2017

The impact of depression on treatment adherence and cardiorespiratory fitness in cardiac rehabilitation

Sheau-Yan Ho
University of Vermont

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THE IMPACT OF DEPRESSION ON TREATMENT ADHERENCE AND CARDIORESPIRATORY FITNESS IN CARDIAC REHABILITATION

A Dissertation Presented

by

Sheau-Yan Ho

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Psychology

October, 2017

Defense Date: May 9, 2017
Dissertation Examination Committee:

Kelly J. Rohan, Ph.D., Advisor
Philip A. Ades, M.D., Chairperson
Karen Fondacaro, Ph.D.
Matthew Price, Ph.D.
Alessandra Rellini, Ph.D.
Cynthia J. Forehand, Ph.D., Dean of the Graduate College
ABSTRACT

Major depression and coronary heart disease are two strongly linked, major causes of death and disability. After an acute coronary event, many patients are referred to cardiac rehabilitation (CR), a medically supervised exercise intervention and lifestyle training program. Depression may partially account for poor CR adherence and resulting cardiovascular problems in patients with a history of heart disease; however, underlying mechanisms through which depression impacts cardiac functioning are not well understood. The current project tests a theoretical model in which CR adherence (i.e., number of CR sessions attended) mediates the relation between baseline depression and cardiorespiratory fitness after CR. A community sample of 858 older adults initiating CR after hospitalization for a coronary event completed a symptom-limited exercise stress test before and after the 12-week program. Cardiorespiratory fitness was measured via VO$_2$max, peak MET, and total duration of the stress test. Depression was measured at baseline using the Patient Health Questionnaire Depression Scale. CR adherence did not mediate the relation between baseline depression scores and fitness outcomes. Path analyses revealed that higher baseline depression severity predicted lower likelihood of CR completion (i.e., completion of all 36 sessions, or fewer if limited by insurance or terminated early for good prognosis) in the full sample. Higher levels of depression predicted poorer CR adherence in a subsample of 74 patients with moderate to severe depression. These findings lend support to depression as a predictor of treatment nonadherence in CR. Screening for depression in the context of coronary heart disease and implementing evidence-based depression interventions in secondary prevention settings can help alleviate a massive public health burden.
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CHAPTER 1: INTRODUCTION

Public Health Significance

Depression and heart disease are two of the leading causes of disability worldwide (CDC, 2016) and among the top five chronic conditions encountered in the care of older adults (Whooley, 2006), a growing demographic worldwide. Major depressive disorder is a debilitating mental health problem estimated to cost more than $210 billion per year in the United States (Greenberg et al., 2015). Depression is also strongly linked to heart disease, the leading cause of death among adult men and women in the United States (CDC, 2016). According to American Heart Association (AHA) statistics, although mortality rates have declined in recent decades, an estimated 785,000 Americans have heart attacks each year and approximately 475,000 Americans will have a recurrent attack each year (Roger et al., 2011). It is estimated that approximately half of all middle-aged men and one-third of middle-aged women in the United States will develop some manifestation of coronary heart disease during their lifetime (Lloyd-Jones et al., 1999). Thus, clinical interventions and prevention efforts focused on depression and heart disease bear a tremendous impact on global public health.

Background on Coronary Heart Disease (CHD)

Medical Terminology. Coronary heart disease (CHD) is a broad term that refers to cardiac disease caused by atherosclerosis (i.e., the hardening and narrowing of arteries) or myocardial ischemia (i.e., restricted oxygenated blood flow to the heart). The narrowing of small blood vessels that supply blood to the heart can weaken the heart muscle over time. Temporary shortages in oxygen to the heart typically result in angina or chest pain. A myocardial infarction (MI), colloquially known as a heart attack, occurs
when the heart suffers severe or prolonged deprivation of oxygen-rich blood. Congestive heart failure is a more severe, chronic condition that occurs when the heart becomes permanently enlarged, the left ventricular ejection fraction or pumping capacity is reduced, and the individual becomes short of breath with little physical exertion.

Medical procedures and treatments for acute coronary events may include surgical intervention. Percutaneous coronary interventions (PCI; e.g., balloon angioplasty, coronary stent placement) are minimally invasive procedures in which a stent is placed to open up coronary arteries, allowing blood to circulate unobstructed to the heart muscle. Coronary artery bypass graft (CABG) is a more complicated type of surgery during which arteries or veins from another area of the body are surgically grafted to bypass the narrowed coronary arteries. Medications (e.g., lipid-lowering drugs, antiplatelet agents, anticoagulants) may also be prescribed for secondary preventative measures.

**Traditional Risk Factors for CHD.** A number of medical conditions and health behaviors are well established as risk factors for heart disease that increase morbidity and mortality. These risk factors include but are not limited to nicotine use, hypertension, hypercholesterolemia, diabetes mellitus, obesity, and physical inactivity. The relative risk of cardiac mortality associated with each pack of cigarettes smoked per day is approximately 1.39 (Multiple Risk Factor Intervention Trial Research Group, 1986). A prolonged increase in blood pressure of 10 mm Hg above normal diastolic pressure is associated with a 37% increased risk of cardiovascular disease (Wilson et al., 1998). Cardiac mortality increases 9% for each 10 mg/dL increase in plasma cholesterol (Anderson et al., 1987), such that individuals in the highest quartile of plasma cholesterol levels are three times more likely to die of cardiovascular disease than those in the lowest
quartile (Multiple Risk Factor Intervention Trial Research Group, 1986). Diabetes is also associated with a three- to four-fold increased risk of cardiovascular disease and mortality (Garcia et al., 1974). The relative risk of cardiovascular disease in overweight (BMI 25.0 to 29.9) and obese (BMI ≥ 30) individuals, compared with individuals of normal weight (BMI 18.5 to 24.9) is approximately 1.2 and 1.64, respectively (Wilson et al., 2002).

The aforementioned risk factors for heart disease are largely modifiable and treatable (Center for Disease Control and Prevention, 2015). Chronic medical conditions such as obesity, hyperlipidemia, hypertension, and insulin resistance/diabetes mellitus can be improved through health behaviors. Hence, lifestyle changes (e.g., heart-healthy dieting, weight management, physical activity, managing stress, quitting smoking, limiting alcohol intake, medication adherence) are emphasized in clinical interventions for CHD as well as in health promotion and disease prevention.

**Epidemiology of Depression in CHD**

Major depressive disorder (MDD) is characterized by clinical impairment and distress associated with five or more symptoms (e.g., depressed mood, anhedonia, change in appetite/weight, disrupted sleep, fatigue, psychomotor retardation or agitation, feelings of worthlessness or inappropriate guilt, poor concentration, suicidal ideation) that have persisted for at least two weeks. CHD patients may differ from depressed but otherwise healthy patients in ways that have important implications for assessment and treatment (Kronish, Krupka, & Davidson, 2012; Lett et al., 2005). First, cardiac patients tend to be older individuals and present with medical comorbidities, which can make it challenging to tease apart depression from symptoms of organic disease. Typical symptoms of depression, like sadness, guilt, or suicidal ideation, are often replaced by feelings of
anger, irritability, anxiety, and/or stress (Lespérance & Frasure-Smith, 2000). Cardiac patients are more likely to endorse somatic symptoms (e.g., fatigue, disturbed sleep, changes in appetite, dyspnea, palpitations) and attribute them to medical conditions than to emotional distress (Kop, 2012). In fact, somatic symptoms are often associated with more severe levels of depression in cardiac patients (Carney & Freedland, 2012). Second, CHD patients may be less willing to participate in emotionally challenging or time-consuming treatments on top of the burden of coping with chronic disease and acute health events or procedures (Lett et al., 2005). Third, depressive symptoms that emerge in reaction to a stressful medical event (e.g., adjustment disorder subsequent to an acute coronary event) may spontaneously remit without treatment (Kronish et al., 2012).

Clinical depression is often comorbid with chronic medical conditions, including heart disease, diabetes, and hypertension. It is also associated with genetic and behavioral risk factors of CHD, namely noncompliance with medical treatments, sedentary lifestyle, obesity, and smoking (Carney & Freedland, 2008; Lett et al., 2004). The estimated point prevalence of MDD in patients following MI is approximately 20% (Lichtman et al., 2008; Thombs et al., 2005), that is, three times the prevalence of current depression in the general adult population (6.6%, Kessler et al., 2003). Some cross-sectional studies report even higher depression prevalence rates in coronary artery disease and MI patients (up to 47%; Lett et al., 2004; van Melle et al., 2004) and in heart failure patients (up to 54%; Rutledge et al., 2006). The highest depression prevalence rates most often characterize patients with congestive heart failure (Jiang et al., 2001; Rutledge et al., 2006; Whooley et al., 2006) and unstable angina (Lett et al., 2004), as well as patients awaiting CABG (Lett et al., 2004). It should be noted that heterogeneity in prevalence rates might be
partially accounted for by varied methodological approaches, with higher rates of depression in studies using self-report measures and lower rates reported in studies that relied on diagnostic interviews (Rutledge et al., 2006).

**Depression as a Risk Factor for Adverse Outcomes in Healthy Patients**

There is an accumulating body of research that not only links depression to adverse outcomes but also supports depression as a consistent predictor of first onset of coronary artery disease and myocardial infarctions (Kessler, 2012; Pratt et al., 1996, Scherrer et al., 2009, Van der Kooy, et al., 2007; Wulsin & Singal, 2003). In order to shed light on the issue of directionality and to definitively conclude whether depression is a significant risk factor for the development of heart disease, researchers have conducted numerous prospective studies in healthy patients without a history of heart disease. In a community-based longitudinal study, 450 subjects with a cardiac disease diagnosis and 2,397 subjects without cardiac disease were followed for 4 years and evaluated for major depression using the Center for Epidemiologic Studies – Depression (CES-D; Penninx et al., 2001). The relative risk of cardiac mortality due to cardiac disease was 3.0 for cardiac patients with major depression compared with nondepressed cardiac patients. Similarly, among patients without cardiac disease, those with MDD were 3.9 times more likely to die of cardiac causes compared with those without depression at baseline, even after controlling for potentially confounding factors such as age, sex, level of education, BMI, smoking status, alcohol intake, blood pressure, and comorbid medical conditions (e.g., stroke, diabetes mellitus, lung disease, cancer). According to a meta-analysis of 11 prospective cohort studies examining depression as a predictor for CHD in healthy subjects with depression, both MDD and depressive symptoms showed a statistically
significant overall effect size (Rugulies, 2002). A sensitivity analysis revealed that MDD (RR = 2.69, 95% CI 1.63–4.43, p < 0.001) was a stronger, more consistent predictor of CHD than depressive mood (RR = 1.49, 95% CI 1.16–1.92, p = 0.02). Another meta-analysis of 30 prospective studies examined the relation between depression and the risk of CHD and MI in participants with no history of CHD over a follow-up duration ranging from 2 to 37 years (Gan et al., 2014). Pooled relative risks were 1.30 (95% CI, 1.22-1.40) for CHD and 1.30 (95% CI, 1.18-1.44) for MI, suggesting that depression is independently and significantly associated with an increased risk of CHD and MI.

**Depression as a Risk Factor for Poorer Outcomes in Patients with Heart Disease**

Epidemiological studies examining the link between depression and CHD have found that major depression and elevated depressive symptoms are associated with worse prognosis (i.e., earlier and more severe cardiac events) in patients with a history of CHD (Lichtman et al., 2008). In a meta-analysis of depression in heart failure patients, aggregated results across a range of clinical outcomes indicated that more severe depression was associated with a substantially worse prognosis, after adjusting for multiple covariates such as age and ejection fraction (Rutledge et al., 2006). This dose-response relationship between depressive symptoms and adverse CHD outcomes is stronger for major depression than for minor depression (Goldston & Baillie, 2008).

There is general consensus that depression is an independent risk factor for heart disease, as it is specifically linked with higher risk for second cardiovascular events, premature death, and cardiac mortality in patients with established heart disease (Lichtman et al., 2008; Whooley et al., 2008). A meta-analysis of 22 prospective studies comparing the cardiovascular prognosis of depressed MI patients to a non-depressed MI
control group examined the association of depression with mortality and cardiovascular events within 2 years of the index MI (van Melle et al., 2004). Post-MI depression was significantly associated with all-cause mortality (OR fixed = 2.38), cardiac mortality (OR fixed = 2.59) and new cardiovascular events (e.g., recurrent MI; OR random = 1.95).

Parashar and colleagues (2006) prospectively followed a sample of 1,873 depressed patients with acute MI and classified patients as having transient (only at baseline), new (only at 1 month), or persistent (at both baseline and 1 month) depression. Depression was assessed with the 9-item Primary Care Evaluation of Mental Disorders Brief Patient Health Questionnaire (PHQ-9), using a standard cutoff of 10 to indicate at least moderate levels of major depression. Higher depression severity during hospitalization for MI predicted more severe depression at 1-month post-discharge, such that higher levels of depression at baseline predicted higher levels of depression at 1-month. In comparison to non-depressed patients, all three “persistence” categories of depressed patients, irrespective of depression onset at baseline or in the first month after hospitalization, demonstrated worse outcomes as defined by more rehospitalizations, higher mortality rates, more frequent angina, greater physical limitations, and poorer quality of life at 6 months after discharge.

Similar findings have been reported in multiple patient cohorts with varying forms of heart disease. The Heart and Soul Study (Whooley et al., 2008) followed 1,017 outpatients with stable CHD over a mean of 4.8 (SD = 1.8) years and found that baseline depressive symptoms measured by the PHQ-9 were associated with a 31% higher rate of adverse cardiovascular events (e.g., heart failure, MI, stroke, transient ischemic attack, death). Connerney and colleagues (2001) followed 309 CABG patients over 1 year and
found that patients who met modified DSM-IV criteria for MDD in the few days after surgery were more than twice as likely as non-depressed patients to have a cardiac event within 12 months after surgery. In a longitudinal study of 817 CABG patients, depression was assessed at baseline and at 6 months post-surgery (Blumenthal et al., 2003). Moderate to severe levels of depression, measured by the CES-D, that persisted 6 months after surgery, were independently associated with a 2- to 3-fold increase in risk for mortality. Another study (Jiang et al., 2001) prospectively followed 374 patients hospitalized with congestive heart failure and found that major depression was associated with increased mortality at 3 months (OR = 2.5) and 1 year (OR = 2.23) as well as rehospitalization at 3 months (OR = 1.90) and 1 year (OR = 3.07).

**Depression: An Independent Risk Factor for CHD**

Traditional cardiac risk factors do not adequately account for the effect of depression on CHD outcomes (Carney & Freedland, 2008). There are obvious methodological differences across studies, including sample size, sample characteristics, selection of covariates, definitions of depression and adverse cardiac outcomes, and length of follow up. However, as a whole, the epidemiological literature provides robust and compelling evidence for a strong, consistent dose-response relationship between depression and prognosis after adjusting for potential confounders (Frasure-Smith & Lespérance, 2005; Goldston & Baillie, 2008; Lichtman et al., 2008). Although it remains to be confirmed whether depression is a causal risk for heart disease, the evidence overwhelmingly supports the assertion that depression is an independent risk factor for CHD in healthy patients as well as a predictor for worse outcomes in individuals with established heart disease, after adjusting for severity of CHD as well as other medical and
demographic factors (Carney & Freedland, 2008). In fact, given the preponderance of evidence linking depression and adverse cardiac outcomes, the AHA issued a scientific statement urging national health organizations to elevate depression to the status of a risk factor for adverse medical outcomes in patients with acute coronary syndrome (Lichtman et al., 2014). This recommendation places depression on par with moderate risk factors such as hypertension, hypercholesterolemia, and obesity (Kronish et al., 2006). Given the public health significance of depression and CHD and the comorbidity of these chronic conditions, depression is arguably the most important psychosocial target in cardiology research (Davidson et al., 2006; Rutledge et al., 2013).

**Mechanisms of Depression in CHD**

Although depression has been identified as a risk factor for the development of CHD, as well as an independent predictor of poor prognosis following cardiovascular events, the underlying mechanisms of these relations are still poorly understood (Carney & Freedland, 2008; Joynt et al., 2003; Skala et al., 2006). A number of studies have proposed and considered plausible mechanisms of a causal relationship between depression and CHD, yet there is little existing work to establish the etiological pathways by which depression contributes to adverse cardiac events and poorer prognosis. Candidate mechanisms that have been proposed to explain the link between depression and increased risk for CHD and subsequent cardiac mortality and morbidity broadly fall into one of two categories: physiological or behavioral processes. Based on the literature examining underlying mechanisms in depressed cardiac patients, Lett and colleagues (2004) proposed a theoretical biobehavioral model in which behavioral risk factors and physiological risk factors are interactive mechanisms that underlie the relation between
depression and CHD. Below, biological, behavioral, lifestyle, and social factors that represent potential mediating pathways are summarized in brief.

**Biological Mechanisms of Depression in CHD.** Biological mechanisms are believed to partially explain the relation between depression and worse cardiac prognosis (Lett et al., 2004; Whooley et al., 2008). Studies have found disturbances in cardiac autonomic tone and decreased heart rate variability, an indicator of autonomic nervous system functioning, in depressed patients with stable coronary disease or a recent history of acute coronary syndrome (Carney & Freedland, 2008; Goldston & Baillie, 2008). Hyperactivity in the hypothalamic-pituitary-adrenocortical (HPA) system is believed to lead to overstimulation of the nervous system and subsequent neurohormonal abnormalities (Goldston & Baillie, 2008; Musselman, Evans, & Nemeroff, 1998). The combination of increased sympathetic stimulation and decreased parasympathetic control may explain the decreased heart rate variability and high risk of fatal arrhythmias displayed in depressed post-MI patients (Joynt et al., 2003). Increased platelet activation and thrombus formation is also an important pathogenic feature in MI and unstable angina, as supported by the therapeutic benefits of anticoagulant and fibrinolytic therapy (Braunwald et al., 2002; Gibbons et al., 2003, Joynt et al., 2003). Compared to nondepressed controls, depressed patients with CHD frequently exhibit higher levels of inflammatory biomarkers that predict cardiac events or promote atherosclerosis (Hasper et al., 1998; Koenig, 2001; Whooley et al., 2008); these include elevated proinflammatory cytokines such as C-reactive protein, interleukin-6, interleukin-1β, and tumor necrosis factor (Carney & Freedland, 2008; Rutledge et al., 2006). Recurrent endothelium damage may, in turn, trigger inflammatory processes that contribute to the
progression of atherosclerosis (Carney et al., 2002).

**Behavioral Mechanisms of Depression in CHD.** Potential behavioral mechanisms linking depression and cardiovascular health include risk behaviors such as smoking, unhealthy diet, physical inactivity, and diminished compliance with medical regimens (Carney & Freedland, 2008; Goldston & Baillie, 2008; Lett et al., 2004). Empirical evidence supports depression as an independent predictor of adherence and participation in an exercise rehabilitation program, as well as depression as an independent predictor of improved cardiac functioning (Glazer, 2002; Kronish et al., 2006). Additional research indicates that exercise training reduces cardiac and total mortality and improves cardiorespiratory fitness, psychological wellbeing, and quality of life (Dugmore et al., 1999; Taylor et al., 2004) in CHD patients. These studies lend empirical support to the relations between depression and treatment adherence, depression and cardiac outcomes, and treatment adherence and cardiac functioning.

Few studies have examined adherence to behavioral recommendations as a mediator of the relation between depression and cardiac events or reduced cardiorespiratory fitness in patients with CHD. The Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) randomized controlled trial assessed 18,809 older adults from 41 countries with unstable angina or MI without ST-segment elevation and reported rates of adherence to physical activity (i.e., > 30 minutes, 3 times per week), dietary modifications (i.e., received counseling and reported compliance), and nicotine (i.e., less than one cigarette per day within the past month) guidelines 30 days following the index cardiac event (Chow et al., 2010). The authors found that 29.9% of patients adhered to both diet and exercise recommendations, whereas 41.6% demonstrated
adherence to either diet or exercise and 28.5% adhered to neither diet nor exercise recommendations. Furthermore, adherence to diet and exercise recommendations 30 days after the acute coronary event was associated with a 50% lower risk of recurrent cardiovascular events including MI, stroke, and death. In the Heart and Soul Study, a prospective study of 1,017 outpatients with CHD, physical activity (defined as 15-20 minutes of moderately intense exercise, at least 3-4 times per month) was associated with a 31.7% reduction in the strength of association between depressive symptoms and cardiovascular events (Whooley et al., 2008). After adjusting for physical inactivity as a mediator, there was no longer a significant association between depression and adverse cardiovascular events. Although the results of the Heart and Soul Study provide preliminary evidence to suggest physical activity is a behavioral mediator of the relation between depression and cardiovascular events, there is little corroborating research to evidence treatment adherence in exercise-based rehabilitation specifically mediates the relation between depression and cardiac outcomes following treatment. The field needs to examine the additional risk reduction in adverse outcomes after the incorporation of secondary prevention strategies such as cardiac rehabilitation (Goldston & Baillie, 2008).

**Cardiac Rehabilitation (CR): Secondary Prevention**

Prior to the 1950s, the prescribed standard of care following MI consisted of bed rest and inactivity (Forman et al., 2000). Over the next few decades, however, CR developed into highly structured, physician-monitored exercise programs that eventually broadened to optimize cardiovascular risk modification and promote healthy lifestyles. Currently, CR is the established process by which cardiac patients undergo physical reconditioning and lifestyle training after acute MI, coronary revascularization, chronic
heart failure, cardiac transplantation, and other coronary events (Ades, 2001). The American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation publicly recognized CR as an integral part of comprehensive care of patients with cardiovascular disease (Balady, et al., 2007). Although some individual elements of CR may vary from program to program and between patients, the core components include prescribed exercise, medical evaluation, and coronary risk factor reduction (Wenger, 2008). Perhaps the most important element of CR is the individualized, structured, and progressive exercise program that needs to be continued long-term (Ades, 2001). Programs vary in length but generally consist of 24-36 sessions held 2-3 times weekly over 3-4 months (Wenger, 2008). The exercise portion of programs can be started safely as soon as 1-2 weeks following hospital discharge (Suaya, et al., 2009), allowing for initiation of the intervention soon after the cardiac event.

Additional core elements of CR include education about secondary prevention guidelines and behavioral and pharmacological interventions designed to help patients develop and sustain lifestyle changes. Major topics include lipid and blood pressure control, behavioral weight management, nutrition counseling, physical activity and exercise training, smoking cessation, medication adherence, and management of psychosocial and emotional distress. A multidisciplinary team of rehabilitation providers (e.g., physician, nurse case manager, exercise physiologist, dietician, psychologist) is typically involved in monitoring clinical progress and reviewing short-term and long-term risk reduction goals, as outlined by national guidelines (Balady et al., 2007).

CR is a highly effective intervention for the secondary prevention of CHD. Numerous studies have demonstrated its effectiveness at reducing morbidity and
mortality rates following acute MI or coronary revascularization, while also reducing
disability and promoting a healthy, active lifestyle (Clark et al., 2004; Suaya et al., 2009;
Wenger, 2008). In a systematic review and meta-analysis of 48 randomized controlled
trials comparing a structured exercise program to a usual care group, and a total sample
of 8,940 patients with CHD (Taylor et al., 2004), CR was significantly associated with
reduced all-cause mortality (OR = 0.80) and cardiac mortality (OR = 0.74) compared
with usual medical care. The effect of CR on mortality was independent of diagnosis,
type of CR, dose of exercise intervention, length of followup, trial quality, and trial
publication date. A recent Cochrane review (Heran et al., 2011) of 47 studies examining
the effectiveness of exercise-based CR (total N = 10,794 patients) found that CR was
associated with reduced risk of overall mortality (RR = 0.87), cardiovascular mortality
(0.74), and hospital admissions within 1 year of the acute coronary episode (RR = 0.69).

CR offers a context within which to study the influence of depression on cardiac
outcomes in patients with established heart disease. Exercise training in a CR setting
improves cardiorespiratory fitness (Dugmore et al., 1999) in CHD patients.
Cardiorespiratory fitness is typically captured via measures of maximal aerobic capacity
during exercise tolerance testing, and has been identified as a quantitative predictor of all-
cause mortality and CHD in healthy patients (Kodama et al., 2009). In addition to
reducing mortality and rehospitalization following coronary events, CR has been shown
to successfully modify and target multiple risk factors (Taylor et al., 2004), including
depression. In a meta-analysis examining the psychological effects of rehabilitation
exercise programs in patients after an initial MI, with stable angina, or after bypass or
valve operations (Kugler, Seelbach, & Krüskemper, 1994), 13 of 15 studies showed
participation in CR was associated with medium effects on both depression ($d = .47$) and anxiety ($d = .31$). A more recent meta-analysis of 13 CR studies found a small but significant effect size ($d = 0.23$) for improving depression severity (Rutledge et al., 2013), with similar effects on depression, regardless of protocol length. Milani and Lavie (2007) retrospectively evaluated the impact of CR on depression and its associated mortality in a group of 522 patients who completed CR versus 179 patients who dropped out of CR within two weeks of entry and received fewer than five sessions. The prevalence of depressive symptoms decreased from 17% to 6% from entry to completion of the program in patients who completed CR. Depressed patients who completed CR also had a 73% lower mortality rate compared with depressed patients who did not complete CR.

Clinical outcomes from CR trials have had a profound impact on national public health. In a total sample of 580 post-coronary event patients, 230 of whom entered an exercise and risk factor modification rehabilitation program, the effect of CR participation on medical costs was determined by measuring cardiac rehospitalization costs over a 3-year period (Ades, Huang, & Weaver, 1992). Per capita rehospitalization costs were $739 lower in CR participants than in nonparticipants over a 3-year period, and this difference between groups was explained by a lower incidence of hospitalizations and lower charges per hospitalization. Benefits were even greater for patients who completed rehabilitation. Another study examining cost effectiveness of CR in MI patients reported $4,950 per year of life saved (Ades, Pashkow, & Nestor, 1997).

**Treatment Adherence in CR**

Although CR is widely recognized as an effective intervention in the secondary
prevention of CHD, CR services are vastly underutilized and overall rates of participation and treatment adherence remain quite low. Much of the literature in this area of research has examined CR participation, or the attendance of at least one CR session. A smaller body of literature has studied treatment adherence, that is, the total number of CR sessions attended. The majority of eligible individuals fail to attend CR altogether or drop out prematurely, with estimated rates of participation in a supervised structured CR program after a cardiovascular event ranging from 10% to 55% (CDC, 2003; Wenger, 2008; Witt et al., 2004). Data collected from a 1990 survey of 500 CR programs (N = 2,740) across the United States indicated that 10.8% of MI patients, 10.3% of CABG patients, and 23.4% of angioplasty patients enrolled in CR (Thomas et al., 1996). Another study utilizing Medicare claims to identify beneficiaries who had an index hospitalization in 1997 (N = 267,427) observed that CR was used by 13.9% of older adult patients hospitalized for MI and 31.0% of those who underwent CABG surgery (Suaya et al., 2007). CR participants received, on average, 24 sessions (SD = 12). The same authors (Suaya et al., 2009) conducted a follow-up study to examine 1- to 5-year mortality rates in a wider sample of older patients with Medicare coverage who were hospitalized for coronary disease or revascularization procedures (N = 601,099). Mortality rates were 21% to 34% lower in CR participants than in nonusers. Moreover, participants who completed at least 25 sessions were 19% less likely to die over 5 years compared to matched CR users who attended fewer than 25 sessions of CR. These statistics reinforce the utility and profound health benefits associated with CR adherence and completion.

Many patient-related factors are likely to impede patient motivation and commitment to CR and measured outcomes. Women and older individuals tend to
present with greater needs in the context of more medical comorbidities and physical
disability, which may contribute to their lower likelihood of participation in CR (Ades et
al., 1992b; Suaya et al., 2007; Thomas et al., 1996; Witt et al., 2004). Contextual factors
such as lower socioeconomic status, lower education, and minority status also tend to
predict lower rates of participation (Ades & Gaalema, 2012; Suaya et al., 2009).
Reluctance to commit to 8- to 12-week programs may be tied to logistic or financial
impediments, or insufficient reimbursement of costs associated with CR (Suaya et al.,
2009). Other common reasons for reluctance or attendance problems may stem from
beliefs related to the self, CHD, CR, other CR-attending patients, and health
professionals’ knowledge base, or from feelings of embarrassment about group or public
exercise (Clark et al., 2004).

**Depression as a Barrier to Treatment Adherence.** Treatment adherence is an
important clinical target in the secondary prevention of CHD. A meta-analysis of data on
376,162 patients across 20 studies showed that approximately one-third of patients with a
history of CHD did not adhere to drugs prescribed to prevent a secondary coronary event,
whereas approximately half of those without CHD did not adhere to drugs prescribed to
prevent a first event (Naderi, Bestwick, & Wald, 2012). A meta-analysis of the effects of
depression and anxiety on treatment noncompliance found that depressed patients were 3
times greater than non-depressed patients to be noncompliant with medical treatment
recommendations (DiMatteo, Lepper, & Croghan, 2000). Treatment non-adherence is of
even greater concern in the context of comorbid depression and CHD. Depression in
cardiac patients tends to be persistent if left untreated (Hance et al., 1996) and is
associated with medication adherence and adherence to other recommended health
behaviors (Gehi et al., 2005; Lespérance & Frasure-Smith, 2000; Pozuelo et al., 2009). In a study conducted by Rieckmann and colleagues (2006), adherence to aspirin therapy after MI was significantly lower in persistently depressed patients (76.1%) compared to patients whose depression improved (87.4%) and patients who were not depressed (89.5%).

Depression severity and non-adherence also play a prominent role in the setting of secondary prevention and CR. In a sample of 348 patients with CHD enrolled in a comprehensive CR program, patients with a Beck Depression Inventory – II (BDI-II) score ≥ 14 showed a 5-fold increased risk of noncompletion (Caulin-Glaser et al., 2007). Prior research has demonstrated that elevated depressive symptoms and MDD following MI predicted poor self-reported adherence to recommended behavioral and lifestyle changes (e.g., low-fat diet, regular exercise, reducing stress, increasing social support) 4 months after acute coronary syndrome (Ziegelstein et al., 2000). In a prospective longitudinal study of 560 cardiac patients, patients who exhibited persistent depression, defined by a BDI score ≥ 10 at hospitalization and 3 months later, reported lower rates of adherence in quitting smoking, taking medications, exercising, and attending CR compared with persistently nondepressed patients (Kronish et al., 2006).

Another study examined the effects of depression and other psychological variables on adherence and physical functioning in a sample of 46 CHD patients during the first week and last week of a 12-week CR program (Glazer et al., 2002). The sample exhibited minimal levels of depression (Mean = 6.2, SD = 5.1), with only 10 participants reporting baseline scores on the BDI ≥ 10. Baseline depression accounted for 9.5% of the variance associated with change in maximum oxygen consumption (VO₂max), a measure
of aerobic capacity, when controlling for relevant demographic variables and program attendance. These findings corroborate previously outlined research and affirm the significant influence of depression on adherence and functional improvement among cardiac patients. Given that depression predicts lower rates of participation in CR (Ades et al., 1992a; Kronish, et al., 2006) and poorer cardiovascular improvement (Glazer et al., 2002), poor adherence to risk-reducing behaviors has been proposed as a potential mediator of the relationship between depression and poor long-term prognosis in patients after acute coronary syndrome (Kronish et al., 2006).

The Current Study

Collaboration across disciplines is recommended to establish clinical practice guidelines for CHD (Goldston & Baillie, 2008) within the context of CR (Rutledge et al., 2013). The current project bridges cardiology and clinical health psychology and extends previous research on the effects of depression on behavioral and physiological cardiovascular health outcomes. More specifically, this project examines the impact of premorbid depression severity on treatment adherence in CR and cardiorespiratory fitness following CR. The theoretical model in Figure 1 is informed by biobehavioral theory (Lett et al., 2004) and tests the predictive value of baseline depression severity and CR attendance on cardiorespiratory fitness measures (e.g., VO$_2$max, peak MET, duration of the exercise stress test) following a 12-week outpatient CR program.
According to this novel theoretical model, CR attendance mediates the relation between baseline depression and cardiorespiratory fitness levels following CR. The major study hypotheses are as follows: (1) higher levels of baseline depression predict poorer cardiorespiratory fitness following CR completion; (2) higher levels of baseline depression predict lower rates of adherence to CR; (3) greater CR adherence (i.e., participation in more CR sessions) predict higher cardiorespiratory fitness; and (4) CR attendance significantly mediates the relation between baseline depression and cardiorespiratory fitness at post-CR while controlling for baseline fitness. The model takes into account the relation between depression and cardiorespiratory fitness at baseline as well as the relation between baseline and post-CR cardiorespiratory fitness.
(i.e., the cross-time point within persons effect).

Testing whether CR adherence mediates the relation between depression and cardiorespiratory fitness project holds implications for improving physical and mental health outcomes in cardiac patients with depression, as well as for treatment and prevention of depression in patients with CHD. The results of this project may inform nonpharmacological interventions and identify concrete behavioral targets (e.g., treatment adherence to CR) that may improve aerobic capacity and cardiovascular health. Further, CR programs may integrate evidence-based depression treatments to significantly impact public health. Thus, additional research in this area of study holds meaningful implications for improving treatment and quality of life for adults facing concomitant CHD and depression. The ultimate goal of this project is to offset the substantial cost and resources spent on individuals who suffer from concomitant cardiac disease and depression by improving early detection, assessment, and treatment.
CHAPTER 2: METHODS

Participants

Data for the current project were collected between 2011-2015 at the Cardiac Rehabilitation (CR) program at the University of Vermont Medical Center. Of note, the Geriatric Depression Scale was administered between 1996-2010 and subsequently replaced with the Patient Health Questionnaire Depression Scale (PHQ-9). Therefore, of the 2,526 patients in the full clinical database, only 858 patients (34.0%) provided valid data on the PHQ-9 and/or maximal exercise capacity for at least one time point (i.e., baseline “T1” and/or post-CR “T2”). Study participants were hospitalized at the University of Vermont Medical Center for an acute coronary event (e.g., angina, MI, coronary revascularization) and planned to enroll in the CR program after discharge. Exclusion criteria for CR enrollment included dementia (Mini Mental State Exam; MMSE < 20), exercise-limiting non-cardiac disease or longevity-limiting systemic disease that would preclude CR participation (e.g., advanced cancer, advanced frailty, severe arthritis, past stroke, severe lung disease).

Table 1 shows the demographics and relevant medical variables for the study sample (N = 858). The mean age was 63.86 years (SD = 11.05). The sample was 74.4% male and 98.0% White. The distribution of coronary diagnosis and treatment during hospitalization was as follows: 36.4% MI (without CABG), 25.5% PCI, 20.7% CABG (with and without MI), 11.9% valve surgery, 1.7% CHF, 1.4% valve surgery and CABG, and 0.7% angina without surgery. Traditional modifiable risk factors for CHD were recorded upon enrollment into CR. The most common comorbid medical conditions were hypertension (63.6%) and Type 2 diabetes (21.6%).
Table 1.

*Descriptive Statistics for Categorical Sociodemographic and Medical Covariates*

<table>
<thead>
<tr>
<th></th>
<th>Frequency (N = 858)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>638</td>
<td>74.4%</td>
</tr>
<tr>
<td>Female</td>
<td>220</td>
<td>25.6%</td>
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<tr>
<td><strong>Race</strong></td>
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<td></td>
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<tr>
<td>White</td>
<td>841</td>
<td>98.0%</td>
</tr>
<tr>
<td>African-American</td>
<td>7</td>
<td>0.8%</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Diagnosis/Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI (no surgery)</td>
<td>312</td>
<td>36.4%</td>
</tr>
<tr>
<td>CABG (MI and no MI)</td>
<td>178</td>
<td>20.7%</td>
</tr>
<tr>
<td>PCI</td>
<td>219</td>
<td>25.5%</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>102</td>
<td>11.9%</td>
</tr>
<tr>
<td>CHF</td>
<td>15</td>
<td>1.7%</td>
</tr>
<tr>
<td>CABG + Valve surgery</td>
<td>12</td>
<td>1.4%</td>
</tr>
<tr>
<td>Angina (no surgery)</td>
<td>6</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Comorbid Medical Condition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>7</td>
<td>0.8%</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus</td>
<td>185</td>
<td>21.6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>548</td>
<td>63.6%</td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>59</td>
<td>6.9%</td>
</tr>
<tr>
<td>Former smoker</td>
<td>445</td>
<td>51.9%</td>
</tr>
<tr>
<td>Never smoker</td>
<td>351</td>
<td>40.9%</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>844</td>
<td>98.4%</td>
</tr>
<tr>
<td>Statins</td>
<td>768</td>
<td>89.5%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>700</td>
<td>81.6%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>443</td>
<td>51.6%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>109</td>
<td>12.7%</td>
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<tr>
<td>Thyroid medications</td>
<td>65</td>
<td>7.6%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>40</td>
<td>4.7%</td>
</tr>
<tr>
<td>Niacin</td>
<td>17</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

*Note.* MI = myocardial infarction, PCI = percutaneous coronary intervention, CHF = congestive heart failure, CABG = coronary artery bypass graft surgery, ACE inhibitors = angiotensin-converting enzyme inhibitors.
The majority of patients were current non-smokers (92.1%) and 40.9% of the sample reported never smoking. However, a significant smoking history was endorsed by more than half the sample, such that 51.9% identified as former smokers and 6.9% identified as current smokers. Prescription medications at baseline included aspirin (98.4%), statins (89.5%), beta blockers (81.6%), angiotensin-converting enzyme (ACE) inhibitors (51.6%), calcium channel blockers (12.7%), and thyroid medications (7.6%).

**Study Site**

Data collection for the current project took place at the outpatient Cardiac Rehabilitation Program affiliated with the University of Vermont Medical Center in South Burlington, Vermont. This facility served as the primary site for study recruitment, exercise testing, and on-site exercise training throughout the 12-week CR program. The facility was equipped with exercise training equipment (e.g., treadmills, ergometers, elliptical trainers, stair steppers, resistance training apparatus) and staffed by trained doctors, nurses, exercise physiologists, and physical therapists, under the direction of cardiologist, Philip A. Ades, M.D.

**Study Procedure**

Following hospitalization and treatment for the incident coronary event, patients deemed medically eligible for exercise-based intervention by their hospital treatment team were referred to the Cardiac Rehabilitation facility and program. The mean duration of time between hospitalization and entry into the CR program was 38.16 days (SD = 28.54, median = 31 days). At their initial CR orientation visit, patients were provided informed consent about exercise testing and general CR procedures in a small group format and then taken on a tour of the facilities on site.
**Exercise Stress Test.** Following the group orientation visit and prior to initiating exercise training, all patients completed a medical evaluation with the Medical Director and performed a symptom-limited exercise tolerance test while taking medications as usual. Patients completed the exercise stress test again after the completion of the CR exercise-based intervention.

The majority of patients completed a Balke (43.5%) or modified-Balke (33.7%) treadmill protocol upon entry into the study. During the test, exercise intensity was increased incrementally by 1 metabolic equivalent task (MET) in 2-minute intervals. A nuclear stress test protocol was used for a smaller subset of patients (17.9%) who required additional diagnostic testing for the purpose of guiding treatment; nuclear medicines (e.g., adenosine, dobutamine) were administered to measure blood flow to the heart at rest and upon exertion. A proportion of patients completed a different stress test protocol at T2. However, the same three protocols were most commonly performed post-CR: Balke (32.8%), modified-Balke (23.4%), nuclear (9.6%).

Across all protocol types, expired air was analyzed to determine peak oxygen consumption (VO$_2$max) and carbon dioxide production with a metabolic cart. Exercise was ECG monitored and stopped prior to exhaustion if the patient developed progressive angina, > 2mm ST segment depression, exercise induced hypertension (230 systolic, 105 diastolic), severe arrhythmias, dizziness or symptomatic hypotension. The occurrence of any untoward responses, other than high threshold angina, excluded a patient from the training protocol unless effective therapy was instituted. Test results included the patient’s peak heart rate (HR) and peak oxygen consumption (VO$_2$max), two markers that were incorporated in designing a safe and individualized training regimen.
Exercise Intervention. The standard CR protocol consisted of three sessions per week for 12 weeks, for a maximum of 36 sessions. An individualized exercise-training program was designed for each CR patient based on the individual’s exercise stress test results (i.e., peak HR, VO₂max). Other factors were considered when developing individualized exercise prescriptions; these included the patient’s familiarity with exercise, level of apprehension, personal goals, and medical co-morbidities. Four key components of exercise were carefully considered in providing exercise prescription, namely intensity, duration, frequency, and mode.

Intensity. Typically, 70-85% of the patient’s peak HR from baseline testing was used to calculate an individual’s target HR zone. As patients improved their aerobic fitness, their exercise intensity was increased to maintain their exercise HR within the desired range. The training intensity was designed beneath the individual’s threshold for angina; however, the exact percentage of an individual’s peak HR that was prescribed varied. For significantly deconditioned patients, an intensity as low as 50-60% of maximal capacity may have been prescribed. Conversely, relatively fit individuals who were familiar with exercise may have been prescribed significantly higher intensities with approval from the Medical Director. During exercise sessions at the Cardiac Rehabilitation Facility, subjective ratings of perceived exertion (RPE) using the Borg Scale (i.e., ranging from “light” to “somewhat heavy,” Borg, 1982) were collected to capture the patient’s perceived level of exercise intensity.

Duration. The initial duration of exercise was dictated primarily by an individual’s functional capacity. For severely deconditioned patients, multiple bouts of short duration were prescribed. Duration was then increased as the individual adapted to
training without adverse events and was able to maintain their prescribed intensity in regards to HR and/or RPE. Within a few weeks of starting CR, patients were typically able to exercise for 45 to 60 minutes. Highly motivated individuals who also benefited from high caloric expenditure exercise (i.e., overweight patients) were strongly encouraged to further increase exercise duration to promote weight loss.

**Frequency.** Frequency is interrelated with fitness level, motivation, exercise intensity and duration. Patients were prescribed 2 to 3 onsite exercise sessions per week based on individual goals, availability, preferences, and physical limitations. Patients were further encouraged to exercise at least 1 to 2 times per week at home so that they were exercising a minimum of 3 to 5 days per week. Highly motivated and fit patients were asked to eventually exercise a total of 5 to 6 days per week as their exercise capacity increased.

**Mode.** The mode of exercise was determined in part by personal preference, accessibility to equipment, fitness level, and physical capabilities. Exercise involving the use of large muscle groups was strongly encouraged. Often, multiple exercise modalities were used to protect against overuse injuries and to help condition a variety of muscle groups. Therefore, a range of aerobic exercise equipment was used, including treadmills, elliptical machines, rowing machines, cycling and arm ergometers, and stair climbers. Additionally, most individuals incorporated weight-training equipment at varying levels in order to increase muscular strength and endurance.

As part of the CR program, participants also attended multiple educational sessions focused on stress management (five sessions), healthy nutrition (two sessions), medication use, symptom recognition, and the importance of risk factor control in
preventing future cardiac events. Smoking cessation was addressed in additional sessions using the five A’s model for treating tobacco use (Fiore, 2008). Long-term maintenance of the exercise program was recommended per standard clinical protocol.

Measures

Demographics and Medical History. Self-reported sociodemographic variables (e.g., age, gender, race) were collected at baseline, prior to exercise testing. Age and gender were examined as covariates, whereas race was not included as a covariate due to lack of heterogeneity in the current sample. Relevant medical health history (e.g., incident coronary event, medical procedure(s), current medications, comorbid medical conditions, smoking history) was collected during the medical evaluation that took place prior to initiating the exercise program.

Patient Health Questionnaire Depression Scale (PHQ-9). The PHQ-9 is a brief screening instrument for depressive symptom severity that was administered to patients at baseline (Appendix 1). The PHQ-9 yields a provisional depression diagnosis in addition to a severity score that can be used for treatment selection and monitoring. The 9 primary items of the PHQ-9 are based on a 4-point Likert scale and ask the patient to rate how often each symptom of depression was experienced in the past two weeks (e.g., Not at all, Several days, More than half the days, Nearly every day). An additional item captures distress and functional impairment by having the respondent rate the level of difficulty associated with their depression symptoms in the context of work, home, and social relationships (e.g., Not difficult at all, Somewhat difficult, Very difficult, Extremely difficult). Patients with a total score ≥10 fall into the range of moderate to severe depression and should be referred for more comprehensive clinical evaluation by a
trained professional in the diagnosis and management of depression (Lichtman et al., 2008). The PHQ-9 was designed for use in primary care and hospital settings because of its brief nature, and has been shown to be a reliable and valid measure of depression severity (Kroenke, Spitzer, & Williams, 2001). Moreover, this measure has been used in patients with CHD and other cardiovascular problems, and is a valid screening tool in the assessment and treatment of depression in this population (Gilbody et al., 2007; McManus, Pipkin, & Whooley, 2005; Stafford, Berk, & Jackson, 2007).

**CR Adherence and Completion Status.** Participation in CR has most commonly been defined in the literature dichotomously, as attendance of at least 1 session or none. CR adherence, on the other hand, is typically conceptualized as a continuous variable and provides richer data about overall treatment engagement. CR adherence in this study was operationally defined as the total number of CR sessions attended; this value ranged from 0 to 36. Due to external circumstances deemed unrelated to depression, some patients in the current sample could not complete the recommended 36 sessions. Secondary analyses were conducted to account for major factors that contributed to early termination of CR. One major limiting factor that affected CR attendance was approved coverage through the insurance provider. Some insurance plans covered only a restricted number of CR sessions (e.g., 3 to 18 sessions). Patients operating under this constraint were thus limited by external circumstances and were unable to complete 36 sessions of CR unless they paid out of pocket. It was important to distinguish these patients from others whose insurance plans covered 36 sessions but did not attend for other reasons. Another major problem with defining CR adherence by attendance arose for a group of patients who were deemed fit to return to work in fewer than 36 sessions due to their clinical
improvements and performance, most likely due to good treatment adherence. These patients were qualitatively different from other patients who were deemed unfit to return to work but chose to do terminate CR prematurely against provider recommendations. Due to these complicating factors in defining CR adherence by the total number of sessions attended, secondary analyses of the full mediation model considered “CR completion status,” a dichotomous variable that was broadly defined as whether the patient completed all possible sessions of CR. “Completers” included patients who completed fewer than 36 sessions if restricted solely by insurance coverage as well as patients who were deemed fit for early termination of CR by their case manager.

**Cardiorespiratory Fitness.** Cardiorespiratory fitness was measured at both T1 and T2 via three separate measures of maximal aerobic capacity: VO$_2$max (mL/kg/min), peak MET, and duration of the exercise stress test (minutes). VO$_2$max refers to the maximum volume or rate of oxygen consumption during exercise testing. This value is reached upon exertion of maximal effort and cardiac output, such that oxygen consumption plateaus despite an increase in workload. VO$_2$max is considered the best index of cardiorespiratory fitness and accurate reflection of aerobic physical fitness and endurance capacity. Higher values correspond to greater cardiovascular fitness. Metabolic equivalents (METs) serve as a standard unit to measure and compare the intensity and expenditure of energy among persons of different weights. By convention, one MET is equivalent to the cost of 1 kcal/kg/hour (energy expenditure) or 3.5 mL/kg/min (oxygen uptake) when sitting quietly. Peak MET in the current protocol was the maximum expenditure of energy required to complete the exercise stress test. Per test protocol, intensity was increased incrementally by 1 MET every 2 minutes. Higher values
are representative of better physical fitness. Duration of time (minutes) required to
complete the exercise stress test was the final proxy for physical endurance and fitness.
Longer duration of time was indicative of higher cardiorespiratory fitness, as participants
were instructed to terminate upon fatigue. The majority of participants requested
termination due to musculoskeletal fatigue and/or difficulty breathing.

Data Analytic Plan

Preliminary Analyses. Descriptive statistics for all major study variables and
outcomes, including PHQ-9 total score, total number of CR sessions attended, and
cardiorespiratory outcomes (e.g., VO$_2$max, peak MET, duration of exercise stress test)
were examined at both time points (i.e., baseline, post-CR). Bivariate correlations across
the same study variables and time points were also calculated. Analysis of variance was
used to examine depression group differences in sociodemographic characteristics,
medical history, attendance in CR, and cardiorespiratory fitness pre-and post-CR.

Primary Analyses. The current study aimed to test a theoretical model (Figure 1)
in which baseline depression predicted post-CR cardiac fitness through CR adherence.
Conducting an a priori power analysis to test the theoretical model was not possible,
given that an existing clinical database was used. However, the data analytic plan
emphasized effect sizes and bias-corrected confidence intervals and used multiple fit
indices for assessment of model fit (Kline, 2011; Little, 2013).

All models were tested with Mplus version 7.0 (Muthén & Muthén, 2010).
Structural equation modeling was proposed to test model fit and to examine individual
paths between major constructs in the model. To specifically test the indirect effect of
baseline depression on cardiorespiratory fitness after rehabilitation through CR
adherence, standardized indirect effect parameters and bias-corrected bootstrap confidence intervals were estimated. Confidence intervals that did not contain zero reflected a statistically significant indirect effect.

**Measurement Model.** A confirmatory factor analytic measurement model was first estimated in order to test fit of the factor structure of the “cardiorespiratory fitness” latent construct at T1 and T2 and to determine the factor loadings for each specified indicator (i.e., $\text{VO}_2\text{max}$, peak MET, duration of the exercise stress test). The latent factors were allowed to freely vary and the following fit statistics were utilized to evaluate model fit: Comparative Fit Index (CFI; $> .90$ acceptable, $> .95$ excellent), Root Mean Square Error of Approximation (RMSEA; $< .08$ acceptable, $< .05$ excellent), and Standardized Root Mean Square Residual (SRMR; $< .08$ acceptable, $< .05$ excellent) (Browne & Cudeck, 1993; Hu & Bentler, 1999). The measurement model failed to obtain good fit ($\chi^2 (8) = 518.60, p = 0.000, \text{CFI} = 0.69, \text{RMSEA} = 0.27, 90\% \text{CI} = 0.25$ to $0.29, \text{SRMR} = 0.10$) such that the proposed structural model also displayed very poor fit ($\chi^2 (25) = 861.21, p = 0.000, \text{CFI} = 0.66, \text{RMSEA} = 0.20, 90\% \text{CI} = 0.19$ to $0.21, \text{SRMR} = 0.12$); thus, path analysis was employed instead.

**Path Analysis.** All cardiorespiratory fitness outcomes (i.e., $\text{VO}_2\text{max}$, peak MET, duration of time until maximal capacity was reached on the exercise stress test) were treated as separate outcomes. More specifically, separate path models were run for each outcome. A total of three path models were run in which CR adherence was defined as the total number of attended CR sessions. Secondary analyses were conducted to account for external factors contributing to CR adherence. Path models were examined in which a probit regression was used to model the dichotomous outcome, CR completion status.
Lastly, another set of secondary path analyses were conducted to examine the same relations between depression, CR adherence and CR completion status, and cardiorespiratory fitness were modeled in a clinical subsample of depressed patients (n = 74, patients with moderate to severe depression on the PHQ-9 with total score ≥ 10).

**Controlling for Confounding Factors.** Coronary diagnosis, surgical procedure, and duration since the acute coronary event were collected at baseline. Traditional risk factors for CHD (e.g., diabetes mellitus, hypertension, smoking history) and common medications (e.g., beta blocker, ACE inhibitors) were coded in a binary fashion. Given that the above medical conditions and health behaviors increase cardiac risk, these confounding factors were accounted for with multiple-indicator/multiple-cause (MIMIC) models (Muthén, 1989), in which all major constructs at each time point in the final model were regressed on the covariates of interest. If paths in the model remained significant with the inclusion of a given variable, it was concluded that the variable did not influence the relations among variables in the model.

**Missing Data**

Missing data were treated as missing at random, and full information maximum likelihood estimation techniques were used for inclusion of all available data at each time point. For patients missing VO$_2$max data, estimated values of VO$_2$max were calculated based on the following regression equations derived from age, gender, and estimated METs (Ades, 2006).

In men: $\text{VO}_2\text{max} = 26.89 - (0.20)(\text{age}) + (0.66)(\text{estimated METs})$

In women: $\text{VO}_2\text{max} = 10.15 - (0.02)(\text{age}) + (1.11)(\text{estimated METs})$
CHAPTER 3: RESULTS

Descriptive Statistics

Measures of cardiorespiratory fitness at baseline and post-CR revealed that peak MET, VO\(_2\)max, and duration of the exercise stress test increased over time (See Tables 2a and 2b), thereby demonstrating patients broadly improved their aerobic capacity and fitness after participation in CR. Although there was considerable variability in the total number of attended sessions, overall CR adherence was relatively good in both the full sample (\(M = 24.70, SD = 12.55\)) and depressed sample (\(M = 23.74, SD = 13.02\)).

The distribution of depression scores at baseline was highly skewed such that the vast majority of patients in the study sample reported minimal or subclinical depressive symptoms (\(M = 4.22, SD = 4.66\)). Only 74 patients (8.6%) screened positive for moderate to severe depression (i.e., PHQ-9 total score ≥ 10). Descriptive statistics for sociodemographic and relevant medical variables are presented separately for the entire sample (\(N = 858\)) and the clinical subsample (\(n = 74\)) in Tables 2a and 2b, respectively.

The subsample of 74 patients who reported elevated depressive symptoms were younger in age (59.93 ± 1.37) compared to patients who reported subclinical depression (64.41 ± 0.46; \(t(630) = 3.32, p = 0.001\)). There were notable group differences in medical history such that the depressed subsample was more likely to carry a diagnosis of Type 2 diabetes \(\chi^2(1) = 4.85, p = 0.03\) and take ACE inhibitors \(\chi^2(1) = 3.76, p = 0.05\). The groups were otherwise comparable on gender, race, diagnosis, and duration of time between the incident coronary event and initiating CR. The depressed group showed poorer cardiorespiratory fitness at baseline according to measures of VO\(_2\)max (\(t(614) = 3.29, p = 0.001\)) and peak MET (\(t(614) = 3.98, p < 0.001\)) compared to the non-depressed
group. However, there were no depression group differences in measures of cardiorespiratory fitness post-CR, CR attendance, or CR completion status based on baseline depression severity. Due to the significant group differences that emerged according to depression severity, secondary path analyses were conducted to explore the impact of baseline depression on treatment adherence and cardiorespiratory fitness in the clinical subsample.

Table 2a.

Descriptive Statistics for Continuous Sociodemographic Covariates and Cardiorespiratory Fitness Outcomes in Full Sample (N = 858)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>858</td>
<td>20</td>
<td>94</td>
<td>63.86</td>
<td>11.05</td>
</tr>
<tr>
<td>Duration after</td>
<td>841</td>
<td>5</td>
<td>300</td>
<td>38.16</td>
<td>28.54</td>
</tr>
<tr>
<td>coronary event (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9 T1</td>
<td>632</td>
<td>0</td>
<td>26</td>
<td>4.22</td>
<td>4.66</td>
</tr>
<tr>
<td>Total CR sessions</td>
<td>856</td>
<td>0</td>
<td>36</td>
<td>24.70</td>
<td>12.55</td>
</tr>
<tr>
<td>attended</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak MET T1</td>
<td>830</td>
<td>0</td>
<td>14</td>
<td>6.03</td>
<td>2.29</td>
</tr>
<tr>
<td>Peak MET T2</td>
<td>594</td>
<td>2.00</td>
<td>20.60</td>
<td>7.63</td>
<td>2.80</td>
</tr>
<tr>
<td>VO_{2max} T1 (mL/kg/min)</td>
<td>830</td>
<td>8.10</td>
<td>43.40</td>
<td>18.92</td>
<td>5.87</td>
</tr>
<tr>
<td>VO_{2max} T2 (mL/kg/min)</td>
<td>594</td>
<td>7.00</td>
<td>48.30</td>
<td>22.32</td>
<td>6.97</td>
</tr>
<tr>
<td>Duration of stress</td>
<td>820</td>
<td>1.00</td>
<td>18.00</td>
<td>7.49</td>
<td>2.68</td>
</tr>
<tr>
<td>test T1 (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of stress</td>
<td>588</td>
<td>3.00</td>
<td>24.00</td>
<td>10.09</td>
<td>2.88</td>
</tr>
<tr>
<td>test T2 (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: T1 = Time 1 (baseline), T2 = Time 2 (post-CR)
Table 2b.

*Descriptive Statistics for Continuous Sociodemographic Covariates and Cardiorespiratory Fitness Outcomes in Depressed Subsample (n = 74)*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74</td>
<td>20</td>
<td>86</td>
<td>59.93</td>
<td>11.76</td>
</tr>
<tr>
<td>Duration after coronary event (days)</td>
<td>71</td>
<td>15</td>
<td>210</td>
<td>45.54</td>
<td>31.17</td>
</tr>
<tr>
<td>PHQ-9 T1</td>
<td>74</td>
<td>10</td>
<td>26</td>
<td>14.36</td>
<td>4.16</td>
</tr>
<tr>
<td>Total attended CR sessions</td>
<td>74</td>
<td>0</td>
<td>36</td>
<td>23.74</td>
<td>13.02</td>
</tr>
<tr>
<td>Peak MET T1</td>
<td>72</td>
<td>0.00</td>
<td>10.03</td>
<td>4.86</td>
<td>1.83</td>
</tr>
<tr>
<td>Peak MET T2</td>
<td>39</td>
<td>2.00</td>
<td>14.00</td>
<td>6.80</td>
<td>2.51</td>
</tr>
<tr>
<td>VO₂max T1 (mL/kg/min)</td>
<td>72</td>
<td>8.50</td>
<td>35.10</td>
<td>17.22</td>
<td>5.33</td>
</tr>
<tr>
<td>VO₂max T2 (mL/kg/min)</td>
<td>39</td>
<td>7.00</td>
<td>42.00</td>
<td>20.52</td>
<td>6.90</td>
</tr>
<tr>
<td>Duration of stress test T1 (min)</td>
<td>70</td>
<td>1.50</td>
<td>14.00</td>
<td>6.74</td>
<td>2.71</td>
</tr>
<tr>
<td>Duration of stress test T2 (min)</td>
<td>40</td>
<td>3.00</td>
<td>18.00</td>
<td>9.19</td>
<td>3.03</td>
</tr>
</tbody>
</table>

*Note: T1 = Time 1 (baseline), T2 = Time 2 (post-CR)*
Bivariate Correlations

Table 3 presents the bivariate correlations between all continuous variables in the theoretical model. All bivariate combinations of cardiorespiratory fitness outcomes at T1 and T2 were moderately or highly correlated. Cross-time point correlations for VO$_2$max ($r = 0.89$), peak MET ($r = 0.84$), and duration of stress test ($r = 0.63$) at T1 and T2 were strongly correlated ($p < 0.01$). Baseline depression showed a weak negative correlation with all cardiorespiratory fitness indices, with the exception of peak MET at T2 ($ns$). There was a weak inverse correlation between the total number of attended CR sessions and cardiorespiratory measures at both T1 and T2, whereas there was no association between baseline depression and the total number of CR sessions.

Path Analysis: CR Attendance (N = 858)

Because the theoretical model could not be tested in the full sample due to poor model fit, path analyses were run separately for each outcome variable of interest (i.e., VO$_2$max, peak MET, duration of exercise stress test). In accordance with bivariate correlational data, stability paths were significant across all cardiorespiratory fitness indicators, and baseline depression was significantly associated with each measure of fitness at baseline. Refer to Figures 2a, 2b, and 2c for visual representation of the path models. Path estimates are presented in Tables 4a, 4b, and 4c. Baseline VO$_2$max significantly predicted post-CR VO$_2$max levels ($\beta = 0.89$, SE = 0.01, 90% CI 0.86 to 0.91, $p < 0.001$). Baseline peak MET also significantly predicted peak MET following CR participation ($\beta = 0.85$, SE = 0.02, 90% CI 0.82 to 0.88, $p < 0.001$). Baseline stress test duration significantly predicted duration of the post-CR stress test ($\beta = 0.61$, SE = 0.03, 90% CI 0.56 to 0.67, $p < 0.001$).
Note. *p < .05, **p < .01, ***p < .001

T1 = Time 1 (baseline), T2 = Time 2 (post-CR)

<table>
<thead>
<tr>
<th></th>
<th>8. CR Attendance</th>
<th>7. PHQ-9 T1</th>
<th>6. Stress Test T2</th>
<th>5. Stress Test T1</th>
<th>4. Peak MET T2</th>
<th>3. Peak MET T1</th>
<th>2. VO2 max T2</th>
<th>1. VO2 max T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1'00</td>
<td>-0.15**</td>
<td>-0.24**</td>
<td>-0.48**</td>
<td>-0.53**</td>
<td>-0.63**</td>
<td>-0.18**</td>
<td>-0.05</td>
<td>1.00</td>
</tr>
<tr>
<td>1'00</td>
<td>-0.16**</td>
<td>-0.11*</td>
<td>0.59**</td>
<td>0.45**</td>
<td>0.63**</td>
<td>-0.10*</td>
<td>-0.12*</td>
<td>1.00</td>
</tr>
<tr>
<td>1'00</td>
<td>0.50**</td>
<td>0.54**</td>
<td>0.64**</td>
<td>0.84**</td>
<td>1.00</td>
<td>0.65**</td>
<td>0.77**</td>
<td>1.00</td>
</tr>
<tr>
<td>1'00</td>
<td>0.65**</td>
<td>0.64**</td>
<td>0.77**</td>
<td>1.00</td>
<td>1.00</td>
<td>0.89**</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1'00</td>
<td>0.89**</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Bivariate Correlations between Major Study Variables

Table 3
Baseline depression was also significantly associated with VO$_2$max ($\beta = -0.16$, SE = 0.04, CI -0.23 to -0.08, $p < 0.001$), peak MET ($\beta = -0.17$, SE = 0.04, CI -0.25 to -0.09, $p < 0.001$), and duration of the exercise stress test ($\beta = -0.11$, SE = 0.05, CI -0.20 to -0.02, $p < 0.05$) at baseline. However, the three models failed to show good fit for the following separate outcomes at post-CR: VO$_2$max ($\chi^2 (1) = 25.08$, $p = 0.000$, CFI = 0.96, RMSEA = 0.17, 90% CI = 0.12 to 0.23, SRMR = 0.06), peak MET ($\chi^2 (1) = 18.10$, $p = 0.000$, CFI = 0.97, RMSEA = 0.14, 90% CI = 0.09 to 0.20, SRMR = 0.05), and duration of the exercise stress test ($\chi^2 (1) = 10.70$, $p = 0.001$, CFI = 0.96, RMSEA = 0.11, 90% CI = 0.06 to 0.17, SRMR = 0.04). Thus, contrary to original hypotheses, CR attendance did not significantly mediate the relations between baseline depression and VO$_2$max, peak MET, or duration of the stress test following CR.
Figure 2a. Path Analysis for VO\textsubscript{2}max

Figure 2b. Path Analysis for Peak MET

Figure 2c. Path Analysis for Stress Test Duration
Table 4a.

**Path Analysis for VO_{2max}**

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO_{2max}(T1) – VO_{2max}(T2)</td>
<td>0.89</td>
<td>0.01</td>
<td>0.86 to 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR – VO_{2max}(T2)</td>
<td>0.02</td>
<td>0.03</td>
<td>-0.04 to 0.07</td>
<td>0.515</td>
</tr>
<tr>
<td>Dep(T1) – VO_{2max}(T2)</td>
<td>-0.01</td>
<td>0.03</td>
<td>-0.07 to 0.03</td>
<td>0.663</td>
</tr>
<tr>
<td>Dep(T1) – CR</td>
<td>-0.04</td>
<td>0.04</td>
<td>-0.12 to 0.03</td>
<td>0.376</td>
</tr>
<tr>
<td>VO_{2max}(T1) – Dep(T1)</td>
<td>-0.16</td>
<td>0.04</td>
<td>-0.23 to -0.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4b.

**Path Analysis for Peak MET**

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET(T1) – MET(T2)</td>
<td>0.85</td>
<td>0.02</td>
<td>0.82 to 0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR – MET(T2)</td>
<td>0.04</td>
<td>0.03</td>
<td>-0.02 to 0.10</td>
<td>0.186</td>
</tr>
<tr>
<td>Dep(T1) – MET(T2)</td>
<td>0.00</td>
<td>0.03</td>
<td>-0.06 to 0.05</td>
<td>0.930</td>
</tr>
<tr>
<td>Dep(T1) – CR</td>
<td>-0.04</td>
<td>0.04</td>
<td>-0.12 to 0.04</td>
<td>0.386</td>
</tr>
<tr>
<td>MET(T1) – Dep(T1)</td>
<td>-0.17</td>
<td>0.04</td>
<td>-0.25 to -0.09</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4c.

**Path Analysis for Duration of Stress Test**

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration(T1) – Duration(T2)</td>
<td>0.61</td>
<td>0.03</td>
<td>0.56 to 0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR – Duration(T2)</td>
<td>0.02</td>
<td>0.04</td>
<td>-0.06 to 0.11</td>
<td>0.570</td>
</tr>
<tr>
<td>Dep(T1) – Duration(T2)</td>
<td>-0.06</td>
<td>0.05</td>
<td>-0.15 to 0.03</td>
<td>0.201</td>
</tr>
<tr>
<td>Dep(T1) – CR</td>
<td>-0.04</td>
<td>0.04</td>
<td>-0.12 to 0.04</td>
<td>0.282</td>
</tr>
<tr>
<td>Duration(T1) – Dep(T1)</td>
<td>-0.11</td>
<td>0.05</td>
<td>-0.20 to -0.02</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Note. T1 = Time 1 (baseline), T2 = Time 2 (post-CR), CR = total number of exercise sessions attended in 12-week Cardiac Rehab program, VO_{2max} = maximum oxygen consumption (mL/kg/min) during exercise stress test, MET = peak MET attained during exercise stress test, Duration = duration of time (minutes) to complete the exercise stress test.
Path Analysis: CR Completion Status (N = 858)

Figures 3a, 3b, and 3c depict path models in which CR completion (i.e., whether the patient completed the maximum number of CR sessions available as determined by the case manager and/or insurance limitations) was considered in lieu of CR attendance. To account for the categorical outcome of completion status, a probit regression with weighted least squares estimation was conducted in secondary path analyses. Refer to Tables 5a, 5b, and 5c for path estimates. Interestingly, only one model in which duration of the stress test was the primary cardiorespiratory fitness outcome emerged with excellent fit statistics. Figure 3c illustrates the path model in which duration of the exercise stress test was the primary outcome ($\chi^2 (1) = 2.98, p = 0.08, \text{CFI} = 0.99, \text{RMSEA} < 0.05, 90\% \text{CI} = 0.00 \text{ to } 0.12$). The stability path between baseline (T1) and post-CR (T2) for duration of time to complete the baseline stress test was highly significant ($\beta = 0.62, \text{SE} = 0.02, 90\% \text{CI} 0.58 \text{ to } 0.65, p < 0.001$). Baseline depression significantly predicted CR completion, whereby higher depression scores were associated with a lower likelihood of completing CR ($\beta = -0.12, \text{SE} = 0.05, 90\% \text{CI} -0.22 \text{ to } -0.02, p < 0.05$). Baseline depression was also inversely associated with stress test duration at baseline ($\beta = -0.12, \text{SE} = 0.04, \text{CI} -0.19 \text{ to } -0.04, p < 0.01$). The significant paths summarized above were largely unaffected by the inclusion of covariates, with one minor exception; CR completion was associated with a longer duration of time to reach maximal aerobic capacity on the exercise stress test post-CR when controlling for age ($\beta = 0.08, \text{SE} = 0.04, \text{CI} 0.01 \text{ to } 0.15, p < 0.05$).
Figure 3a. *Path Analysis for VO₂max*

![Path Analysis for VO₂max](image)

Figure 3b. *Path Analysis for Peak MET*

![Path Analysis for Peak MET](image)

Figure 3c. *Path Analysis for Stress Test Duration*

![Path Analysis for Stress Test Duration](image)

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Table 5a.

Path Analysis for VO$_2$max

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\beta$</th>
<th>SE</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$max(T1) $\rightarrow$ VO$_2$max(T2)</td>
<td>0.89</td>
<td>0.01</td>
<td>0.87 to 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ VO$_2$max(T2)</td>
<td>-0.14</td>
<td>0.05</td>
<td>-0.21 to -0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ VO$_2$max(T2)</td>
<td>0.01</td>
<td>0.04</td>
<td>-0.08 to 0.07</td>
<td>0.911</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.12</td>
<td>0.05</td>
<td>-0.21 to -0.02</td>
<td>0.020</td>
</tr>
<tr>
<td>VO$_2$max(T1) $\rightarrow$ Dep(T1)</td>
<td>-0.16</td>
<td>0.04</td>
<td>-0.24 to -0.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 5b.

Path Analysis for Peak MET

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\beta$</th>
<th>SE</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET(T1) $\rightarrow$ MET(T2)</td>
<td>0.86</td>
<td>0.01</td>
<td>0.82 to 0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ MET(T2)</td>
<td>-0.09</td>
<td>0.04</td>
<td>-0.17 to -0.01</td>
<td>0.021</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ MET(T2)</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.05 to 0.15</td>
<td>0.360</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.11</td>
<td>0.05</td>
<td>-0.21 to -0.02</td>
<td>0.022</td>
</tr>
<tr>
<td>MET(T1) $\rightarrow$ Dep(T1)</td>
<td>-0.17</td>
<td>0.04</td>
<td>-0.25 to -0.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 5c.

Path Analysis for Duration of Stress Test

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\beta$</th>
<th>SE</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration(T1) $\rightarrow$ Duration(T2)</td>
<td>0.62</td>
<td>0.02</td>
<td>0.58 to 0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ Duration(T2)</td>
<td>-0.03</td>
<td>0.04</td>
<td>-0.12 to 0.06</td>
<td>0.477</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ Duration(T2)</td>
<td>-0.06</td>
<td>0.05</td>
<td>-0.15 to 0.04</td>
<td>0.258</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.12</td>
<td>0.05</td>
<td>-0.22 to -0.02</td>
<td>0.016</td>
</tr>
<tr>
<td>Duration(T1) $\rightarrow$ Dep(T1)</td>
<td>-0.12</td>
<td>0.04</td>
<td>-0.19 to -0.04</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Note. T1 = Time 1 (baseline), T2 = Time 2 (post-CR), CR = completer status in the 12-week Cardiac Rehab program, VO$_2$max = maximum oxygen consumption (mL/kg/min) during exercise stress test, MET = peak MET attained during exercise stress test, Duration = duration of time (minutes) to complete the exercise stress test.
Path Analysis: CR Attendance (n = 74, Depressed Subsample)

Secondary path analyses explored the effects of depression severity on CR adherence and cardiorespiratory fitness in 74 patients with moderate to severe depressive symptoms at baseline. The same series of path analyses conducted using the full sample was re-run in the clinical subsample. Refer to Figures 4a, 4b, 4c to visualize the models in which VO$_2$max ($\chi^2 (1) = 0.03, p = 0.86, \text{CFI} = 1.00, \text{RMSEA} < 0.001, 90\% \text{CI} = 0.00$ to $0.17, \text{SRMR} = 0.01$), peak MET ($\chi^2 (1) = 0.16, p = 0.69, \text{CFI} = 1.00, \text{RMSEA} < 0.001, 90\% \text{CI} = 0.00$ to $0.23, \text{SRMR} = 0.01$), and duration of the exercise stress test ($\chi^2 (1) = 0.21, p = 0.65, \text{CFI} = 1.00, \text{RMSEA} < 0.001, 90\% \text{CI} = 0.00$ to $0.24, \text{SRMR} = 0.02$) represent indicators of cardiorespiratory fitness. All three models showed excellent fit and were thus interpreted. Table 6a, 6b, and 6c display the path estimates for each model. The stability paths were highly significant in each model. VO$_2$max at baseline (T1) predicted VO$_2$max at post-CR (T2) ($\beta = 0.85, \text{SE} = 0.05, 90\% \text{CI} 0.75$ to $0.95, p < 0.001$); peak MET at T1 predicted peak MET at T2 ($\beta = 0.76, \text{SE} = 0.07, 90\% \text{CI} 0.62$ to $0.90, p < 0.001$); and stress test duration at T1 predicted stress test duration at T2 ($\beta = 0.55, \text{SE} = 0.09, 90\% \text{CI} 0.38$ to $0.72, p < 0.001$). Baseline depression significantly predicted CR attendance across all three models, whereby higher depression scores were associated with lower CR attendance ($\beta = -0.23, \text{SE} = 0.11, 90\% \text{CI} -0.45$ to $-0.02, p < 0.05$). No additional significant pathways emerged. MIMIC models demonstrated that all pathways were largely unaffected by demographic and medical covariates.

Path Analysis: CR Completion Status (n = 74, Depressed Subsample)

Secondary path analyses considered CR completion status in place of CR attendance in the clinically depressed subsample. Again, all three models showed
excellent fit for the following separate outcomes at post-CR: VO$_2$ max ($\chi^2 (1) = 0.11, p = 0.74, \text{CFI} = 1.00, \text{RMSEA} = 0.00, 90\% \text{CI} = 0.00 \text{ to } 0.11$), peak MET ($\chi^2 (1) = 2.00, p = 0.16, \text{CFI} = 0.99, \text{RMSEA} = 0.06, 90\% \text{CI} = 0.00 \text{ to } 0.18$), and duration of the stress test ($\chi^2 (1) = 2.40, p = 0.12, \text{CFI} = 0.98, \text{RMSEA} = 0.07, 90\% \text{CI} = 0.00 \text{ to } 0.18$). See Figures 5a, 5b, and 5c and Tables 7a, 7b, and 7c for corresponding data. Stability paths between VO$_2$ max ($\beta = 0.88, \text{SE} = 0.01, 90\% \text{CI} 0.86 \text{ to } 0.91$), peak MET ($\beta = 0.86, \text{SE} = 0.02, 90\% \text{CI} 0.83 \text{ to } 0.90$), and duration of the stress test ($\beta = 0.62, \text{SE} = 0.04, 90\% \text{CI} 0.56 \text{ to } 0.69$) were significant ($p < 0.001$). No additional significant pathways emerged for models in which peak MET and duration of the stress test represented cardiorespiratory fitness. However, when VO$_2$ max was the primary fitness outcome in the model, CR completion significantly and negatively predicted fitness at post-CR ($\beta = -0.27, \text{SE} = 0.07, 90\% \text{CI} -0.40 \text{ to } -0.14, p < 0.001$). These pathways were not affected by the inclusion of covariates in MIMIC models.
Figure 4a. *Path Analysis for VO2max in the Depressed Subsample*

![Path Analysis Diagram for VO2max](image)

Figure 4b. *Path Analysis for Peak MET in the Depressed Subsample*

![Path Analysis Diagram for Peak MET](image)

Figure 4c. *Path Analysis for Duration of Stress Test in the Depressed Subsample*

![Path Analysis Diagram for Stress Test Duration](image)
**Table 6a.**

*Path Analysis for VO$_2$max in the Depressed Subsample*

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\hat{b}$</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$max(T1) $\rightarrow$ VO$_2$max(T2)</td>
<td>0.85</td>
<td>0.05</td>
<td>0.75 to 0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ VO$_2$max(T2)</td>
<td>0.17</td>
<td>0.20</td>
<td>-0.22 to 0.56</td>
<td>0.392</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ VO$_2$max(T2)</td>
<td>-0.06</td>
<td>0.10</td>
<td>-0.26 to 0.14</td>
<td>0.570</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.23</td>
<td>0.11</td>
<td>-0.45 to -0.02</td>
<td>0.033</td>
</tr>
<tr>
<td>VO$_2$max(T1) $\rightarrow$ Dep(T1)</td>
<td>0.03</td>
<td>0.12</td>
<td>-0.21 to 0.26</td>
<td>0.823</td>
</tr>
</tbody>
</table>

**Table 6b.**

*Path Analysis for Peak MET in the Depressed Subsample*

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\hat{b}$</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET(T1) $\rightarrow$ MET(T2)</td>
<td>0.76</td>
<td>0.07</td>
<td>0.62 to 0.90</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ MET(T2)</td>
<td>-0.03</td>
<td>0.31</td>
<td>-0.63 to 0.57</td>
<td>0.919</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ MET(T2)</td>
<td>-0.14</td>
<td>0.14</td>
<td>-0.42 to 0.14</td>
<td>0.318</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.23</td>
<td>0.11</td>
<td>-0.45 to -0.02</td>
<td>0.033</td>
</tr>
<tr>
<td>MET(T1) $\rightarrow$ Dep(T1)</td>
<td>0.10</td>
<td>0.12</td>
<td>-0.14 to 0.33</td>
<td>0.434</td>
</tr>
</tbody>
</table>

**Table 6c.**

*Path Analysis for Duration of Stress Test in the Depressed Subsample*

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>$\hat{b}$</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration(T1) $\rightarrow$ Duration(T2)</td>
<td>0.55</td>
<td>0.09</td>
<td>0.38 to 0.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CR $\rightarrow$ Duration(T2)</td>
<td>0.21</td>
<td>0.27</td>
<td>-0.32 to 0.74</td>
<td>0.441</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ Duration(T2)</td>
<td>0.03</td>
<td>0.14</td>
<td>-0.25 to 0.31</td>
<td>0.841</td>
</tr>
<tr>
<td>Dep(T1) $\rightarrow$ CR</td>
<td>-0.23</td>
<td>0.11</td>
<td>-0.45 to -0.02</td>
<td>0.033</td>
</tr>
<tr>
<td>Duration(T1) $\rightarrow$ Dep(T1)</td>
<td>-0.03</td>
<td>0.13</td>
<td>-0.28 to 0.22</td>
<td>0.826</td>
</tr>
</tbody>
</table>

*Note.* T1 = Time 1 (baseline), T2 = Time 2 (post-CR), CR = total number of exercise sessions attended in Cardiac Rehab 12-week program, VO$_2$max = maximum oxygen consumption (mL/kg/min) during exercise stress test, MET = peak MET attained during exercise stress test, Duration = duration of time (minutes) to complete the exercise stress test
Figure 5a. Path Analysis for VO\textsubscript{2}max in the Depressed Subsample

Figure 5b. Path Analysis for Peak MET in the Depressed Subsample

Figure 5c. Path Analysis for Duration of Stress Test in the Depressed Subsample
Table 7a.  

*Path Analysis for VO₂max in the Depressed Subsample*  

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max(T1) → VO₂max(T2)</td>
<td>0.88</td>
<td>0.01</td>
<td>0.86 to 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR → VO₂max(T2)</td>
<td>-0.27</td>
<td>0.07</td>
<td>-0.40 to -0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dep(T1) → VO₂max(T2)</td>
<td>-0.02</td>
<td>0.13</td>
<td>-0.27 to 0.23</td>
<td>0.854</td>
</tr>
<tr>
<td>Dep(T1) → CR</td>
<td>-0.18</td>
<td>0.12</td>
<td>-0.41 to 0.04</td>
<td>0.113</td>
</tr>
<tr>
<td>VO₂max(T1) → Dep(T1)</td>
<td>0.03</td>
<td>0.10</td>
<td>-0.18 to 0.23</td>
<td>0.776</td>
</tr>
</tbody>
</table>

Table 7b.  

*Path Analysis for Peak MET in the Depressed Subsample*  

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET(T1) → MET(T2)</td>
<td>0.86</td>
<td>0.02</td>
<td>0.83 to 0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR → MET(T2)</td>
<td>-0.07</td>
<td>0.10</td>
<td>-0.26 to 0.12</td>
<td>0.444</td>
</tr>
<tr>
<td>Dep(T1) → MET(T2)</td>
<td>0.06</td>
<td>0.17</td>
<td>-0.27 to 0.39</td>
<td>0.716</td>
</tr>
<tr>
<td>Dep(T1) → CR</td>
<td>-0.19</td>
<td>0.12</td>
<td>-0.42 to 0.04</td>
<td>0.100</td>
</tr>
<tr>
<td>MET(T1) → Dep(T1)</td>
<td>0.02</td>
<td>0.10</td>
<td>-0.18 to 0.22</td>
<td>0.868</td>
</tr>
</tbody>
</table>

Table 7c.  

*Path Analysis for Duration of Stress Test in the Depressed Subsample*  

<table>
<thead>
<tr>
<th>Estimated Path</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration(T1) → Duration(T2)</td>
<td>0.62</td>
<td>0.04</td>
<td>0.56 to 0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR → Duration(T2)</td>
<td>0.03</td>
<td>0.10</td>
<td>-0.17 to 0.24</td>
<td>0.759</td>
</tr>
<tr>
<td>Dep(T1) → Duration(T2)</td>
<td>0.05</td>
<td>0.19</td>
<td>-0.31 to 0.41</td>
<td>0.790</td>
</tr>
<tr>
<td>Dep(T1) → CR</td>
<td>-0.18</td>
<td>0.12</td>
<td>-0.40 to 0.05</td>
<td>0.124</td>
</tr>
<tr>
<td>Duration(T1) → Dep(T1)</td>
<td>-0.03</td>
<td>0.10</td>
<td>-0.23 to 0.17</td>
<td>0.784</td>
</tr>
</tbody>
</table>

*Note.* T1 = Time 1 (baseline), T2 = Time 2 (post-CR), CR = completion status in the 12-week Cardiac Rehab program, VO₂max = maximum oxygen consumption (mL/kg/min) during exercise stress test, MET = peak MET attained during exercise stress test, Duration = duration of time (minutes) to complete the exercise stress test.
CHAPTER 4: DISCUSSION

In order to reduce major depression and coronary heart disease, the two leading causes of death and disability, researchers in behavioral cardiology should strive to understand the mechanisms through which depression contributes to CHD and cardiac functioning. The current project draws upon biobehavioral theory (Lett et al., 2004) and tests the hypothesis that CR adherence is a behavioral mechanism through which depression indirectly predicts cardiorespiratory fitness. Findings from this study contribute uniquely to a growing body of literature on depression and cardiovascular health, and hold important clinical implications for older adults following a coronary event.

In summary, the major significant findings from the current study support the hypothesis that baseline depression significantly predicts CR adherence. More specifically, higher levels of baseline depression predicted lower CR attendance in a subsample of clinically depressed patients, whereas in the full sample of both depressed and non-depressed patients, those with more severe depression at baseline were more likely to be non-completers of CR. Given that the measurement model failed to obtain good fit, we can conclude that VO\textsubscript{2max}, peak MET, and duration of the stress test did not map onto the same underlying construct “cardiorespiratory fitness,” as predicted. Furthermore, contrary to initial hypotheses: (1) higher levels of baseline depression did not predict poorer cardiorespiratory fitness following CR; (2) CR adherence (i.e., attending more sessions) did not predict higher cardiorespiratory fitness post-CR; and (3) CR attendance did not significantly mediate the relation between baseline depression and cardiorespiratory fitness post-CR.
Measures of Cardiorespiratory Fitness

Taken as a whole, study results provide empirical evidence that VO$_2$max, peak MET, and duration of the exercise stress test are unique fitness outcomes of exercise in CR. Given that the proposed structural equation model (Figure 1) failed to obtain good fit, these indicators may not map onto the same underlying construct. Future studies should further test the cardiorespiratory fitness latent construct and consider alternative indicators to VO$_2$max, peak MET, and duration of the exercise stress. However, for the purposes of this study, we will continue to refer to VO$_2$max, peak MET, and duration of the exercise stress test as cardiorespiratory fitness outcomes.

Path Analyses in the Full Sample: CR Attendance and CR Completion

The main study hypotheses about relations between baseline depression, CR adherence (i.e., total number of exercise sessions attended), and cardiorespiratory fitness were tested via a series of path analyses. VO$_2$max, peak MET, duration of the maximal exercise stress test were treated as individual outcomes in three separate models. Contrary to hypothesis, all three models showed poor statistical fit and were not interpreted. Secondary analyses were conducted in which CR attendance was replaced by CR completion (i.e., a dichotomous variable that accounted for external factors that limited CR attendance, such as limited insurance coverage or early termination due to good clinical progress). The model in which duration of the stress test was the primary indicator of cardiorespiratory fitness showed good fit, suggesting that CR completion status, or alternative constructs to attendance or adherence, are important to consider when examining relations between depression severity and cardiorespiratory fitness pre- and post-CR.
Additionally, the interpretable model showed that baseline depression severity on the PHQ-9 predicted CR completion, but not attendance. Higher levels of depression predicted early termination of CR whereas lower levels of depression predicted CR completion. Depression was also negatively associated with baseline measures of peak MET and total duration of the exercise stress test. These significant findings are in line with literature concluding baseline depression severity is a predictor of lower rates of CR participation (Ades et al., 1992a) and completion (Caulin-Glaser et al., 2007) as well as research showing an inverse relation between depression symptom severity and cardiorespiratory fitness (Galper et al., 2006; Papasavvas et al., 2015). One possible explanation for the negative relation between depression severity and CR adherence is that depressed individuals may be less motivated to engage in physical activity than non-depressed individuals and, therefore, may have shown reduced attendance. Alternatively, depressed CHD patients may tolerate a lower threshold of fatigue due to increased somatic symptoms of depression, which may result in reduced CR attendance.

Contrary to prediction, both baseline depression severity and CR completion did not predict cardiorespiratory fitness outcomes post-CR. Consequently, CR adherence did not mediate the relation between baseline depression and cardiorespiratory fitness after CR. These non-significant findings were surprising given that prior studies have evidenced a dose-response relationship between depression and cardiorespiratory fitness (Glazer et al., 2002) and between participation in exercise rehabilitation and post-CR aerobic capacity (Dugmore et al., 1999).

There are a number of possible explanations for the non-significant path estimates in the aforementioned path models. First, the stability path estimates for cardiorespiratory
fitness measures between baseline and post-CR were large (e.g., $\beta = .85$ for peak MET and $\beta = .61$ for duration of stress test between time points), indicating that maximal aerobic capacity at baseline was a very good predictor of the same outcome post-CR. The size of the stability path estimate accounted for the majority of variance, thus leaving little remaining variance in the model and making it difficult to detect other significant path relations. Second, there was a small inverse correlation between CR attendance and all three measures of cardiorespiratory fitness following CR, which likely impacted the relation between CR attendance and cardiorespiratory fitness post-CR. Although the directionality of the bivariate correlation is surprising at face value, this can at least partially be explained by certain external factors (e.g., approval to terminate the program prematurely due to good clinical progress, limited insurance coverage) that reduced attendance in patients who otherwise showed good treatment adherence. This interpretation provides additional support for the secondary analyses in which CR adherence was replaced by CR completion status.

**Path Analyses in the Depressed Subsample**

Given that the study sample was predominantly comprised of non-depressed individuals (91.4%), the path model results were likely influenced by the highly skewed depression scores in the full sample. Therefore, secondary path analyses were conducted in a smaller subset of patients ($n = 74$) who scored above a clinical cut-point on the PHQ-9 indicating moderate to severe levels of depression. Interestingly, when the same path models were tested in the depressed subsample, all six models showed excellent fit statistics and were therefore interpreted. As predicted, higher levels of baseline depression predicted lower CR attendance. This is consistent with previous research
indicating higher levels of depressive symptoms predict poorer CR adherence (Kronish et al., 2006; Ziegelstein et al., 2000), thus providing further evidence that depression is a risk factor for poor treatment adherence after acute coronary syndrome.

Unlike results for the full sample, baseline depression did not predict CR completion in the subsample of clinically depressed patients. Contrary to hypothesis, baseline depression also did not predict cardiorespiratory fitness outcomes in the depressed sample. There was a significant relation between CR completion and post-CR VO$_2$max, suggesting that patients who completed the CR program exhibited higher levels of cardiorespiratory fitness. However, this may be a spurious finding as no similar findings emerged within the other path models. According to the path models, CR completion did not mediate the relation between baseline depression and each of the cardiorespiratory fitness outcomes. Similar to what was discussed above for the full sample results, the stability path estimates for VO$_2$max, peak MET, duration of the exercise stress test were large (e.g., $\beta = .85$ between VO$_2$max at T1 and T2; $\beta = .77$ between peak MET at T1 and T2; $\beta = 0.55$ between duration of stress test between T1 and T2), thus leaving little variance to detect other significant path relations in the models.

**Clinical Implications**

The current study concludes that patients who enter CR with higher depression scores are more likely to prematurely drop out of CR, the gold standard treatment in the secondary prevention of CHD. Nonadherence to CR coincides with other modifiable risk factors (e.g., quitting smoking, taking medications regularly; Kronish et al., 2006) and places patients at greater risk of rehospitalization and cardiac mortality. Furthermore,
patients with moderate and severe levels of depression show poorer attendance in CR. As previously discussed, depression is a major contributor to lower quality of life and increased healthcare costs for CHD patients. Thus, clinical implications of the current study pertain to treatment and prevention of concomitant CHD and depression.

Findings from the current study underscore the importance of screening and treating depression in the aftermath of hospitalization for an acute coronary event and more broadly in the secondary prevention of cardiovascular events. Compared to the estimated point prevalence of depression in CHD patients (20%; Lichtman et al., 2008; Thombs et al., 2005), a much smaller proportion (8.6%) of patients in the current sample screened positive for depression on the PHQ-9. This likely reflects a large proportion of patients who did not follow up with physician referrals to CR after hospitalization and never attended CR orientation; the low rate of clinical depression in the current CR sample may be directly related to baseline depression and/or motivational factors. Thus, the window of time between acute hospitalization and the weeks immediately following discharge represents a critical period during which patients should be screened for depression and provided psychoeducation about managing heart disease, emotional stress, and risk factors. Psychological coping skills and evidence-based treatments for depression may also be introduced, as needed, during this critical window before discharge. Both hospitals and outpatient CR programs may benefit from staffing trained behavioral health consultants who can assess depression, triage mental health concerns, and enhance patient motivation to engage in CR and modify lifestyle factors.

There are three broad categories of depression treatment that have been applied to depression in the context of CHD: pharmacological, psychological, and exercise-based
interventions. Selective serotonin reuptake inhibitors (SSRIs) are considered the safest form of antidepressants for CHD patients (Kronish et al., 2012), with sertraline and citalopram among the front-line prescriptions that have demonstrated efficacy in the treatment of moderate, severe, or recurrent depression (Glassman et al., 2002; Lespérance et al., 2007; Lichtman et al., 2008). According to a meta-analysis of 16 antidepressant trials (Baumeister, Hutter, & Bengel, 2011), SSRIs produced a small but clinically significant reduction in depressive symptoms when compared to placebo. Still, approximately 15% to 25% of patients fail to continue antidepressant medication treatment because of adverse side effects or perceived lack of efficacy (Lichtman et al., 2008); yet others benefit from combined interventions involving pharmacotherapy, psychotherapy, or other therapies (Kronish et al., 2012). Thus, there has been great interest in the evaluation and development of psychosocial interventions for MDD in CHD patients.

Relevant to CHD patients enrolled in CR, there is mounting evidence in support of physical activity as an effective nonpharmacological intervention for depression that also positively impacts a wide array of risk factors linking depression and CHD (Lett et al., 2004). Results from psychological and exercise intervention studies demonstrate that exercise significantly improves mood (e.g., depression severity) and physiological (e.g., peak VO₂ consumption, exercise duration on a treadmill stress test) outcomes; these effects are better than medications or treatment as usual (Blumenthal et al., 2007; Blumenthal et al., 2012). In order to maximize clinical health outcomes, patients with CHD and depression may benefit most from interventions that simultaneously target both depression and cardiovascular risk factors (Lett et al., 2005). More specifically, depressed
patients with CHD may benefit from evidence-based treatments such as cognitive-behavioral therapy (CBT) for depression (Beck et al., 1979; Beck, 1995) or stress management training (Blumenthal et al., 2005; Freedland et al., 2009). These treatments emphasize psychoeducation about heart disease, risk factors, and emotional stress; skills training (e.g., progressive muscle relaxation, imagery, cognitive restructuring, problem solving, time management) to manage somatic symptoms and stress; and social support. Although CR typically incorporates multidisciplinary education and stress management, programs remain heterogeneous in structure. Systematic dissemination and implementation of evidence-based treatments for depression within inpatient settings (i.e., during hospitalization for the incident coronary event) and outpatient CR programs may serve to improve mental health and cardiovascular outcomes, thereby alleviating an enormous public health burden.

In a review of 64 randomized controlled trials of psychological interventions among CHD patients, characteristics of interventions associated with improvement in depressive symptoms were identified in attempt to isolate the effects of psychological components of treatment (Dickens et al., 2013). Among 12 studies that presented data on depressed coronary patients, the overall effect size for psychological interventions was small but significant ($d = .18$). Significant effects were seen for general education ($d = .52$), behavioral therapy ($d = .44$), CBT ($d = .29$), and relaxation ($d = .30$); however, only CBT showed a significant effect ($d = .31$) within the subset of 7 studies that met standards for high methodological quality.

Although CBT for depression and stress management training are effective in the reduction of depressive symptoms in cardiac patients, there is currently no direct
evidence to demonstrate that psychological treatment improves cardiac outcomes or mortality. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study was the largest and only randomized controlled trial powered to test the efficacy of depression treatment in cardiac patients post-MI (Berkman et al., 2003). The ENRICHD study design included a psychosocial intervention (CBT), singly and in combination with sertraline. Compared to usual care, the enhanced CBT intervention yielded significant but modest improvements ($d = 0.31$) in depression, as evidenced by a 49% vs. 33% mean decrease on the BDI, and a comparable difference observed on the structured interview assessment of depressive symptom severity. There were no significant differences in all-cause mortality or MI recurrence between the enhanced psychological intervention and usual care conditions (Carney et al., 2004). Therefore, until there is evidence that treatment of depression improves outcomes or survival, it remains unproven whether depression is a causal risk factor for CHD.

**Limitations**

Study limitations should be taken into account when interpreting results and drawing conclusions. First, there were some important limitations related to the composition of the current sample. As discussed in the clinical implications section above, the vast majority of the sample (91.4%) reported minimal symptoms of depression at baseline. Thus, results of the current study may not be broadly generalizable, as previous studies show much higher rates of depression in patients with MI and coronary artery disease (Lett et al., 2004; Rutledge et al., 2006; van Melle et al., 2004). Moreover, although this study was conducted in a community sample, demographic homogeneity limits generalizability. Replication of results is needed to verify specific findings and to
better understand the unique determinants of cardiovascular health in ethnic minority, female, and socioeconomically disadvantaged patients with CHD. As mentioned earlier, these minority populations are in greater need of health promotion and secondary prevention efforts, as they show lower rates of enrollment in CR and higher rates of medical comorbidities and physical disability.

A second limitation of this project relates to the operational definition of treatment adherence. Although CR is a comprehensive multidisciplinary program, for the purposes of the current project, CR attendance and completion referred to engagement in the exercise portion of the program and did not include adherence to or completion of other multimodal interventions that are integral to CR. Baseline depression very likely influenced participation in stress management, nutrition, smoking cessation, and medical education sessions. Participation in these interventions likely also impacted exercise adherence and completion as well as cardiorespiratory fitness outcomes. Another related limitation pertains to the definition of CR completion status. Treatment completion status was broadly defined by collapsing cases in which there was a clear external factor that contributed lower attendance in CR. However, the definition of CR completion is not well defined in the literature; more research is needed to determine how best to account for early termination, insurance coverage, and other factors unique to CR. Although this definition accounted for major external factors that affected attendance rates, it is possible that methodological issues remained in the operationalization of CR completion status. For example, combining patients who terminated CR early for differing reasons (i.e., insurance limitations, good clinical progress) may have failed to distinguish important subgroup differences, such as motivation or willingness to engage in exercise.
Third, important covariates (e.g., BMI, cholesterol levels, physiological markers of heart disease severity, mental health history, motivation to change lifestyle or risk factors) that impact treatment adherence and cardiorespiratory fitness were not available for the current project and therefore, could not be accounted for in MIMIC models. Previous research indicates that patients with a prior history of depression face higher risk for secondary cardiovascular events and poorer adherence in CR than patients who experience depression secondary to a coronary event (Ades et al., 1992a). In the current study, without mental health history information, it was not possible to delineate whether baseline depression preceded the incident coronary event. Additionally, no data were collected to assess attendance in stress management sessions or formal mental health treatment; patients with elevated depressive symptoms who were engaged in these concurrent treatments may have uniquely benefited with respect to cardiorespiratory fitness outcomes, treatment adherence, and CR completion.

Fourth, although the PHQ-9 has been demonstrated to be a valid and reliable measure of depression, it should be noted that the measure includes items that tap into somatic symptoms that may be conflated with comorbid medical symptoms in patients with coronary heart disease. Other measures, such as the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), have been normed in hospital patients and do not include certain items (e.g., fatigue, sleep, appetite/weight), and may be a good alternative measure of depression.

**Study Conclusions and Future Directions**

The current study contributes uniquely to the growing field of behavioral cardiology by examining the relations between baseline depression and cardiorespiratory
fitness in a large community sample of predominantly non-depressed patients enrolled in CR. This study provides further evidence to support the impact of clinical levels of depression on treatment adherence in a secondary prevention setting and contributes to a growing body of research that indicates depression is an independent risk factor for CHD and adverse cardiac events.

As suggested above, replication of results in a more ecologically valid sample will lend credibility to the novel findings presented in this paper. Replication will be particularly important to confirm that higher depression scores predict a lower likelihood of CR completion, as this major finding has the greatest clinical implications for treatment and prevention efforts. Although this study did not lend support for CR attendance or completion status mediating the relation between depression and cardiorespiratory fitness, future studies examining mechanisms of depression in CHD may extend current research by further testing the latent construct of cardiorespiratory fitness and considering the role of important covariates (e.g., BMI, cholesterol levels, disease severity index, mental health history, motivation to change behavioral risk factors). The adherence constructs, CR attendance and CR completion, should be further studied and may be refined through the development of a reliable metric to define treatment adherence to rehabilitation protocols. One possibility is to develop an underlying latent construct for CR adherence, with rates of attendance (percentage of total possible sessions attended) across individual components of intervention (e.g., exercise, stress management, nutrition, smoking cessation) representing individual indicators. Future studies would also benefit from integrating biological mechanisms such as heart rate variability, hormone levels, and inflammatory biomarkers and testing
the interactions between biological and behavioral mechanisms of depression in CHD. The ultimate goal of this line of work would be to improve early detection of depression in the context of CHD and to recommend specific treatments that are tailored to specific predisposing risk factors in the prevention of secondary cardiovascular events.
REFERENCES


Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gaulden, L. H., Cuffe, M. S., & O’Connor, C. M. (2001). Relationship of depression to increased risk of
mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine, 161*(15), 1849-1856.


Appendix.

*Patient Health Questionnaire Depression Scale – 9 item*

<table>
<thead>
<tr>
<th>PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Over the last 2 weeks, how often have you been bothered by any of the following problems?</strong></td>
</tr>
<tr>
<td><em>(Use “✓” to indicate your answer)</em></td>
</tr>
<tr>
<td><strong>Not at all</strong></td>
</tr>
<tr>
<td>1. Little interest or pleasure in doing things</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
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<tr>
<td>4. Feeling tired or having little energy</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
</tr>
</tbody>
</table>

**For office coding**

\[0 + _+ _+ _= \text{Total Score: _____}\]

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
</table>