (2009) (**89**) found that the Bypassing the Blues intervention improved HRQOL after 8 months. This intervention yielded a difference of 3.2 points on the SF-36 MCS (95% CI: 0.5-6.0), compared with MoodCare which yielded a difference of 5.6 points on the SF-12 MCS (95% CI: -0.20, 11.3). The minimal clinically important difference for the SF measures is between 3 and 5 units (**291**). For physical HRQOL, the Bypassing the Blues intervention yielded a difference of 1.6 points (95% CI: −0.5 to 3.8), compared with Moodcare which yielded a difference of 6.7 points on the SF-12 PCS (95% CI: 1.1, 12.3). While it is acknowledged that one of the difficulties associated with the analysis of behavioural interventions is ascertaining which particular components of a program have led to improved participant outcomes (APPENDIX A2), we hypothesise that the magnitude of effects observed in the Moodcare study, particularly related to physical health functioning, may reflect the multi-faceted approach of the intervention. The novel inclusion of CVD-related lifestyle modification was intended both for disease management and secondary prevention of heart disease, and for mood enhancement. Indeed, previous research has highlighted the benefits of sleep/relaxation (**318**) and exercise (**319**) in depressed populations, therefore it is likely that the combination of these intervention components contributed to the observed benefits in this study. Alternatively, as depressive symptoms in the intervention group were shown to be mild at baseline, it is possible that these participants simply spent a greater amount of intervention time dedicated to lifestyle modification. This is

unlikely, however, given that fidelity assessments of the intervention indicated that mood was more commonly addressed than lifestyle (100% versus 83% of reviewed participant sessions, respectively).

In contrast to the Bypassing the Blues intervention (**89**), the MoodCare program did not produce significant between group differences in depression scores. Where it has previously been argued that improvements in HRQOL may simply be a by-product of reducing depressive symptoms (**320**), these findings provide some evidence that HRQOL status can be substantially improved without significantly alleviating depression and provide further justification for the inclusion of HRQOL outcomes in the evaluation of these programs. It is acknowledged that reductions in depression levels were observed for both groups (providing some evidence of spontaneous remission) and further, that intervention effects were most pronounced for those with a history of MDD; the intervention was found to significantly improve mental health functioning in this group. Therefore HRQOL and depression are seemingly linked in some way. It is possible that the greatest effects were observed for those with major depression because this sub-group had the greatest scope for improvement. Results from the larger trial are required to confirm this hypothesis.

While there appears to be limited evidence regarding the impact of depression treatment on vocational outcomes of cardiac patients, our second finding is consistent with some of the studies previously conducted in depressed populations. Simon et al (1998) propose that sustained remission of depression may be necessary to achieve good occupational outcome (**93**). By this theory, the null effect on vocational functioning observed in the present study may be explained by the null effect on depression outcomes. Alternatively, it is likely that any

between-group differences in vocational outcomes as a result of the intervention, would have remained undetected due to the small number of employed participants at follow up.

A significant interaction was shown to exist between participant health service utilisation at baseline and treatment condition, indicating that those in more frequent contact with a GP at the time of their heart event were more responsive to the intervention. There are several explanations for these findings. First, participants most responsive to the MoodCare intervention were those who exhibited good help seeking behavior upon enrolment, therefore were highly adherent to the intervention schedule. Alternatively, the MoodCare program may have been useful in regularly reinforcing initial practitioner advice throughout the ensuing recovery period. Consistent advice from both GP and MoodCare therapist regarding recovery may have promoted adherence to health and lifestyle recommendations, thereby leading to improvements in HRQOL outcomes. In the future, those designing studies of a similar nature or, alternatively, key stakeholders considering wide-scale implementation of a program such as MoodCare should consider the important link between patient, practitioner and interventionist to maximise patient benefit.

A strength of this preliminary study was the sound attrition rate observed, to date. An attrition rate of 12.8% further indicates good retention, comparable with other tele-health studies of this nature. For example, Rollman et al (2009) reported an attrition rate of 16.5% at 8 month follow up (**89**). It is likely that the telephone-delivered approach to both intervention delivery and data collection used in the present study enhanced retention rates because of greater convenience and flexibility to the participant. While not as cost-efficient as postal administration (**321**), this follow up technique is advantageous because of the immediate acquisition of data, and has been demonstrated to be an effective mode of follow up for

cardiac patients (**322**). Indeed, the instruments used to assess depression (**323**) and HRQOL (**324**) in this study have been found to be reliable when delivered over the telephone. CBT has also been shown to be effectively delivered over the telephone to individuals with chronic disease (**325**).

Several limitations were observed when conducting this study. First, while impressive retention rates have been observed for enrolled participants to date, the recruitment rate for the overall MoodCare trial was poor (~8%)(Figure 8.1). Reasons for this are discussed in Chapter 9, but briefly, may include: reduced motivation or interest levels of patients as a result of depressive symptoms, insufficient information provided about the trial by the recruiters, or the stigma related to enrolment in a depression treatment study. It is recognised that as a result of poor recruitment rates, the sample on which our findings are based is subject to bias. Second, it is acknowledged that the statistical power associated with these preliminary findings is limited by the small sample size. As trial recruitment and assessments of participants is currently ongoing, the overall efficacy of the intervention will ultimately be based on the full sample of n=120 after all assessments are complete and will provide greater scope about the efficacy of the intervention. These analyses will explore imputation methods used to manage missing data (**326**) and identify variables associated with missing values.

Third, it is acknowledged that the usual care group was not a control condition in the purest sense. As this was a "real world" feasibility trial it was deemed unethical to deprive this group of the resources provided as part of usual medical care for ACS patients in Australia (e.g. cardiac rehabilitation). Therefore, there is likely to be wide variance in the level of usual care received by the control group; across site and state. For example, a Queensland study demonstrated a significant under-utilisation of cardiac rehabilitation services in that state

(**297**). However, while notable between group differences in cardiac rehabilitation enrolment were observed at baseline, no significant interactions between cardiac rehabilitation and treatment condition were observed for any of the outcomes explored in this chapter.

In conclusion, these preliminary results provide some promising evidence regarding the benefits of this telephone-delivered intervention for cardiac patients experiencing depression; meaningful improvements in HRQOL outcomes were observed. Both clinically and statistically meaningful, the magnitude of the intervention effect on PCS provides some support for the inclusion of a CVD-related lifestyle component in depression management programs delivered in cardiac populations. Conversely, the improvements in mental health functioning of those with MDD history as a result of the intervention, suggests that the inclusion of a more structured depression management component of cardiac rehabilitation may be warranted. A cost-effectiveness analysis due to be conducted at the completion of the larger MoodCare trial will provide key data to guide the development of a funding model for such a program to be developed within the context of the Australian health care setting.

8.6. Figures

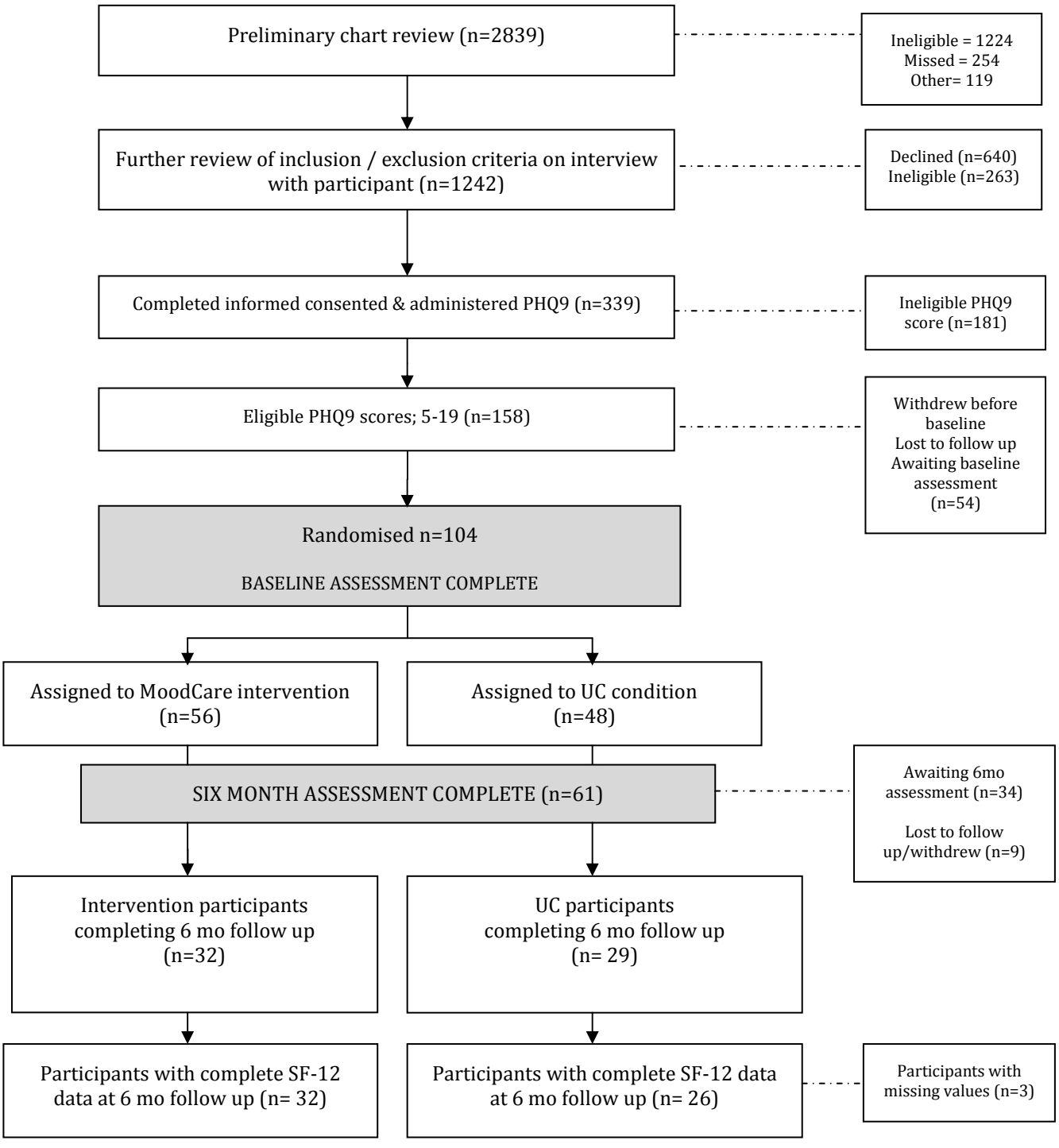

Figure 8.1. Flowchart of participant recruitment in the MoodCare trial

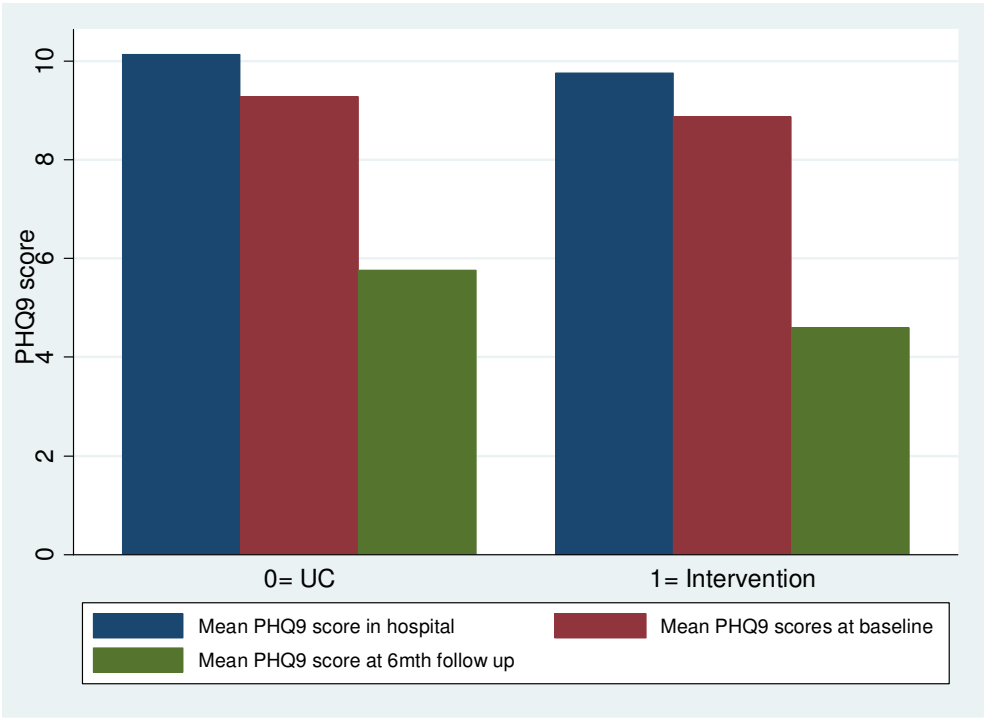

Figure 8.2. Mean depression score (PHQ9) at initial screening, baseline and six month follow up, by group

8.7. Tables

Table 8.1. Baseline characteristics of intervention and Usual Care (UC) participants for those completing six month follow up (n=61)

		UC			Intervention	
Variable	Mean/%	SE	95% CI	Mean/%	SE	95% CI
Age	59.8	1.7	56.3, 63.3	61.8	1.9	58.0, 65.6
Male	72.4%	0.1	55.1, 89.7	75.0 %	0.1	59.1, 90.9
Employed	51.7%	0.1	32.4, 71.1	37.5%	0.1	19.8, 55.2
Private Health insurance	34.5%	0.1	16.1, 52.9	28.1%	0.1	11.6, 44.6
Primary/Secondary qualifications only	51.7%	0.1	32.4, 71.1	59.4%	0.1	41.4, 77.4
Income (>$50k/yr)^	20.7%	0.1	5.0, 36.4	34.4%	0.1	17.0, 51.8
Number of children	4.4	0.3	3.7, 5.1	4.3	0.0	3.4, 5.1
Australian-born	72.4%	0.1	55.1, 89.7	84.4%	0.1	71.1, 97.7
English speaking	93.1%	0.0	83.3, 100	98.7%	0.1	75.4, 99.6
Smoker (never)	17.2%	0.1	2.6, 31.9	21.9%	0.1	6.7, 37.0
Number of days on past week taken meds for heart	3.1	0.1	3.0, 3.3	3.2	0.1	3.0, 3.3
Number of days on past week taken meds for depression*	3.0	0.2	2.5, 3.5	3.3	0.2	2.8, 3.7
SF-12 MCS	35.7	2.4	30.9, 40.6	37.8	1.8	34.2, 41.5
SF-12 PCS	44.5	2.1	40.2, 48.8	44.3	1.7	40.9, 47.8
Number of days in past 4 weeks stayed away from work due to health problem&	8.8	0.7	7.3, 10.2	7.1	1.2	4.6, 9.55
Number of days in past 4 weeks went to work with health problem&	6.0	0.5	4.9, 7.1	4.6	0.9	2.8, 6.4
Number of GP visits in past 6 months	11.4	1.2	8.9, 13.9	13.1	1.0	11.0, 15.2
PHQ depression score	8.8	1.1	6.6, 11.1	7.8	0.8	6.2, 9.4
CDS depression score	86.7	5.3	75.8, 97.6	85.9	4.0	77.8, 94.1
GAD-9 Anxiety score	6.9	1.2	4.5, 9.3	5.6	0.9	3.8, 7.4
ESSI score	25.0	1.0	22.9, 27.1	26.2	0.9	24.4, 28.0

Pre-ACS drinking status (at least once/week)	31.0%	0.1	13.1, 48.9	21.9 %	0.1	6.7, 37.1
Time spent walking for recreation or exercise in past week (mins)	12.8	1.1	10.5, 15.1	11.4	1.3	8.7, 14.0
Doctor-diagnosed:						
Diabetes	20.7%	0.1	5.0, 36.4	43.7%	0.1	25.6, 61.2
High cholesterol	75.9%	0.1	59.3, 92.4	65.6 %	0.1	48.2, 83.0
Hypertension	62.1%	0.1	43.3, 80.8	65.6 %	0.1	48.2, 83.0
Coronary Heart Disease	79.3%	0.1	63.6, 95.0	78.1 %	0.1	63.0, 93.3
Stroke	6.9%	0.0	-0.0, 0.2	9.4 %	0.1	-0.0, 20.0
Vascular disease	41.4%	0.0	22.3, 60.4	28.1%	0.1	11.6, 44.6
Lung disease	13.8%	0.1	4.4, 27.1	21.9%	0.1	6.7, 37.0
Depression/anxiety/nervous disorder	37.9%	0.1	19.1, 56.7	53.1%	0.1	34.8, 71.4
Stomach, gastrointestinal problems	10.3%	0.1	-0.0, 22.1	25.0%	0.1	9.4, 40.9
Arthritis	37.9%	0.1	19.1, 56.7	50.0%	0.1	31.7, 68.3
Kidney disease	3.4%	0.0	-0.0, 10.5	9.4%	0.1	-0.0, 2.0
Cancer	17.2%	0.1	2.6, 31.9	18.7%	0.1	0.0, 33.0
Enrolled in cardiac rehabilitation+	32.1%	0.1	13.7, 50.0	10.0%	0.1	-0.0, 21.4

*n=27; ^n=57; & only those indicating they were employed at baseline; +n=39

Table 8.2. Mean difference in HRQOL, depression and anxiety scores between intervention and UC groups (baseline to six month follow up); all participants

Outcome+	**n**	**Mean change scores (95% CI) UC**	**Mean change score (95% CI) Intervention**	**Mean Difference (95%CI)***	***p-value***
SF-12 MCS (mental HQROL)	57	2.7 (-1.9, 7.4)	8.3 (4.8, 11.9)	5.6 (-0.20, 11.3)	0.06
SF-12 PCS (physical HRQOL)	57	0.3 (-4.1, 4.8)	7.0 (3.4, 10.6)	6.7 (1.1, 12.3)*	0.02
PHQ9 (Depression)	61	-3.1 (-5.7, -0.4)	-3.3 (-4.9, -1.6)	-0.2 (-3.2, 2.9)	0.91
CDS (Depression)	61	-8.4 (-20.6 3.8)	-7.7 (-13.7 -1.6)	-0.7 (-12.5, 13.9)	0.91
GAD-7 (Anxiety)	61	-2.6 (-4.7, -0.5)	-1.6 (-2.7, -0.5)	-1.0 (-1.3, 3.3)	0.40

* between intervention and UC

Table 8.3. Mean difference in HRQOL, depression and anxiety scores between intervention and UC groups (baseline to six month follow up); for the sub group of participants with a history of MDD

Outcome	**N**	**Mean change scores (95% CI) UC**	**Mean change score (95% CI) Intervention**	**Mean Difference (95%CI)***	***p-value***
SF-12 MCS (mental HQROL)	26	0.2 (-6.6 7.0)	9.3 (3.8, 14.7)	9.1 (0.02, 18.1)*	0.05
SF-12 PCS (physical HRQOL)	26	1.2 (-4.3, 6.7)	6.0 (0.9, 11.0)	4.8 (-3.4, 12.8)	0.24
PHQ9 (Depression)	28	-1.3 (-5.1, 2.5)	-3.6 (-6.1, -1.0)	-2.3 (-6.7, 2.2)	0.31
CDS (Depression)	28	-12.7 (-35.3, 9.9)	-4.9 (-13.5, 3.7)	7.8 (-12.5, 28.1)	0.44
GAD-7 (Anxiety)	28	-3.1 (-7.0, 0.8)	-1.9 (-3.5, -0.3)	-1.2 (-2.4, 4.8)	0.50

Chapter 9: DISCUSSION

Chapter overview

In this chapter, the key findings of the thesis will be discussed. Additionally, implications for the prevention of co-morbid CVD and depression and the identification and management of depression in cardiac populations will be explored. The limitations and directions for future research will also be examined.

This thesis aimed to answer the following research questions:

In individuals with co-morbid depression and cardiovascular disease:

1. *What is the impact of this co-morbidity on mental, physical and vocational functioning?*
2. *What is the effectiveness of depression treatment on mental and physical functioning?*
3. *Can a targeted depression management and CHD secondary prevention program, improve mental, physical and vocational functioning?*

9.1. Key findings related to study hypotheses

Hypothesis 1a. Individuals with co-morbid CVD and diagnostically-defined, major depressive disorder will demonstrate poorer workforce participation, productivity and absenteeism and lower HRQOL (as measured by the Assessment of Quality of Life), than individuals with one or neither condition.

Findings from Chapters 2 and 4 provide support for Hypothesis 1a. In Chapter 2, evidence was presented that co-morbid MDD and CVD was significantly associated with work related impairments at the population level. Compared with those reporting one or neither condition, individuals reporting co-morbid MDD and CVD were less likely to be participating in the workforce, and more likely to experience work functioning impairments and absenteeism. The combination of MDD and CVD, over the independent effects of the individual conditions, was associated with more pronounced reductions in workforce functioning. These findings are consistent with cross-sectional studies conducted in Europe (**125**), Northern America (**109**) and Australia (**124**) in which other co-morbid populations have also demonstrated poorer work outcomes. This study adds to the literature by confirming a synergistic effect of co-morbid MDD and chronic physical conditions on functioning (**127**), but not work absenteeism (**126**). Prior to this epidemiological analysis of the burden of MDD and CVD on work outcomes, the impact of this co-morbidity in Australia was not well documented, particularly at the population level.

In Chapter 4, the burden of co-morbid MDD and CVD on HRQOL in Australia was also highlighted. Compared with those with one or neither condition, individuals with co-morbid CVD and depression reported the greatest deficits in HRQOL. These findings are consistent with studies of clinical populations that have demonstrated the magnified effects of this co-morbidity on HRQOL, but may be more accurate than past studies as estimates derived from clinical populations can often be inflated. The influence of MDD and CVD on HRQOL was shown to be additive, rather than synergistic in nature. While a significant dose-response relationship was also observed between depression severity and HRQOL, CVD and depression severity were shown to act independently of each other to influence HRQOL. While this is consistent with studies comprising MI populations (**77**), to my knowledge, this was the first study to demonstrate this effect in the broader CVD population, using a robust measure which is designed specifically to detect nuanced differences in HRQOL.

Hypothesis 1b. Depression recorded after a cardiac event will predict poor return to work outcomes at 6-12 month follow up.

Evidence presented in Chapter 3 provides support for Hypothesis 1b; depression recorded between admission and up to two months post discharge significantly predicted poorer RTW outcomes 6 to 12 months after a cardiac event, in the majority of studies. There was some evidence that increases in depression severity reduced the likelihood of RTW. Age and patient perceptions of their illness or work performance were also shown to predict RTW in these populations. These findings are consistent with earlier studies conducted in the 1980s (**160**), which found depression to be a strong determinant of work outcomes. This study adds to the existing evidence by providing an up-to-date review of the recent literature where inconsistent findings have previously been reported.

Hypothesis 2. Cardiac patients receiving any depression treatment (pharmacologic, psychological, composite approaches) will demonstrate significantly greater improvements in mental and physical HRQOL compared with those assigned to a control condition, at six month follow up.

Chapter 5 revealed that HRQOL outcomes have often been neglected as a primary endpoint for depression intervention trials conducted in cardiac populations. This provided the rationale to conduct a meta-analysis to determine the impact of depression treatment on key components of HRQOL. After systematically reviewing existing randomised controlled trials in this area, findings from Chapter 6 provide support for Hypothesis 2, demonstrating the effectiveness of depression treatment on both mental and physical HRQOL of cardiac patients. Effect sizes were greatest for mental versus physical HRQOL. The effect of depression treatment remained significant regardless of comparator group or HRQOL instrument used. Treatment had little impact upon physical HRQOL of patients undergoing surgical intervention. While the number of studies included in a sub-analysis conducted to evaluate treatment type was limited, psychological approaches appeared to be potentially the most effective for improving mental HRQOL. These findings are consistent with studies of heart failure patients, demonstrating that depression treatment has a more significant impact on mental HRQOL compared with physical HRQOL. To my knowledge, this was the first meta-analysis of its kind to systematically demonstrate that depression treatment significantly improves HRQOL of depressed cardiac patients.

Hypothesis 3. Compared with those receiving usual medical care, ACS patients participating in a telephone-delivered, depression management and secondary prevention program (MoodCare) will report significantly greater improvements in HRQOL and work outcomes at six month follow up, as measured by the Short Form-12 and absenteeism/presenteeism measures, respectively.

In Chapter 7, the development of a telephone-delivered, CBT-based, depression management and CHD secondary prevention program for ACS patients reporting depression was detailed.

Preliminary evidence from a randomised, feasibility trial presented in Chapter 8 provides partial support for Hypothesis 3; while the MoodCare intervention was not associated with significant improvements in odds of return to work, workplace absenteeism or presenteeism, intervention participants reported significant improvements in physical HRQOL at follow-up, compared with UC participants. A similar pattern was observed for mental HRQOL but was not statistically significant. Intervention effects were more pronounced for those with a history of MDD; the MoodCare program was associated with statistically significant improvements in mental HRQOL in this sub-group. Overall, a significant interaction between frequency of General Practitioner visits at baseline and the intervention was found to improve physical HRQOL scores. Mean depression levels of each group followed a similar trajectory between hospital screening, baseline and six months, and did not differ significantly at any time. While consistent with other studies in this area which have demonstrated the positive effects of depression treatment on HRQOL outcomes of CAGB patients, the preliminary findings of this study show that combining depression and lifestyle management using the telephone can produce similarly positive effects, related to physical HRQOL. As far as I am aware, this is the first time this has been demonstrated.

9.2. Implications of findings

9.2.1 Implications for the prevention of co-morbid depression and cardiovascular disease

From a public health perspective, the assessment of the national burden of CVD and MDD on work and HRQOL outcomes (Chapters 2 & 4) provides useful information about the characteristics of Australians affected by depression, CVD or both; the findings from which could subsequently be used to guide recommendations for targeted prevention strategies.

First, these analyses provide a basic profile of those individuals experiencing co-morbid MDD and CVD. This group featured the highest proportion of: females, and individuals reporting low levels of physical activity, high BMI and low socio-economic status. While it is acknowledged that the cross-sectional nature of the data precludes a determination of causality, further exploration of such data in the future could aid our understanding of the association between these variables, CVD and depression. For example, taking into account the factors that were shown to mediate the relationship between the two conditions in Chapter 1, it is possible that: (i) features of low SES hierarchy (e.g. poor access to fresh foods, unsafe exercise environment) or characteristics associated with gender (e.g. females show a greater risk of MDD onset than males (**327**) allow these sub-groups to be more susceptible to this medical co-morbidity, (ii) due to reduced functioning or other restrictions, individuals reporting this co-morbidity are less physically active, resulting in overweight or obesity, or conversely these individuals are restricted in their physical activity because of overweight or obesity, (ii) lack of exercise and/or overweight and obesity (and the poorer clinical outcomes associated with these conditions such as high blood pressure and cholesterol) interfere with individuals' adherence to primary prevention activities and thus contribute to the initial onset of MDD and/or CVD. Future studies using a longitudinal study design could use a mediator analysis to determine this, as well as the intricate pathways that contribute to the relationship between MDD, CVD and functioning. Identifying which risk factors, at which stage of the disease process, are the most appropriate to target for the purpose of early intervention could help maximise prevention efforts at the broader level.

Second, in light of the evidence presented in this thesis and data showing depression most often occurs in the decades prior to CVD onset (APPENDIX A), public health campaigns for the primary prevention of CVD could potentially target those with existing MDD. While it is

acknowledged that much is known about the traditional, clinical risk factors that are associated with CVD primary prevention and public health strategies targeting these have been implemented accordingly (e.g smoking cessation and lowering cholesterol and blood pressure), less attention has been placed on depression as a key risk factor for the primary prevention of CVD. As international studies have shown that the average age of MDD onset is 32 (with an inter-quartile range of 19-44 years of age (**327**)), and data presented in this thesis suggest that the average age of Australians with MDD is 36.7 years, early interventions that promote primary prevention of CVD could attempt to target a younger age demographic than is conventionally targeted, with a greater focus on those with existing or history of affective disorders. This recommendation is supported by previous National Heart, Lung, and Blood Institute Task Force Reports which have recommended that research on the prevention of CVD focus on psychosocial, amongst other factors, particularly depression (**328**). Further, given that MDD is generally most common in women, and CVD prevention campaigns have traditionally targeted men, this may be an area of prevention on which to focus (gender specific interventions will also be discussed in Section 9.3.3).

In summary, understanding the key characteristics of individuals who experience co-morbid major depression and CVD (and the way in which they inter-relate), could aid prevention efforts at the broader level. Moreover, because there has been arguably less focus on depression in the primary prevention of CVD compared with traditional risk factors, developing a risk factor profile and early intervention strategy that is based on MDD status or history, could help target those particularly vulnerable to CVD. Future studies should explore primary prevention of CVD by targeting depression improvement as well as improvement in CVD risk factors in depressed populations.

9.2.2 Implications for the identification of depression in patients with existing CVD

There remains much conjecture regarding the appropriateness of depression screening in patients who are admitted to hospital after a heart event. The ethical issue exists; what if depression is identified using a routine screening procedure but treatment options are not available or accessible? Conversely, what if depression is not detected because routine screening procedures are not in place and thus remains unrecognised? Despite preliminary evidence from the MoodCare study of spontaneous remission in depressive symptoms for patients who did not receive an intervention (i.e. trends in mean PHQ9 scores were similar for both UC and intervention groups, at follow up), the identification and treatment of depression after a cardiac event remains of clinical importance. In their evaluation of AHA recommendations regarding depression screening in ACS populations, Smolderen et al found that even when routinely implementing a depression screening procedure (using a two-step process comprising the PHQ2 and subsequently, the PHQ9), one in four cardiac patients failed to get screened. They recommend that "simplifying the protocol by using the PHQ-9 alone and providing more support and feedback may improve the rates of depression detection and treatment (**329**)." Indeed, these results parallel those observed in the MoodCare study. When the original recruitment protocol was developed for the MoodCare study, a two-step screening process was advocated, using the PHQ9 depression screener in hospital, and the PHQ2 two weeks after discharge. This was to ensure that enrolled participants were symptomatic of depression at study commencement, and to exclude those patients for whom symptoms had dissipated. However, eventually, the logistical complexity of this strategy was realised. Thus, the latter step of this process was eliminated. While this protocol amendment had implications on recruitment, in that the final sample was perhaps a more mildly depressed sample than may have originally been recruited, these findings support the recommendations of Smolderen et al. A simplified depression screening procedure is

required, for the benefit of both staff and patient, if routine screening is to be effective and feasible in the hospital setting.

While the most appropriate and effective screening instrument for identifying depression in cardiac populations (for the purpose of clinical management) is a topic for further investigation, future studies which use depression screening for clinical trial recruitment should consider the recruitment challenges observed in the MoodCare trial. For example, it is recommended that future intervention trials in this area consider employing a modified strategy that involves simply obtaining consent to contact the patient within one month of hospital discharge, at which time recruiters could undertake eligibility assessment and obtain the patients' full consent to participate. There are several benefits associated with such an approach: first, recruitment staff could still access patients in the ward while minimising the burden to the patient. Second, enrolling participants based on their depression screening results at one month post-discharge may provide a more accurate assessment of depression severity, eliminating those experiencing only adjustment disorder. Other recent studies in this area have used a similar approach, employing a three month observation period before intervention commencement, which was shown to be feasible (**258**). Third, where patients often stay with relatives or carers immediately after discharge, participants are more likely to be settled back into their home environment at this point, and may be easier to contact.

9.2.3 Implications for the management of depression in patients with existing CVD.

The results presented in this thesis have important implications regarding the management of cardiovascular disease and depression. As the burden of this co-morbidity was assessed within the Australian population, and moreover MoodCare was an implementation trial conducted within Australian health care settings, the implications of these findings will be

discussed largely within the context of the Australian health care system. The following recommendations are proposed:

- *Targeted depression and lifestyle management programs should be integrated into Australian hospitals.* Evidence that: (i) a synergistic relationship exists between depression and cardiovascular disease on functioning (Chapter 2), (ii) depression severity contributes more strongly than CVD to HRQOL impairments (Chapter 4), (iii) depression treatment leads to benefits in mental HRQOL (Chapter 6) and (iv) a combined depression and lifestyle management program leads to improvements in physical HRQOL (Chapter 8), provides support for the use of a multi-faceted approach to care management if overall improvements in HRQOL, and potentially vocational functioning, are to occur. This recommendation is in alignment with previous research of Gaynes et al (2002) who recommend "adopting a multidimensional approach to HRQOL rather than treating it unidimensionally"(**83**). As routine rehabilitation programs are already available in many hospitals in Australia, administering depression treatment as a key component of cardiac rehabilitation is likely to be beneficial and this may be the appropriate setting for wide-scale program implementation. Regardless of how these programs are structured or integrated into routine practice, the key results of this thesis suggest that a combined approached to care management may be preferable if patients' overall functioning is to be maximised.
- *The telephone (and other non-conventional approaches) should be considered as a platform from which to deliver depression and lifestyle management programs to cardiac patients.* Evidence presented in Chapter 5 demonstrated that telephone-delivered interventions are an effective mode of delivering depression treatment in various cardiac populations. Chapter 8 further provided some support for this approach. The MoodCare program, specifically, could be considered by key stakeholders for wide-scale implementation in

Australian health care settings if: (i) the intervention effects observed in this preliminary study are further corroborated by the larger trial, (ii) MoodCare is demonstrated to be cost effective and (iii) a sound business model can be developed from the perspective of each of the responsible fund-holders (e.g. hospital cost-centres, hospital/health network, state/federal health budgets). The integration of this program into existing care management plans could be particularly advantageous because of its mode of delivery. For example, the impressive retention rates observed in this study may be the result of the telephone platform that may have eliminated some of the patient-level barriers to rehabilitation often experienced by cardiac patients. The major advantage of MoodCare, where currently few similar programs exist, is the potential for care management to be provided to those who are unwilling to attend traditional forms of therapy or centre-based cardiac rehabilitation, older patients with reduced mobility, or those living in rural and remote areas. The latter is of particular importance in Australia because of the widely geographically-dispersed population. The states of Australia cover large distances; for example the state of Queensland (where two MoodCare recruitment sites were based) spreads over 1.7 million km2 (**330**). These factors further support the tele-health mode of program delivery for wide spread implementation, if the burden of MDD and CVD on the Australian population observed in Chapters 2 & 4 is to be reduced. Future research should also consider the potential for this approach to be applied in resource poor countries, especially in developing countries where the delivery of medical care or rehabilitation services may be difficult, or in countries that cover large geographical distances.

- *The MoodCare program should be expanded upon to target those with other chronic co-morbidities.* Findings from Chapter 8 indicate that ~20% of UC and ~40% of intervention participants had previously been diagnosed with diabetes. Indeed, multiple chronic

conditions can severely impede secondary prevention activities, particularly those which are unmanaged. As the model of care management used in the MoodCare program addresses both mood and lifestyle management in a broader sense, much of this content is applicable to the management of other chronic conditions (e.g. medication adherence, improving healthy eating and physical activity). The data presented in Chapter 8, which reflect a high prevalence of other medical co-morbidities in this population (85.25% reported at least one medical co-morbidity: kidney disease, previous diagnosis of depression, anxiety or nervous disorder, cancer, stomach problems lung disease, arthritis or diabetes), further support the use of a multifaceted approach to disease management. The different intervention components could thus be modified to target symptoms (of varying severity) for each condition to suit individual patient need. As well as targeting other medical co-morbidities in this population to enhance disease self-management, treatment of other common and co-morbid mental health disorders may need to be considered; for example, anxiety is common in cardiac patients. While the study was not powered to detect changes in anxiety, the (preliminary) null effects of MoodCare on anxiety outcomes may suggest that a more targeted program which specifically manages phobic avoidance, panic disorder and post traumatic stress, as well as depression and more generalised anxiety, is required.

9.3. Limitations

The evidence presented in this thesis regarding the significant burden of co-morbid CVD and MDD, the predictive role of depression on RTW outcomes of cardiac patients and the benefits of depression treatment in this population, is based on: data derived from well enacted, large-scale, epidemiological studies and randomised controlled trials which included defined

samples, multi-site and multi-stage study designs, and sound retention and response rates. However, several study limitations were observed.

9.3.1 Assessment of the burden of CVD and MDD. As mentioned in previous chapters, there were several limitations associated with the data used to assess the burden of CVD and MDD at the population level (Chapters 2 and 4). First, data were based on a cross-sectional study, which generated only prevalence, not incidence rates. It is acknowledged that while population-based, epidemiological studies have many advantages, this study design precluded a more comprehensive analysis of the causal influence of these conditions on vocational and HRQOL outcomes. Future longitudinal or panel studies are required to disentangle the association between CVD and MDD in relation to functional outcomes.

An inherent issue associated with large-scale, population-based epidemiological studies that are conducted to assess disease burden is related to measurement validity. For example, due to resource constraints and/or minimising participant burden, many national health surveys or longitudinal studies rely on self-report data over objective measures (blood samples, hospital records, Medicare records) to assess disease status. Indeed, this can lead to recall bias, misclassification or incorrect identification, and an overall under-reporting of disease prevalence. Additionally, more comprehensive information about the severity of a chronic condition is often desirable but not available.

Measurement and assessment of mental disorders is also an issue associated with studies involving complex survey designs. While the under-reporting of mental disorders may occur due to participants providing socially desirable answers or lower participation rates by those with mental disorders, prevalence estimates may be affected by the assessment instruments utilised. For example, mental health screening instruments using self report data do not always provide the same assessment accuracy as diagnostic interviews such as the CIDI

(National Survey of Health and Wellbeing) (**128**) and Structured Clinical Interviews for DSM Disorders (SCID) (Geelong Health Study) (**145**). While it is acknowledged that there are practical issues associated with the administration of diagnostic interviews (e.g. they are time consuming and staff administering the instrument require specialised training), and additionally they have been criticised for over-estimating mental disorder burden because of the breadth of the DSM and ICD diagnostic criteria (**331**), the data generated from these assessments are comprehensive and provide information on co-morbid mental disorders, severity of disorder, past history of disorder, age of onset, recency of episode and other important data. As increasing emphasis is being placed on the important link between mental and physical health conditions in Australia, it is recommended that newly established longitudinal or panel studies (or existing disease related cohort studies without robust mental health measures) consider these factors.

9.3.2 Recruitment of MoodCare trial participants. A clear limitation of the MoodCare study was the low recruitment rate (Figure 8.1). Only 104 participants were recruited from the 1242 approached (~8% recruitment rate). While other trials of this nature have reported comparable recruitment rates (the MIND-IT study (**226**) recruited 4780 patients for a total of 331 randomised participants; 7% recruitment rate), there are several emerging issues that warrant further exploration. The poor recruitment rate observed in this trial could be the result of several factors: the sensitive nature of the program; the stigma associated with mental disorders; feelings of being overwhelmed by not one but potentially two, chronic conditions; the demeanour of the recruitment officer or the way in which participant information is conveyed; the overwhelming environment of an acute hospital setting or an acute cardiac episode. All could have interfered with recruitment and program uptake. Indeed, it is possible that cardiology wards are not the appropriate setting in which to recruit

eligible participants, but rather, potential participants should be identified or approached after discharge. Upon designing this trial, hospital wards were considered the appropriate setting for recruiting this study population; our previous studies have recruited MI patients from several of the same hospital sites and have demonstrated sound recruitment rates (**332**). Using this strategy, patients were considered accessible and thus more easily followed up after discharge. As other studies in this area have encountered similar issues, the use of alternative recruitment strategies is recommended, such as those detailed in Section 9.2.2, in order to enhance recruitment rates in this population in the future.

9.3.3 Improving recruitment and retention of women. Despite a higher proportion of women reporting co-morbid MDD and CVD in the general population (Chapter 2 & 4), only 25% of all enrolled participants in the MoodCare trial were women. Other depression treatment trials in this area have also observed an under-representation of women (APPENDIX A3). Arguably, much of the focus of previous studies in this area has been placed on investigating the outcomes of male cardiac patients (particularly related to work and recovery), compared with females. For example, one third of the studies included in the systematic review presented in Chapter 3 comprised only male participants. Evidently, future studies should focus on recruiting and retaining women. APPENDIX A3 outlines the potential reasons for gender differences related to recruitment, enrolment and retention in depression treatment trials, but briefly, these include: limited free time as a result of paid or unpaid work (including primary carer responsibilities for children, ageing parents and spouses); prioritisation of health and wellbeing of family members; or lack of responsiveness to help or advice regarding lifestyle and mental health issues. Such factors require further investigation.

It is therefore recommended that greater focus be placed on enrolling women into clinical trials, where evidence suggests that they are often under-represented (**333**).

While the preliminary findings presented in Chapter 8 did not assess gender-specific intervention effect due to limited numbers, such effects have been demonstrated in previous studies. Rollman et al (2009) (**89**) found a stronger effect in males than females for reducing depression in the Bypassing the Blues study. Females also failed to demonstrate significant improvements in mental and physical HRQOL or Duke Activity Status Index. The authors recommended that "additional research is necessary to develop improved treatments for women" (**89**). While the larger MoodCare trial will also explore outcomes by gender, these findings may have limited statistical power due to the low numbers of enrolled female participants.

9.3.4 Generalisibility of the MoodCare program. In relation to future, wide-spread integration of the MoodCare program into the Australian health care system, an important limitation to its generalisability is the requisite of psychologists to deliver the program. If such a program were to be implemented within the existing structures of acute or primary health care settings, it is recognised that the associated costs would be substantial when compared with employing nurses or other health professionals to deliver the program. When we developed the MoodCare intervention, we considered training junior psychologists/masters students, or qualified nurses for program delivery. However, the need for qualified interventionists was recognised, particularly related to: previous experience using CBT, competency in the management of participants whose condition may deteriorate throughout the course of the study or who exhibited suicidality or severe distress at any stage of the program. Should this program be 'scaled up' in the future, it is recommended that these considerations be taken into account in order to avoid compromising quality of care.

9.4. Summary and Conclusions

The impact of depression on mental, physical and vocational functioning of those with cardiovascular disease is significant in the Australian population. Targeted depression treatment can significantly improve mental, and to a lesser extent, physical HRQOL outcomes of cardiac patients. When a CHD secondary prevention program is combined with targeted depression management, meaningful improvements in physical health functioning have the potential to occur in those experiencing depression after a cardiac event. Improvements in mental health related functioning can occur in those with a prior history of depression. Research comprising a greater number of participants is required to confirm these effects. The use of the telephone to deliver such a program can overcome some of the barriers associated with program uptake and promote retention. Additional research is required to further explore the effects of this and other programs on vocational functioning.

Appendix A: OTHER RELATED PUBLICATIONS

Related Publication #1

Co-morbid cardiovascular disease and depression: sequence of disease onset is linked to mental but not physical self-rated health. Results from a cross-sectional, population-based study.

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Abstract

Purpose: Self-rated health has been linked to important health and survival outcomes in individuals with co-morbid depression and cardiovascular disease (CVD). It is not clear how the timing of depression onset relative to CVD onset affects this relationship. We aimed to first identify the prevalence of major depressive disorder (MDD) preceding CVD and secondly determine whether sequence of disease onset is associated with mental and physical self-rated health.

Methods: This study utilised cross-sectional, population-based data from 224 respondents of the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB). Participants were those diagnosed with MDD and reported ever having a heart/circulatory condition over their lifetime. Age of onset was reported for each condition. Logistic regression was used to explore differences in self-rated mental and physical health for those reporting pre-cardiac and post-cardiac depression.

Results: The proportion of individuals in whom MDD preceded CVD was 80.36% (CI: 72.57-88.15). One-fifth (19.64%, CI: 11.85-27.42) reported MDD onset at the time of, or following, CVD. After controlling for covariates, the final model demonstrated that those reporting post-cardiac depression were significantly less likely to report poor self-rated mental health (OR:0.36, CI:0.14-0.93) than those with pre-existing depression. No significant differences were found in self-rated physical health between groups (OR:0.90 CI:0.38-2.14).

Conclusions: MDD is most common prior to the onset of CVD. Further, there is an association between pre-morbid MDD and poorer self-rated mental health. To our knowledge, this is the first time this has been demonstrated in a national, population-based survey. As self-rated health has been shown to predict important outcomes such as survival, we recommend that those with MDD be identified as vulnerable to CVD onset and poorer health outcomes.

Introduction

Relationship between major depressive disorder & cardiovascular disease

Major depressive disorder (MDD) and cardiovascular disease (CVD) are major contributors to the global burden of disease, with CVD the leading cause of death and depression the top-ranking cause of disability (**3**). When depression co-exists with chronic disease, the burden is accentuated. Co-morbid depression significantly worsens health compared with depression alone, any chronic disease alone, or with any combination of chronic diseases without depression (**334**). Evidence suggests that this is true for the co-morbidity of depression and CVD; this combination is significantly more harmful to overall health than either one of these conditions in isolation (**335**). Depression can manifest after a cardiac episode as a reaction to a life-threatening event such as myocardial infarction (MI) (post-cardiac depression). Conversely, depression can present prior to CVD onset (pre-cardiac depression), with shared risk factors contributing to both disorders (**336**). Depression is now an established and robust risk factor for the development of CVD (**141**). Severity of depressive symptoms has been shown to predict nonfatal and fatal CVD as well as all-cause mortality in CVD patients (**339**). However, it is not clear how the timing of depression onset relative to CVD onset affects subsequent health outcomes.

Prevalence of pre-cardiac versus post-cardiac depression

Of the one in five cardiac patients who report MDD in hospital, it has been estimated that 26% will have a history of depression (**337**). Pre-cardiac depression can be more persistent and chronic compared with depression which manifests after a cardiac event, and depression history has been linked to further depressive recurrences and relapses (**338**). Post-cardiac depression can be transient in nature, and in some cases, spontaneously remit after the stress

of a life threatening event has subsided (**339**). There is evidence that post-cardiac depression may comprise different symptom subtypes compared to pre-cardiac depression (**337**). Studies of MI patients indicate that the majority of patients will experience some degree of post-cardiac depression (65%), with the remaining one-third reporting more persistent depression (**340**). However, as these and other studies have used data from clinical populations, these estimates may be over-represented. Determining the prevalence of pre- and post-cardiac depression using a population-based sample could importantly provide more accurate estimates. Such data could be useful for guiding prevention and management and help disentangle the temporal association of depression and CVD and vice versa. Moreover, these data could help determine the way in which the sequence of disease onset impacts upon health outcomes.

Does sequence of disease onset impact on self-rated health?

Self-rated health is a strong predictor of health outcomes (even over objective outcomes) (**341**), health service utilization (**342**), quality of life (QOL) and mortality (**343**). In the association between depression and cardiovascular mortality, the role of self-rated health is important, with the relationship partially attenuated by self-rated health status (**344**). As depression has also been found to predict poor self-rated health amongst CVD populations, the impact of the sequence of disease onset on overall self-rated health has been investigated. In a longitudinal study of female cardiac patients, Ruo (2006) observed that while pre-cardiac depression influenced self-rated health, post-cardiac depression was a stronger predictor of poorer overall self-rated health (**345**). In contrast, data from cross-sectional studies have revealed that any depression type can adversely affect patient outcomes (**340**). Cardiac patients with persistent depression, or new onset depression were all found to have poor health status (QOL) (**340**). However, neither study provided data on the impact of sequence of

disease onset on specific domains of self-rated health (e.g. mental and physical self-rated health).

Most, if not all, studies investigating this association have been conducted using clinical populations. There remains little understanding of this relationship across the lifespan. Epidemiological data have the potential to provide important insights about differences in self-rated health as a result of pre- and post-cardiac depression at a population level. Such data have already provided important insights about the role of chronic physical conditions in mental health (e.g. as a risk factor for suicide (**346**), and about the role of mental health in the development of other chronic illnesses (e.g. osteoporosis (**347**)). Given the previous links between self-rated health and survival, health service utilisation (**341-343**) and other health outcomes in co-morbid depression and CVD populations, we aimed to address the current research gaps by identifying: i) the proportion of depression preceding CVD; ii) whether sequence of disease onset is associated with differential mental and physical self-rated health in individuals reporting co-morbid depression and CVD, using a nationally representative, population-based sample. As the average age of onset for depression across the life span would be expected to be lower than that of CVD onset, we hypothesized that there would be a greater proportion of individuals whose depression precedes their CVD condition, compared with those whose depression occurs after CVD onset. Furthermore, in light of findings from a cohort of female cardiac patients that new onset depression most strongly predicts poorer (overall) self-rated health, we hypothesized that there would be significant differences in both mental and physical health status among those whose depression precedes their CVD condition, compared with those in whom depression occurs after CVD onset.

Methods

Study design

This study utilised cross-sectional, population-based data from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB). Recruitment methods have been described in detail elsewhere (**128**). Briefly, the NSMHWB sample was based on a stratified, multistage probability sample of persons aged 16-85 years living in private dwellings in Australia, excluding very remote areas. The survey was conducted from August to December 2007, with 14,805 households approached. Interviews took on average 90 minutes per fully-responding household. One randomly selected person in each selected household was interviewed. The overall response rate was 60% and there were 8841 fully responding participants.

Participants and data collection

Participants were those who responded to questions assessing whether they had: (1) A diagnosis of a non-fatal CVD condition; heart or circulatory condition (e.g. heart attack, angina, high blood pressure) over the lifetime (**348**), and (2) a diagnosis of major depressive disorder. The Composite International Diagnostic Interview (CIDI 3.0) was used to diagnose depression. The CIDI 3.0 is among the most widely used structured diagnostic interviews globally for psychiatric disorders. As part of the interview, onset of depressive symptoms was obtained by asking respondents their age the very first time they had a particular symptom or episode. Participants also reported age of CVD onset. Participants self-rated their current mental and physical health using validated 5-point scales (excellent to poor). Lower scores reflected better health. This measure of self-rated health is considered valid for measuring general health as it has been found to correlate well with other measures of health (**137**), and has been shown to demonstrate good test-retest reliability (**349**).

Other variables included: registered marital status, area socioeconomic disadvantage (Decile 1-10; where 1=most disadvantage and 10=least disadvantage))(**128**), national priority area, chronic medical condition in the past 12 months (diabetes, cancer, arthritis, asthma), physical activity in the past week (number of times spent walking for recreation, exercise or gain) (**128**), level of active employment (full-time, part-time, not participating) (**128**), rurality (residing in major urban, other urban, other) (**128**), education (attainments other than those of pre-primary, primary or secondary education) (**128**), body mass index (BMI) (calculated using the standard equation of weight divided by height squared (**135**), psychological distress (Kessler-10)) (**136**), treatment for CVD in past year, length of CVD (>6 months), quality of life (the Terrible-Delighted scale), current smoking status and years since first CVD or MDD episode (age of first episode subtracted from participant's current age).

Data analysis

Participants were categorised as having 'pre-cardiac' or 'post-cardiac' depression by comparing their individual age of first depression onset to their age of CVD onset, across their lifetime. Estimates and standard errors (SE) were derived accounting for the stratified multistage survey design, oversampling and non-response (**128**) using the Jack-knife delete-2 technique. Significant differences between group characteristics were identified using logistic regression, adjusting for age and sex. Using methods described by Hosmer and Lemeshow (2000) (**128, 138**), multivariate, logistic regression analyses were performed to explore differences in self-rated mental and physical health according to order of disease onset. Briefly, the variables entered into the multivariate model were those identified in the literature as potential confounders or covariates (e.g. age, sex, marital status, area socioeconomic disadvantage, number, physical activity, employment, education, smoking status, time between disease onset and assessment). The influence of these variables were

explored using univariate analysis; those significant at the p<0.25 level were entered into the model along with clinically relevant variables, as more traditional levels such as 0.05 can fail in identifying variables known to be important. We then observed the magnitude of each variable; those without significant effect (i.e. causing <20% change) were removed. Finally, post estimation tests were conducted to assess goodness of fit of the final model.

Self-rated health scales were dichotomised into 0= Excellent, Very Good or Good; 1= Fair or Poor, for comparability with other studies (**345**)(where 0 was the Reference Group). Adjusted odds ratios (OR) were presented with Jack-knife Standard Errors and 95% confidence intervals (CIs). Probability (sampling) weights were applied, in order to weight the sample back to the population from which the sample was drawn. Re-running the analysis in the same way without weights indicated similar ORs to the reported results (data not shown). Stata 11 was used for statistical analyses, using the *svy* function. STROBE guidelines were applied for the reporting of cross-sectional studies (**139**).

Results

Data were available for 224 respondents; 80.4% indicated that depression preceded their CVD onset (CI: 72.57-88.15) and the remaining one-fifth (19.6%, CI: 11.85-27.42) reported onset of first MDD at the time of, or following, CVD (key characteristics displayed in Table A1.1). On average, those with post-cardiac depression were younger, were more likely to be male, have a greater number of depressed episodes in the year preceding the survey and higher psychological distress. A lower proportion of these participants were smokers, had CVD lasting longer than six months, received CVD treatment in the past year, or had a chronic physical condition. Those with post-cardiac depression reported a shorter time frame over which their co-morbid MDD and CVD conditions occurred (mean=10 years) compared with

those with pre-cardiac depression whose depression occurred, on average, 17 years prior to CVD onset (Figure A1.1).

After controlling for age, sex, marital status, area socioeconomic disadvantage, number, length and severity of depressive episodes, chronic conditions, physical activity, employment, rurality, education, BMI, and smoking status, a logistic regression analysis revealed that those reporting post-cardiac depression were significantly less likely to report poor self-rated mental health (OR:0.36 CI:0.14-0.93) compared with those with pre-existing depression (Table A1.2). No significant differences were found in self-rated physical health, after controlling for age, sex, physical activity, depression severity and BMI (OR:0.90 CI:0.34-2.40). Overall, females and those reporting more frequent physical activity were significantly less likely to report worse physical health. Higher BMI and depression severity were significantly associated with poorer self-rated physical health (Table A1.2). The wide CIs reflect small numbers of participants across depression recency categories. Post-estimation tests which compared weighted observed and predicted probabilities, revealed goodness-of-fit for both self-rated mental (F-adjusted mean residual test statistic = 0.64; p=0.76) and physical health models (F-adjusted mean residual test statistic = 0.85; p=0.56). We further explored the influence of time (in years) between onset of CVD and MDD and self-rated health. Time difference (continuous) was treated as a predictor variable in the regression model, with self-rated health as the outcome. No significant differences were detected.

Discussion

Using a population-based sample, the aim of the study was to measure the proportion of MDD either preceding or following CVD, and identify whether the sequence of disease onset was associated with differential mental and physical self-rated health. In alignment with our first hypothesis, these data suggest that the majority of individuals with co-morbid MDD and CVD

experience major depressive disorder prior to CVD onset. This finding differs substantially from figures reported in other studies which have explored depression history in cardiac patients, conducted in clinical settings (**340**). However, given the age at which depression is most often first diagnosed (≥14 years with high incidence up to age 40, particularly in women) and the age at which CVD is first diagnosed (50s for men, 60s for women), this finding was anticipated. Indeed, we found that those with pre-cardiac depression experienced MDD, on average, 17 years prior to CVD onset, compared to those with post-cardiac depression who reported a shorter time frame over which their conditions occurred (mean=10 years).

Second, we observed significantly poorer mental but not physical self-rated health in those with pre-cardiac depression; a finding only partially in support of our second hypothesis. While significant differences in self-rated health have been observed in co-morbid depression and CVD populations previously (**345**), to our knowledge, this is the first time this has been demonstrated in a national, representative, population-based survey which distinguishes between mental and physical self-rated health.

These findings are of importance as subjective health status has been found to influence health and mortality outcomes (**343**). The precise mechanisms through which this occurs remain unclear (**341**), but it is likely that this association is due to self-rated health being an 'inclusive' measure that summarises objective health status (**349**). As we found that those with pre-cardiac depression reported MDD onset, on average 17 years prior to CVD, it seems likely that the poorer self-rated mental health observed in this group may be the result of depressive symptoms of greater persistence, as opposed to extrinsically influenced depression. It is also possible that deficits in psychological health may have contributed to

atherosclerosis. Additionally, it is possible that shared risk factors moderate the risk for both disorders (**350, 351**).

Because the cross-sectional design of the study precludes a temporal examination of causality, large scale, longitudinal studies are required to determine causality. The pathways mediating depression in the pathogenesis of CVD remain unclear, but are thought to involve both psycho-physiological and bio-behavioral mechanisms. One explanation for this relationship is the presence of shared risk factors for CVD and depression. In particular, systemic inflammation appears to pre-date the development of both depression (**350, 351**) as well as those systemic disorders that are commonly co-morbid with depression, particularly CVD and diabetes (**352**). If there is persistent elevation of risk biomarkers associated with longstanding depression, this may in part explain the worse outcomes of those with pre-cardiac depression. Common environmental factors such as low socio economic status, smoking, lack of exercise and poor diet have also been shown to increase the risk of both disorders (**143-145**).

The population-based nature of our data is a strength of this study. Previous studies investigating associations between depression and CVD have employed study cohorts comprising hospitalised cardiac patients. The advantage of our study is its robustness and representativeness due to the use of a large, probability sample from the general population. There are additional advantages associated with using these data, including the use of a validated diagnostic interview to identify depression. Although diagnostic interview is more time consuming than self-report methods, it is acknowledged as a more accurate method for the classification of depression.

Several limitations need to be noted. CVD diagnosis was identified through self report. While research has demonstrated reasonable correlation between self-reported chronic diseases

and those identified in medical records (**133**), this method may enhance poor recall or recognition of disease status on the part of the respondents. This may help explain unexpected results. For example, the slightly younger mean age among those with post-cardiac depression was surprising. Therefore prospective studies are required to corroborate these findings in the future. Second, the definition of individuals as those with a heart condition may have included people with other circulatory (angina, hypertension) or genetic heart conditions. These findings require confirmation with objective outcome data.

In conclusion, our findings indicate that MDD more commonly occurs prior to the onset of CVD, and that pre-morbid depression is associated with poorer self-rated mental health status. Individuals with MDD should be identified as being at high risk of CVD. For patients presenting with MDD and a medical co-morbidity such as CVD, having a history of depression should be identified as a significant risk factor for poorer health. These profiles should be used to guide treatment options for patient sub-populations in order to improve mental health outcomes, and possibly survival.

Ackowledgments

This work was supported by a Post Graduate Award from the National Heart Foundation of Australia (PP 08M4079)(AO), a Diabetes UK Moffat Travelling Fellowship (EDW), a NHMRC Health Services Research Grant (465130)(CES) and an Australian Research Council Future Fellowship (FT991524)(KS). The authors gratefully acknowledge the Australian Bureau of Statistics for conducting the survey and the Commonwealth Department of Health and Ageing for funding the survey.

Figures

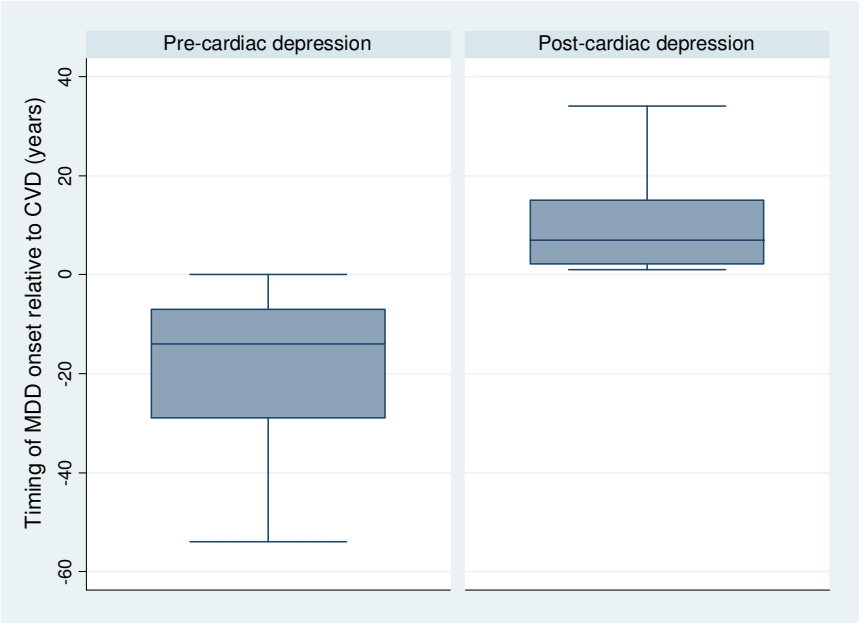

Figure A1.1. Timing of MDD onset relative to CVD (pre-cardiac versus post-cardiac depression)

Tables

Table A1.1. Key characteristics of survey participants reporting (1) Depression preceding CVD, (2) Depression occurring after CVD, NSMHW 2007 (Person weighted, survey corrected percentages/means and 95% confidence intervals) (n=224)

Variable	**Pre-cardiac depression (n=183)**	**Post-cardiac depression (n=41)**
Age	51.67 (48.81, 54.52)	49.83 (44.66, 55.01)
Sex (male)	41.48% (33.25, 49.71)	52.46% (29.35, 75.57)
Registered marital status (single)	57.56% (46.00, 69.13)	57.43% (36.14, 78.72)
Graduate qualifications[a] (yes)	49.22% (36.51, 61.93)	42.29% (18.03, 66.55)
Level of Disadvantage (Decile 1-5)[b]	52.34% (41.44, 63.23)	49.85% (23.96, 75.75)
Labour force status (Participating)	49.69% (40.52, 58.85)	43.66% (19.73, 67.60)
Disability (WHODAS-12)	23.92 (14.57, 33.28)	22.75 (7.87, 37.63)
Quality of Life [c]	3.46 (3.16, 3.76)	3.60 (3.21, 3.99)
Self-rated physical health [c]	3.49 (3.27, 3.70)	3.52 (2.93, 4.12)
Self-rated mental health [c]	3.10 (2.91, 3.30)	2.98 (2.73, 3.24)*
Number of days in past year had depressive episode	77.85 (50.99, 104.72)	90.53 (26.63, 154.43)
Depressive episode(s) in past year	35.78% (26.48, 45.09)	38.55% (17.87, 59.23)
Psychological distress (Moderate to high distress)	69.50% (61.62, 77.37)	80.08% (64.36, 95.81)
Smoke (yes)	30.55% (18.96, 42.14)	28.99 % (-2.45, 58.22)
Body Mass Index[d]	30.02 (28.40, 31.64)	30.09 (26.42, 33.77)
CVD lasting longer than 6 months	75.01% (66.61, 83.42)	66.14% (40.09, 92.20)

CVD treatment in past 12 months	67.34% (58.08, 76.60)	54.16% (28.95, 79.37)
Number of times walking for exercise in past week	5.33 (3.90, 6.76)	4.50 (3.33, 5.66)
Chronic medical condition in the past 12 months (diabetes, cancer, asthma, arthritis)	73.73% (65.80, 81.66)	66.72% (41.03, 92.43)
Mean time of onset of MDD in relation to CVD (years)	-17.48 (-19.80, -15.15)	9.88 (6.07, 13.68)

[a] =educational attainments other than those of pre-primary, primary or secondary education. [b] =Most disadvantaged; [c] =higher score indicates worse health; [d] =missing data (n=219); *= Between group difference statistically significant, $p<0.05$, those with pre-cardiac depression as reference group

Table A1.2. Logistic regression model for the relationship between order of disease onset and self-rated mental/physical health for individuals with co-morbid depression and heart condition

	Adjusted Odds ratio	Jack-knife Standard Error	Confidence intervals
Self-rated mental health[a] (n=219)			
Condition			
Pre-cardiac depression	1.0		
Post-cardiac depression	0.36*	0.17	0.14, 0.93
Age	0.97	0.02	0.93, 1.01
Sex (Female)	0.58	0.26	0.24, 1.41
Level of Socio-economic Decile 6-10[b]	1.23	0.51	0.53, 2.83
Chronic medical condition in the past 12 months (diabetes, cancer, asthma, arthritis) (Yes)	1.42	0.78	0.47, 4.27
Minutes of physical activity in past week	0.98	0.04	0.90, 1.07
Labour force status (Participating)	0.61	0.35	0.20, 1.93
BMI	0.95	0.04	0.88, 1.02

Self-rated physical health[a] (n=219)			
Condition			
Pre-cardiac depression	1.0		
Post-cardiac depression	0.90	0.44	0.34, 2.40
Age	1.00	0.01	0.97, 1.03
Sex (Female)	0.43*	0.17	0.19, 0.96
Minutes of physical activity in past week	0.88*	0.04	0.80, 0.97
Body Mass Index	1.11*	0.04	1.03, 1.20
Depression severity			
Mild	4.20	3.47	0.80, 21.95
Moderate	3.74*	2.31	1.09, 12.88
Severe	3.40*	1.47	1.15, 8.00

*p<0.05. [a] =Self-rated health scales were dichotomised into 0= Excellent, Very Good or Good; 1= Fair or Poor, where 0 was the Reference Group. Statistically non-significant variables removed from final models included marital status, number and length of depressive episodes, rurality, education, chronic conditions, employment, time between disease onset and assessment, and smoking status. Depression severity removed from self-rated mental health model because of too few cases. [b] = Least disadvantaged.

Related Publication #2

The use of Cognitive Behavioral Therapy (CBT) for secondary prevention in patients with Coronary Heart Disease (CHD) [published letter]. *Archives of Internal Medicine*. 171, 16.

Adrienne O'Neil[1]

Kristy Sanderson[2]

[1]Department of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia.

[2]Menzies Research Institute Tasmania, Hobart, Tasmania, Australia

To the Editor: Dr Gulliksson et al report the results of a randomized controlled trial of cognitive behavioral therapy (CBT), measuring its effects on Cardiovascular Disease (CVD) recurrence in 362 Coronary Artery Disease (CAD) patients (**264**). The authors found that, after 94 months, the CBT group had a 41% lower rate of fatal and nonfatal recurrent CVD events, and 45% fewer recurrent acute myocardial infarctions (AMI) after adjustment for covariates.

As the authors acknowledge, a large body of evidence exists to link psychosocial factors such as depression, anxiety and low social support to adverse cardiovascular outcomes. There is compelling evidence that up to 42% of coronary patients experience depression (**153**). Co-morbid depression, even mild symptoms, can predict mortality (**6**), morbidity and poorer clinical and wellbeing outcomes.

Indeed, the intervention detailed by Dr Gulliksson and colleagues, which comprised a group-based CBT program, addressed these psychosocial influences. Twenty two-hour sessions were conducted over one-year (plus usual medical care), with the overall goal of treatment "to develop emotional and behavioral coping strategies for dealing with stress. The focus was particularly on stress reactivity and stress behaviors characterized by negative affect like hostility, anxiety, and depressive mood reactions" (**264**) (eAppendix: http://www.archinternmed.com).

However, in the absence of depression, anxiety and social support outcome measures documented in this study, ascertaining the components of this group-based, CBT intervention which led to these improvements, is particularly difficult. Post-AMI depression has been identified as a predictor of 1-year cardiac mortality, and moreover, high levels of social support have been found to provide a protective influence from depression on mortality (**10**). As the authors have not discussed the mediating role of these variables, readers can only speculate about their influence.

Further, while this study highlights the benefits of a protocol-driven program, whether its effectiveness is fully explained by the CBT approach to treatment, from enhanced social support via regular, face-to-face, group-based contact with peers, or via improvements in anxiety and depression as a direct consequence of therapy or as a by-product of other behavioral modifications, remains unanswered.

Unlike other trials using CBT in cardiac populations which have failed to produce significant survival benefits (**81**), this study demonstrates the positive effects of a CBT approach in the secondary prevention of CAD. However, we hypothesize that while the contribution of putative influences such as depression, anxiety and social support, remains unaccounted for in this study, it is likely that they are, in fact, elucidating the observed relationship between survival and treatment.

Related Publication #3

Improving the identification and treatment of depression in women after acute myocardial infarction.

Published online at:
http://circoutcomes.ahajournals.org/cgi/eletters/4/3/283#288. July 14, 2011.

Adrienne O'Neil[1]

Kristy Sanderson[2]

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[2]Menzies Research Institute Tasmania, Hobart, Tasmania, Australia

To the Editor: We read with interest the article by Smolderen et al[1], which reported real-world lessons from the implementation of an American Heart Association (AHA) recommended depression screening protocol in Acute Myocardial Infarction (AMI) patients. After implementing a routine, two-step depression screening process using the PHQ2 and 9, the study revealed that more than 1 in 4 (n=135, 26.8%) Coronary Artery Disease (CAD) patients failed to be screened for depression. Specifically, women were likely to be missed. Of those who were screened, almost 7 of 10 patients with significant depressive symptoms (PHQ-9 score≥10) failed to be recognized and thus were ineligible for treatment.

Importantly, these findings add to those from other studies conducted in cardiac populations which have highlighted poor outcomes in women, including fewer benefits from surgical interventions, such as coronary artery bypass surgery and post-AMI psychosocial interventions, such as depression management.[2,3] Additionally, these findings are consistent with evidence indicating that women are under-represented in cardiac rehabilitation[4] and clinical trials[5].

Indeed, the under-representation of women in both randomised controlled trials of acute coronary syndromes[5] and those which have evaluated depression treatment in cardiac populations is notable. Although some have reported equal gender ratios[2,6,7], major studies in this area have commonly reported an over-representation of men.[8-10]

When the gender specific effects of depression treatment after a cardiac event have been explored, the Bypassing the Blues study,[11] for example, found a stronger effect in males (effect size = 0.55) than females (effect size= 0.32) for reducing depression. Additionally, females failed to demonstrate significant improvements in mental and physical health related quality of life and Duke Activity Status Index, compared with their males counterparts. The authors demonstrated gender differences in the utilisation of program components; men were more

likely to use a supplementary workbook whereas women used pharmacotherapy. The authors concluded that: "additional research is necessary to develop improved treatments for women."[11]

The study by Smolderen and colleagues addresses an important research gap; it provides evidence that female cardiac patients - even with the implementation of routine depression screening - are vulnerable to under-recognition of depression which inevitably results in their under-treatment. This may partly explained the under-representation of women in clinical trials related to post-AMI depression. These findings add to existing evidence from depression treatment trials in cardiac populations which suggest that even when women are identified and enrolled in such programs, they may, in fact, be less responsive to treatment than men[11] or respond to different treatment approaches. Evidently, further efforts are required not only to ensure the identification of post-AMI depression in female patients, but to recruit and retain women in these types of clinical trials to ensure tailored and appropriate interventions are developed and available.

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Appendix B: ETHICS APPROVALS (THE MoodCare TRIAL)

Monash University

MONASH University

Standing Committee on Ethics in Research Involving Humans (SCERH)
Research Office

Human Ethics Certificate of Approval

Date:	**23 June 2009**
Project Number:	**2009000933**
Project Title:	**MOOD-CARE (Managing cO-mOrbid Depression: Coronary Aftercare Randomized Evaluation)**
Chief Investigator:	**Prof Brian Oldenburg**
Approved:	**From: 23 June 2009 To: 23 June 2014**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to SCERH before any data collection can occur at the specified organisation. **Failure to provide permission letters to SCERH before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by SCERH.
4. You should notify SCERH immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to SCERH and must not begin without written approval from SCERH. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. SCERH should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by SCERH at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

Professor Ben Canny
Chair, SCERH

cc: Assoc Prof Bruce Hollingsworth; Assoc Prof Andrew Forbes

Postal – Monash University, Vic 3800, Australia
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Telephone +61 3 9905 5490 Facsimile +61 3 9905 1420
Email scerh@adm.monash.edu.au www.monash.edu/research/ethics/human/index/html
ABN 12 377 614 012 CRICOS Provider #00008C

Royal Brisbane and Women's Hospital

Royal Brisbane and Women's Hospital
Metro North Health Service District

Office of the Human Research Ethics Committees

Queensland Government
Queensland **Health**

Enquiries to: Odette Petersen Coordinator
Phone: 07 3636 5490
Fax: 07 3636 5849
Our Ref: HREC/09/QRBW/82
E-mail RBWH-Ethics@health.qld.gov.au

Professor Brian Oldenburg
Department of Epidemiology & Preventive Medicine
School of Public Health & Preventive Medicine
Alfred Hospital
89 Commercial Road
Melbourne Vic 3004

Dear Professor Oldenburg,

Re: Ref Nº: HREC/09/QRBW/82: A telephone-delivered intervention (MOOD-CARE) [Managing cO-mOrbid Depression: Coronary Aftercare Randomized Evaluation] for depression in patients following myocardial infarction (MI)

Thank you for submitting the above project for ethical and scientific review. This project was considered at the Royal Brisbane & Women's Hospital Human Research Ethics Committee (HREC) meeting held on 20 April, 2009.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.* Attached is the HREC Composition with specialty and affiliation with the Hospital *(Attachment I).*

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval will also be sent to the District Research Governance Office (RGO). Please ensure you submit a completed Site Specific Assessment (SSA) Form to the RGO for authorisation from the CEO or Delegate to conduct this research at the Royal Brisbane & Women's Hospital Metro North District.

I am pleased to advise that the Human Research Ethics Committee has granted approval of this research project on 15 May, 2009. HREC approval is valid for three (3) years from the date of this letter. The documents reviewed and approved include:

Document	*Version*	*Date*
Application: NEAF	2.0	
Recruitment Flyer		
Budget Schedule (unsigned) *(Noted by HREC)*		
Workcover Certificate valid to 30/06/2009		
Certificate of Currency valid to 31/10/09 - Professional Indemnity		
Certificate of Currency valid to 31/10/2009 - General and/or Public Liability		
NHMRC Chief Investigator & Associate Investigator Consent Form		25 February 2008
Letter of Support from Professor John McNeil, School of Public Health & Preventive Medicine, Monash University		20 March 2009
Letter of Support from A/Professor John Atherton, Cardiology Department, RBWH		20 March 2009
LSCT Peer Review Report		
ONHMRC - GrantNet Assessment Report for Applicant		14 July 2008
Response to Assessors' questions and issues		
Protocol: Detailed Background & Reseach Plan		
Work Limitations Questionnaire		
Patient Health Questionnaire (PHQ-9)		
Active Australia Survey		
Cardiac Depression Scale (CDS) Questionnaire		
Response to Request for Further Information		11 May 2009
Response to Request for Further Information		08 May 2009
MOOD-CARE Covering Letter/Summary		20 March 2009
MOOD-CARE Participant Information Sheet	5	11 May 2009
MOOD-CARE Consent Form	2	04 May 2009

Please note the following conditions of approval:

1. The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
    - Unforeseen events that might affect continued ethical acceptability of the project. Serious Adverse Events must be notified to the Committee as soon as possible. In addition, the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Principal Investigator, including duration of treatment and outcome of event.

2. Amendments which do not affect either the ethical acceptability or site acceptability of the project (e.g. typographical errors) should be submitted in hard copy to the HREC Coordinator. These should include a covering letter from the Principal Investigator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.

3. Proposed amendments to the research project which may affect both the ethical acceptability and site suitability of the project must be submitted firstly to the HREC for review and, once HREC approval has been granted, then submitted to the Research Governance Office.

4. Amendments to the research project which only affect the ongoing site acceptability of the project are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office (by-passing the HREC).

5. Amendments to the research project which may affect the ongoing ethical acceptability of a project must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a covering letter from the Principal Investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents with tracked changes must also be submitted to the HREC Coordinator as per standard HREC SOP. Further advice on submitting amendments is available from http://www.health.qld.gov.au/ohmr/documents/researcher_userguide.pdf

6. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

7. The Principal Investigator will provide an Annual Report to the HREC and at completion of the study in the specified format.

8. The District Administration and the Human Research Ethics Committee may inquire into the conduct of any research or purported research, whether approved or not and regardless of the source of funding, being conducted on Hospital premises or claiming any association with the Hospital, or which the Committee has approved if conducted outside Royal Brisbane & Women's Hospital Metro North Health Service District.

Should you have any queries about the HREC's consideration of your project please contact the HREC Coordinator on 07 3636 5490. The HREC terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.health.qld.gov.au/ohmr/html/regu/regu_home.asp

Once authorisation to conduct the research has been granted, please complete the Commencement Form *(Attachment II)* and return to the office of the Human Research Ethics Committee.

The HREC wishes you every success in your research.

Yours sincerely,

[redacted]

Dr Lorna Kratzing
Deputy Chairperson RBWH Human Research Ethics Committee
Metro North **DISTRICT**
15/05/2009

cc A/Professor John Atherton

The Austin Hospital

Austin Health

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Human Research Ethics Committee
Research Ethics Unit
Henry Buck Building
Austin Hospital

TO:	**Prof Brian Oldenburg** **Department of Epidemiology and Preventative Medicine** **89 Commercial Road**
PROJECT:	**Melbourne Vic 3004**
PROTOCOL NO:	An implementation trial of a telephone-based care management program targeting depression for patients following myocardial infarction (MOOD-CARE)
PROJECT NO:	H2009/03647
FROM:	**Jill Davis Research Ethics Unit Manager**
DATE:	12 October 2009
RE:	**Protocol Version 2 dated 7 September 2009** **Participant Information and Consent Form Version 3 dated 7 September 2009** **Data Collection Forms and Questionnaires – Inpatient data collection form** **PHQ9 screening instrument** **Contact details collection form** **Schedule for measurements** **CATI baseline survey (draft dated 19 June 2009)**
Approval Period:	**12 October 2009 to 12 October 2012**

Agenda Item: 6.5

Further to my letter dated 27 August 2009 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the Human Research Ethics Committee at their meeting on 20 August 2009 is satisfactory. This project now has full ethical approval for a period of three years from the date of this letter.

For trials involving radiation to volunteers, the research must be added to the Austin Health Research with Human Volunteer's licence issued by the Department of Human Services – Radiation Safety Section prior to commencement. The HREC must be notified when the research has been added to the licence

It is now your responsibility to ensure that all people associated with this particular project are made aware of what has actually been approved. Any changes to the original application will require a submission of a protocol amendment to the

Committee for consideration as this approval only relates to the original application as detailed above.

It is now your responsibility to make arrangement for progress reports to be submitted to the Committee annually, or sooner if the project is completed within twelve (12) months. Should your study not commence twelve (12) months from the date of this letter this approval will lapse. A resubmission to the Human Research Ethics Committee would then be necessary before you could commence.

DETAILS OF ETHICS COMMITTEE:

It is the policy of the Committee not to release personal details of its members. However I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairperson
Lay Man
Lay Woman
Minister of Religion
Lawyer
Person with Research Experience
Person with Counselling Experience

Additional members include:

- Nurse Administrator
- Surgeon
- Pharmacologist
- Pharmacist

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), annotated with TGA comments; and The National Statement on Ethical Conduct in Human Research (NHMRC The National Statement) and the applicable laws and regulations; and the Health Privacy Principles in The Health Records Act 2001. This hospital is registered under the United States DHHS Federal Wide Assurance number 00001363

PLEASE NOTE: The Committee requests that the Research Ethics Unit (ethics@austin.org.au) is informed of the actual starting date of the study as soon as the study commences. A written notice (e-mail, fax or letter) is considered the appropriate format for notification.

The Prince Charles Hospital

Queensland Government

Office of the Human Research Ethics Committee

Enquiries to: Philip Lee
Phone: 07 3139 4500
Fax: 07 3359 5756
Our Ref: HREC/09/QPCH/126
E-mail Philip_Lee@health.qld.gov.au

Queensland **Health**

05 October 2009

Prof Brian Oldenburg
Department of Epidemiology and Preventive Medicine
Monash University
Alfred Hospital
Melbourne VIC 3004

Dear Prof Oldenburg

HREC Reference number: HREC/09/QPCH/126
Project title: HREC/09/QPCH/126 :A telephone-delivered intervention (MOOD-CARE) [Managing cO-mOrbid Depression: Coronary Aftercare Randomized Evaluation] for depression in patients following myocardial infarction (MI)B.Oldenburg, D.Walters, J.Horn
Protocol number: 1

Thank you for submitting the above project for ethical and scientific review.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise that the Human Research Ethics Committee has granted final approval of this research project on 5 October 2009. The documents reviewed and approved include:

Document	*Version*	*Date*
Questionnaire: Baseline Questionnaire		06 August 2009
Protocol	1	01 July 2009
Inpatient Data Collection Forms		06 August 2009
Master Participant Information Sheet	1	03 July 2009
Master Consent Form	1	03 July 2009
Application: NEAF		06 August 2009
Response to Request for Further Information		15 September 2009
Patient Information Sheet/Consent Form	2	11 September 2009

This information will be tabled at the next HREC meeting held 29 October 2009, for noting.

Please note the following conditions of approval:

1. The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
    a. Unforeseen events that might affect continued ethical acceptability of the project.

Serious Adverse Events must be notified to the Committee as soon as possible. In addition the Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Patient Information and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Principal Investigator, including duration of treatment and outcome of event.

2. Amendments to the research project which may affect the ongoing ethical acceptability of a project must be submitted to the HREC for review. Major amendments should be reflected in a revised online NEAF (accompanied by all relevant updated documentation and a cover letter from the principal investigator, providing a brief description of the changes, the rationale for the changes, and their implications for the ongoing conduct of the study). Hard copies of the revised NEAF, the cover letter and all relevant updated documents with tracked changes must also be submitted to the HREC coordinator as per standard HREC SOP. Further advice on submitting amendments is available from http://www.health.qld.gov.au/ohmr/html/regu/regu_home.asp

3. Amendments to the research project which only affect the ongoing site acceptability of the project are not required to be submitted to the HREC for review. These amendment requests should be submitted directly to the Research Governance Office/r (by-passing the HREC).

4. Proposed amendments to the research project which may affect both the ethical acceptability and site suitability of the project must be submitted firstly the HREC for review and, once HREC approval has been granted, then submitted to the RGO.

5. Amendments which do not affect either the ethical acceptability or site acceptability of the project (e.g. typographical errors) should be submitted in hard copy to the HREC coordinator. These should include a cover letter from the principal investigator providing a brief description of the changes and the rationale for the changes, and accompanied by all relevant updated documents with tracked changes.

6. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

7. The Principal Investigator will provide an annual report to the HREC and at completion of the study in the specified format.

8. The District administration and the Human Research Ethics Committee may inquire into the conduct of any research or purported research, whether approved or not and regardless of the source of funding, being conducted on hospital premises or claiming any association with the Hospital; or which the Committee has approved if conducted outside The Prince Charles Hospital Health Service District.

HREC approval is valid for 2 years from the date of this letter.

Should you have any queries about the HREC's consideration of your project please contact myself on the above phone number or email. The HREC terms of Reference, Standard Operating Procedures, membership and standard forms are available from
http://www.health.qld.gov.au/ohmr/html/regu/regu_home.asp

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the District CEO or Delegate of that site has been obtained.

A copy of this approval must be submitted to the District Research Governance Officer/Delegated Personnel with a completed Site Specific Assessment (SSA) Form for authorisation from the CEO or Delegate to conduct this research at the Metro North Health Service District.

Once authorisation to conduct the research has been granted, please complete the Commencement Form (Available on our website) and return to the office of the Human Research Ethics Committee.

The HREC wishes you every success in your research.

Yours faithfully

Philip Lee
for
Mr Philip Masel
CHAIR
HUMAN RESEARCH ETHICS COMMITTEE
METRO NORTH HEALTH SERVICE DISTRICT

c.c. Dr Darren Walters
Cardiology Clinical Research Centre
The Prince Charles Hospital

The Royal Melbourne Hospital

PO Royal Melbourne Hospital
Parkville Victoria 3050
Telephone: 61 3 9342 7215
Facsimile: 61 3 9342 8548
Email: research.directorate@mh.org.au
Website: http://hrec.mh.org.au
ABN 73 802 706 972

MELBOURNE HEALTH

Mental Health Research and Ethics Committee Approval Certificate

The MHREC operates in accordance with the *NHMRC National Statement on Ethical Conduct in Human Research 2007*

This is to certify that

MHREC Project No: 2010.020 **Approval date: 4/03/2010** **Expiry date: 3/03/2013**

Project Title: A telephoned-delivered intervention (MOOD-CARE)[Managing cO-mOrbid Depression: Coronary Aftercare Randomized Evaluation] for depression in patients following myocardial infarction(MI)

Principal Investigator: A/Professor Leeanne Grigg
Director of Cardiology
Cardiology Department
The Royal Melbourne Hospital

Protocol No: Version 3 dated 5 November 2009

Participant Information and Consent Form: Version 3 dated 25 February 2010

Other: Recruitment Manual Version 3 dated 5 November 2009, Questionnaire and Baseline Survey

Conducted at: The Royal Melbourne Hospital, City Campus **has been approved.**

This proposal meets the requirements of the *NHMRC National Statement on Ethical Conduct in Human Research 2007.*

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Manager of the Mental Health Research and Ethics Committee of:

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study;
- Serious adverse effects on subjects and the action taken to manage them, including an amended Patient Information and Consent Form where appropriate;
- Any unforseen events;
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study;
- A delay of more than 12 months in the commencement of the project; and
- The actual date of commencement of the study.

You are required to submit the following reports to the Mental Health Research and Ethics Committee:

- An Annual Report every twelve months for the duration of the project; and
- A detailed Final Report at the conclusion of the project.

The Mental Health Research and Ethics Committee may conduct an audit at any time.
An extension of the project beyond the stated conclusion date should be sought from the Mental Health Research and Ethics Committee.

Signed:

[redacted]

Michelle Clemson
Manager, Mental Health Research and Ethics Committee

The Geelong Hospital

OFFICE FOR RESEARCH
P.O. Box 281
Geelong Victoria 3220
Telephone: 03 5226 7920
Facsimile: 03 5226 7306
e-mail: hrec@BarwonHealth.org.au

Correspondence: Anthony Budden
Health Economics Associate
Pretium Pty Ltd
Level 12
60 Margaret Street
Sydney NSW 2000

ETHICS COMMITTEE APPROVAL STATEMENT

HREC Project Number	10/79
Site	Barwon Health
Date Approved	8/09/2010
Principal Investigator	John Amerena
Title:	An implementation trial of a telephone based care management program targeting depression for patients following myocardial infarction.
Co investigators	
Student names	

Thankyou for submitting the above for our consideration. Your project is approved and you may commence.

Your obligations under this approval include notifying the Committee of any intent to deviate from the approved protocol and of the occurrence of any untoward events.

It is now your responsibility to undertake the following:

1. To inform any personnel who should be aware of this project

2. To ensure, if applicable, that accurate documentation of the consent process is recorded in the participant's hospital history and that a photostated copy of the consent form is also placed in the hospital history.

3. To advise the Committee, in writing, of any changes you wish to make to the running of the project, including extending beyond the anticipated completion date.

4. To advise the Committee, in writing, of any serious adverse events

5. To supply written annual reports on the anniversary of your approval advising of the progress of the project and a final report advising of completion

6. To ensure that, if applicable, the project is registered on a Clinical Trials Registry and that the number is made available to the Committee for out records

Please note: Research projects to be undertaken at private institutions are not covered by the Barwon Health Medical Malpractice Policy.

In the case of medical research, care should be taken to ensure that the investigator's medical insurance policy is current and the institute in which the research is conducted is adequately insured.

It is the responsibility of the investigator to ensure adequate coverage in the event of litigation

Should you require any further information concerning the Committee's approval of your research or have any concerns regarding the reporting requirements please contact the Office for Research, on 5226 7920.

Finally, in all future correspondence regarding your study please quote the HREC Project Number and full title of your research project.

On behalf of the Committee, best wishes for your project.

Yo[redacted]

SIMON FRENCH
CHAIR
Human Research Ethics Committee

St Vincent's Hospital

Research Governance Unit
Ph: (03) 9288 2394 Fax: (03) 9288 3949

Monday, 14 September 2009

Prof B Oldenburg
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School of Public Health Alfred Hospital 89
Commercial Rd
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Fitzroy Victoria 3065 Australia
Telephone 03 9288 2211
www.svhm.org.au

St. Vincent's Hospital
(Melbourne) Limited
Incorporating:
Caritas Christi Hospice
St. George's Health Service
Prague House
ABN 22 052 110 755

Dear Prof Oldenburg

Protocol No: HREC-A 084/09

'A telephone -delivered intervention (MOOD-CARE- Managing cO-mOrbid Depression: Coronary Aftercare Randomised Evaluation) for depression in patients following myocardial infarction (MI).'

Prof B Oldenburg A/Prof M Jelinek

The Professional Secretariat of Human Research Ethics Committee-A (HREC-A) has agreed that your latest correspondence dated Wednesday 05 August 2009, has satisfied the conditions imposed and granted full approval for this project to be undertaken at the following site/s:

St Vincent's Hospital (Melbourne)

HREC-A is constituted and operates in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007).

HREC-A has a policy of granting approval for four years. Ethical approval is valid for four years from the date of this letter. Approval may be renewed at the end of this period by resubmission to HREC-A.

Approval is subject to:

1. Registration of the project on a clinical trial register before the first patient is enrolled (only applies if the project is a clinical trial requiring registration).
2. immediate notification to HREC-A and sponsor of any serious adverse effects on participants;
3. immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
4. notification and reasons for ceasing the project prior to its expected date of completion;
5. the completion of an annual report on progress of the project;

St Vincent's

Continuing the Mission of the Sisters of Charity

6. HREC-A approval of any proposed modification to the project; and
7. the submission of a final report and papers published on completion of project.

HREC approval includes the following :

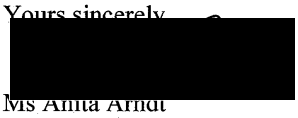
Other - MOODCARE - Schedule for measurements

Data Collection Form - Hospital Baseline data collection form:Hospital records

Questionnaire - CATI baseline survey, draft version, dated 19 June 2009

If you are using participant information and consent forms, please remember to include the HREC protocol # at the top of page 1.

Yours sincerely,



Ms Anita Arndt
Senior Administrative Officer and HREC-A Secretary
Direct Tel: 9288 3924

Appendix C: CONTRIBUTION TO MoodCare TRIAL

Table C.1. Academic and administrative contribution to the MoodCare Study

Date	*Task Completed (2008-2009)*
	PROJECT FUNDING
	Co-ordinated submission of funding proposal for MoodCare [*Managing cO-mOrbid Depression: Coronary Aftercare Randomized Evaluation*] trial, to
Jan-Mar 2008	(1) National Health Medical Research Council
	(2) Commonwealth Department of Health and Ageing
June-July 2008	(3) National Heart Foundation / *beyondblue*
Jan-Feb 2009	Once funding offer was received, organised required paperwork for execution of Agreement between Commonwealth and Monash University via Monash Solicitor's Office
March 2009	Developed a modified research plan for submission to funding body at commencement of funding period
April 2009	Attended Commonwealth Department workshop for grantees to discuss the MoodCare project (Adelaide, South Australia); acted as Liaison Officer with Department's Research Administrator for the period Jan-April, 2009
	ETHICS AND REGISTRATION
Feb 2009	Co-ordinated and co-wrote submission to ethics committee of the first recruitment site, the Royal Brisbane and Women's Hospital (Approval number HREC/09/QRBW/82)
Mar – Apr 2009	Registered and updated study details at Australian and New Zealand Trial Registry
	RECRUITMENT/SITE PARTICIPATION
April 2009	Met with all key hospital staff and investigators at the Melbourne hospitals to promote the MoodCare study and provide required information to staff for potential involvement (St Vincent's, Austin, Royal Melbourne)
March 2009	Liaised with Senior staff at Monash Medical in attempt to gauge interest levels in MoodCare for potential participation in the project
Aug 10, 2009	Attended internal 'Prevention Committee' meeting at St Vincent's Hospital, Melbourne with Project Manager to brief committee on MoodCare project
	PROJECT TEAM COMMUNICATION
March 2009	Set up initial MoodCare project website run off Monash Faculty domain, which included obtaining faculty approval and collating content material for website
2 + 3 April 2009	Organised and co-ordinated two Melbourne based workshops and dinner for Investigator team members (one with Intervention Working Group and the other with all Investigators) including preparation of

	agenda, Powerpoint presentations and key documents for attendees coming from different areas of the country
Mar-Apr 2009	Arranged regular monthly teleconference agendas, minutes and related communications for all project staff and investigator team members
April 2009	Met with Senior IT staff within the Department to initiate development of web based platform for project data collection
2008-2011	Attendance of monthly MoodCare Investigator and weekly Project member team meetings
	STATISTICS AND SAMPLE SIZE
May 2009	Collected papers and extracted key data for statistician to calculate sample size for MoodCare trial
Mar-May 2009	Met with Senior Biostatisticians on several occasions to discuss scenarios for design of the trial, required sample size, recruitment and more specifically to plan future statistical analysis of work and quality of life outcomes
	STUDY INSTRUMENTS
March 2009	Drafted first version of Computer Assisted Telephone Survey for use at baseline assessment for collection of information on all outcome measures
April 2009	Developed employment, work productivity, absenteeism, presenteeism and income related sections of the surveys for use at all assessment points throughout the study
May 2009	Liaised with Health Economists to help shape direction of the study economic evaluation, surrounding Quality of Life instruments
May 2009	Co-developed discussion paper on advantages and disadvantages of using particular study instruments to guide investigators' decisions
	MoodCare PROJECT TEAM STAFF
Mar 2008-2009	Developed original project budget for personnel and updated to advise
Feb- Mar 2009	Investigators on appropriate hiring of project staff within budgetary constraints
April 2009	Co-wrote position description for Project Manager position
17/4/09	Co-interviewed candidate for Project Manager position
29/6/09	Co-developed advertisement to recruit MoodCare psychologists for delivery of intervention
9/11/09	Member of interview panel assessing candidates for psychologist positions; Co-Assessor of candidate applications for CATI Research

	Assistant position
	INTERVENTION
Ongoing	Member of Intervention Working Group
April 2009	Contributed to draft of original Intervention development paper, took minutes at Intervention Working Group first meeting and communicated on progress of this meeting to wider team
April 2009	Involvement in co-development, testing and troubleshooting of IT platform from which Psychologists would deliver the intervention and
Aug 2009	Research Assistants would conduct participant surveys. Frequently attended regular, related IT meetings
	Alongside key project staff, met with key researchers at Monash Medical Centre who had conducted similar programs in heart failure patients for advice on development of MoodCare study
	KEY DOCUMENTS
September-October, 2009	Co-author of the MoodCare Participant manual: contributed to aspects of conceptualisation and content, development of three drafts, final edits of manual
Aug 2009	Contributed to drafts of MoodCare intervention manual
Mar- Dec 2009	Produced two related literature reviews (first author) directly relevant to the MoodCare study, in order to provide key background information to shape the components of the program directly related to quality of life and work outcomes
July 2009	Assisted in co-writing "sub project" proposal to funding body which will explore depression trajectory MI patients who do no exhibit depression at hospitalisation
November 2009	Co-developed study protocol, and assisted with updates
	DATA COLLECTION
October 19 2009	Piloted web based data base for data collection, trouble shooting and providing feedback to Project Manager and IT staff
November 18	Piloted telephone-delivered CATI survey with Research Assistant (role plays), documenting ease of participation, problems associated with answering questions, social desirability of questions, ordering of instruments and the like
November 19 2009	Attending half day training session for up skilling in administration of CIDI depression diagnostic instrument, a component of the CATI survey

	PUBLICATIONS/ACADEMIC OUTPUT
Sept 2009	Presented MoodCare poster at Monash University Higher Degrees in Research showcase
Aug 6, 2009	Oral Presentation of MoodCare program at Monash University's Higher Degrees in Research Three Minute thesis competition
Dec 4, 2009	Abstract accepted for oral presentation at Asia-Pacific Academic Consortium of Public Health Conference (41st annual APACPH), Taipei, Taiwan December 2009 (first author) : A randomized controlled trial managing co-morbid depression after myocardial infarction: MoodCare

For period March 2009- February 2010:

Name: Prof Brian Oldenburg Position: Chief Investigator Signed: [redacted] Date: 14/3/10

Name: Bianca Chan Position: Project Manager Signe[redacted] Date: 2/3/10

Appendix D: BIBLIOGRAPHY

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