THE ROLE OF PHYSICAL FITNESS IN THE RELATIONSHIP BETWEEN DEPRESSIVE SYMPTOMS AND CHRONIC INFLAMMATION IN PATIENTS ENROLLED IN CARDIAC REHABILITATION

A dissertation submitted to Kent State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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August, 2012
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ACKNOWLEDGEMENTS

I would like to extend huge thanks to Annie Keary, Colleen Cole Mattson, and Tracy Hammonds who were instrumental in gathering data for this study. I would also like to thank Joel Hughes who was my advisor for this dissertation. Thanks also to Doug Delahanty, Margaret Doheny, John Gunstad, and Derek Damron for serving as members of my dissertation committee. I would also like to thank members and affiliates of Summa Health System’s Center for Cardiopulmonary Research, most notably Richard Josephson, Jim Rosneck, and Donna Waechter for the wealth of information and continuous support for this and numerous other studies. Also I would like to thank the immunology and molecular pathology department at Summa Health System, especially Tom Alexander and Linda Define, for their collaboration and help with this project. Finally, I would like to thank all of the patients who were willing to participate in this study in order to provide us with more information about depression in patients with cardiovascular disease.
INTRODUCTION

Cardiovascular disease is a crucial health issue in the United States. An estimated 81,100,000 American adults (more than one in three) have one or more types of cardiovascular disease (Lloyd-Jones et al., 2010). Cardiovascular disease includes a wide range of conditions related to the heart. Although specific conditions may not always be interchangeable, terms describing cardiovascular disease (CVD) such as coronary heart disease (CHD) and coronary artery disease (CAD) will be used interchangeably for the purposes of this paper. Mortality due to cardiovascular disease is slightly declining in recent years due to awareness, prevention, and effective treatments, but cardiovascular disease accounts for more than one million deaths annually (Kung et al., 2008). According to the American Heart Association, cardiovascular disease claims as many lives each year as accidents, cancer, respiratory disease, and diabetes mellitus combined (Rosamond et al., 2007). The economic impact of cardiovascular diseases on our nation’s health care system continues to grow as the population ages. The cost of heart disease and stroke in the United States was estimated at $503 billion in 2010, including health care expenditures and lost productivity from death and disability (American Heart Association, 2010). Treatments of cardiovascular disease vary from medication and surgery to diet and lifestyle changes disability (American Heart Association, 2010).

Depression and cardiovascular disease

Depression frequently accompanies cardiovascular disease. Depression, a psychological condition characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, poor concentration, and
suicidal thinking, can contribute to the difficulty of living with cardiovascular disease. The prevalence of major depressive disorder after an acute myocardial infarction is 18-25% (Herridge et al., 2005) and 16-27% among patients with coronary heart disease (Lett et al., 2004). Depression may contribute to cardiovascular disease and having heart disease may cause depression (Frasure-Smith & Lesperance, 2006; Freedland et al., 1992; Glassman et al., 2002a; Lichtman et al., 2008). The link between depression and cardiovascular disease could be explained by numerous variables, including physiological changes, lifestyle habit changes, social support changes, and unmanaged stress and health. The high prevalence of depression is particularly concerning because depression is associated with increased risk of mortality among cardiac patients.

Depression increases risk of mortality for patients with coronary artery disease (Carney et al., 1988), for patients who have experienced a myocardial infarction (Frasure-Smith et al., 1993; Frasure-Smith et al., 1995; Frasure-Smith et al., 1999; Lesperance et al., 2002; van Melle et al., 2004), for patients treated with coronary artery bypass graft surgery (Connerney et al., 2001), and for patients with heart failure (Sherwood et al., 2007). Major depression makes cardiac mortality four times more likely in the first six months (Frasure-Smith et al., 1993) and over three times more likely in the first year (Frasure-Smith et al., 1999) following a myocardial infarction. Individuals with higher levels of depressive symptoms are also 1.5 times more likely to die within five years after being hospitalized for acute coronary syndrome compared to patients without high levels of depressive symptoms (Grace et al., 2005). A one-point increase on a self-report depression questionnaire was associated with a 7% increase in
risk of cardiovascular hospitalization and mortality (Sherwood, et al., 2011). A meta-analysis showed that the risk of depressed patients with coronary heart disease dying in the two years after diagnosis was two times higher than the risk for nondepressed patients (Barth et al., 2004). Similarly, another meta-analysis showed that depression after a myocardial infarction was associated with over a two-fold increase in all-cause and cardiac mortality (van Melle et al., 2004). The relationship between depression and increased risk of cardiovascular mortality remains even after controlling multiple other factors, such as disease severity, age, gender, medications, and overlap of cardiac and depressive symptoms.

A number of possible mechanisms have been proposed to specifically explain the relationship between depression and cardiac mortality (Carney et al., 2002a; Carney et al., 2005b). Compared to non-depressed patients, depressed cardiac patients may have more major cardiac risk factors such as smoking, hypertension, diabetes, physical inactivity, and reduced adherence to medical treatment regimens. Physiological mechanisms may account for the risk associated with depression among cardiac patients, including more severe coronary disease, exaggerated platelet reactivity (Bruce & Musselman, 2005), increased inflammatory processes (Kop & Gottdiener, 2005), and dysregulation of the autonomic nervous system (Freedland et al., 2005).

_Treatments for depression in cardiac patients_

Determining the mechanisms by which depression is related to increased risk of mortality is the first step in developing effective interventions for depressed cardiac patients. Previous intervention trials failed to provide evidence that treating depressed
cardiac patients reduces risk of mortality. The ENhancing Recovery in Coronary Heart Disease (ENRICHD) randomized clinical trial of cognitive behavioral therapy for depression and social isolation failed to demonstrate that treating patients for depression after an acute myocardial infarction reduces mortality or recurrent myocardial infarctions (Berkman et al., 2003). In the Sertraline and Depression Heart Attack Randomized Trial (SADHART), improvements in depression only occurred in patients with severe or recurrent depression (Glassman et al., 2002b). Citalopram was an effective treatment for depression in the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial, but interpersonal psychotherapy for depression was not more effective than clinical management among patients with coronary artery disease (Lesperance et al., 2007). Treatment with anti-depressants (mirtazapine or citalopram) did not reduce post-MI depression or improve cardiac prognosis compared to control groups in the Myocardial Infarction and Depression – Intervention Trial (MIND-IT) (van Melle et al., 2007). Antidepressant medication use was associated with increased likelihood of death or cardiovascular hospitalization in heart failure patients (Sherwood et al., 2007). Depression treatment (antidepressants and therapy) reduced risk of incident cardiovascular disease in the IMPACT trial (Stewart, Perkins, & Callahan, 2012), but only for those individuals who were not already clinically diagnosed with cardiovascular disease.

*Exercise as a treatment for depression.* Although there is little support for the effectiveness of treating depression in cardiac patients with psychotherapy and pharmacology, there is evidence for exercise as an effective treatment. Physical activity
is consistently inversely related to depression. Individuals reporting none or low levels of physical activity are at greater risk for developing depression (Camacho et al., 1991), whereas increased physical activity serves as a protective factor to prevent depression (Strawbridge et al., 2002). Depression is also related to reduced levels of physical fitness as measured by exercise capacity on a treadmill exercise stress test (Ruo et al., 2004).

Exercise appears to have anti-depressive effects for non-cardiac samples (Blumenthal et al., 1999; Babyak et al., 2000). Exercise was as effective as sertraline in reducing depressive symptoms after 16 weeks of treatment for individuals with major depressive disorder above the age of 50 years old (Blumenthal et al., 1999). Exercise yielded similar reductions in depressive symptoms in a four-month follow-up compared to sertraline treatment or medication/exercise combined and was associated with lower relapse rates in a 10-month follow-up (Babyak et al., 2000). In the SMILE (Standard Medical Intervention and Long-term Exercise) study, home exercise, supervised group exercise, sertraline, and placebo were equally effective in reducing depressive symptoms (Blumenthal et al., 2007a). A one-year follow-up of the SMILE study showed that regular exercise during the one year follow-up period was associated with reductions in depressive symptoms (Hoffman, et al., 2011). There is also support for a relationship between greater energy expenditure during exercise and greater reductions in depressive symptoms when aerobic exercise treatment groups were compared to flexibility-only exercise treatment groups (Dunn, et al., 2005).

There is little research investigating the effectiveness of exercise in reducing depression and cardiac mortality among depressed cardiac patients. Although physical
inactivity did not account for depression contributing to an increased risk in cardiovascular mortality, physical inactivity and depression interacted to increase risk (Kamphuis et al., 2007). The ENRICHED trial provided some support for the benefits of exercise in depressed men and women who experienced acute myocardial infarction. Patients self-reporting regular exercise had greater reductions in depression after six months compared to patients who did not exercise. In addition, patients reporting regular exercise had less than half the fatal events compared to patients who did not regularly exercise (Blumenthal et al., 2004).

Similarly, prevalence of depressive symptoms substantially decreased for heart failure patients who participated in an exercise training program compared to heart failure patients who dropped out of the exercise training program (Milani, et al., 2011). In the same sample, patients with depression who improved exercise capacity as a result of the exercise training program had lower mortality rates compared to those depressed patients who did not have improvements in exercise capacity. In another study, heart failure patients with major depression had significantly reduced depressive symptomology, improved physical functioning, and improved quality of life when participating in a combined exercise and cognitive-behavioral therapy program compared to those with cognitive-behavioral therapy alone or usual care treatment (Gary, et al., 2010).

Additional research is needed to clarify how exercise contributes to reductions in depression and reduced risk of mortality. The methodology for a randomized clinical trial, Understanding Prognostic Benefits of Exercise and Anti-depressant Therapy (UPBEAT), comparing the effects of exercise, sertraline, and placebo treatments on
depression and biomarkers of cardiovascular risk in individuals with depression and coronary heart disease, was previously proposed, but the findings of this research have not yet been published (Blumenthal et al., 2007b). The results of UPBEAT could potentially provide more conclusive evidence for the effectiveness of exercise in reducing depression in cardiac patients. However, additional research is needed to examine the impact that physical activity has on various cardiovascular risk factors. Although physical activity likely mediates the relationship between depression and multiple cardiovascular risk factors, the present study will focus on the role of physical fitness in mediating the relationship between depression and inflammation.

**Depression and Inflammation in Cardiovascular Disease**

The beneficial effect of exercise for depression reduction and improved cardiac outcomes may be due to the role that physical activity and physical fitness play in reducing inflammation through improved vagal control.

*Chronic inflammation and cardiovascular disease.* Cardiovascular disease has been recently conceptualized as an inflammatory disease due to a chronic inflammatory response to damage to the endothelium and endocardium (Ross, 1999). Inflammation is the normal immune system response to injury or infection with the goal of destroying both the cause (e.g. microbes, toxins) and the consequences (e.g. necrotic cells and tissues) of injury (Cotran et al., 1999; Rankin, 2004). However, without proper regulation, inflammation may lead to the body using its own cells to produce molecules, such as pro-inflammatory cytokines, that could potentially injure or kill the body’s own tissues (Tracey, 2007). Cytokines are proteins produced by a variety of cell types, such
as lymphocytes and macrophages, that mediate the process of inflammation by orchestrating the promotion and inhibition of inflammation (Cotran et al., 1999; Opal & DePalo, 2000).

The cytokine theory of disease posits that high levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), can cause tissue damage and disease syndromes (Clark et al., 1981; Fruchart, 2003; Pearson et al., 2003). Research showing that inhibitory drugs, such as anti-TNF and IL-1 antagonist, can be used to treat inflammatory conditions, provides additional support for the cytokine theory of disease (Tracey, 2002; Tracey, 2006; Tracey, 2007).

An effective inflammatory response requires a balance of pro- and anti-inflammatory cytokines. Levels of pro-inflammatory cytokines that are too low will lead to immunodeficiency and limit the body’s ability to fight infection, whereas levels too high can lead to chronic or systemic inflammation (Tracey, 2002; Tracey, 2007; Tracey, 2006). Chronic inflammation can contribute to the cause or progression of disabling diseases such as rheumatoid arthritis, arthrosclerosis, tuberculosis, chronic lung disease, Crohn’s disease, diabetes, Alzheimer’s disease, multiple sclerosis, and cerebral and myocardial ischemia (Cotran et al., 1999; Tracey, 2002; Tracey, 2006). If inflammation escapes from the confines of the immediate tissue and enters into the bloodstream, systemic inflammation can occur, potentially leading to septic shock syndrome, meningitis, and severe trauma (Tracey, 2002; Tracey, 2006).

Atherosclerosis, the thickening and loss of elasticity in artery walls, was formerly known only as a disease of lipid accumulation, but is recently also considered as a
condition of low-grade vascular inflammation (Libby et al., 2002). Inflammatory markers, such as CRP, TNF-α, and IL-6, are independent predictors of the risk of cardiovascular events in healthy individuals (Ridker et al., 2000a; Ridker et al., 2000c; Ridker, 2003; Pradhan et al., 2002; Cesari et al., 2003; Pearson et al., 2003). Inflammatory markers also predict risk of recurrent cardiovascular events and mortality in men and women who previously experienced a cardiac event (Ridker et al., 2000b; Volpato et al., 2001).

**Relationship between depression and inflammation.** Depression is associated with elevated levels of inflammatory markers in cardiac and non-cardiac samples (Maes et al., 1995; Suarez et al., 2003; Suarez et al., 2004; Panagiotakos et al., 2004b). Depressive symptoms are associated with elevated levels of CRP in patients recovering from coronary heart disease (Miller et al., 2005b), as well as elevated levels of TNF-α and IL-6 in patients with congestive heart failure (Parissis et al., 2004). The results of cross-sectional studies suggest that a relationship exists between depression and inflammatory markers, but this relationship may be attenuated when other variables, such as body mass index, age, smoking status, medications, or gender are taken into account (Tiemeier et al., 2003; Kop et al., 2002; Miller et al., 2002; Steptoe et al., 2003; Whooley et al., 2007; Glassman & Miller, 2007; Lesperance et al., 2004; Raison et al., 2006).

Experimental manipulations show a bidirectional relationship between depression and inflammation (Castanon et al., 2002). Pro-inflammatory cytokine injections, such as IL-1β or TNF-α, induce depression-like behaviors, such as decreased motor activity, social withdrawal, reduced food and water intake, increased slow-wave sleep and altered
cognition (Anisman et al., 2005; Dantzer, 2001). Pro-inflammatory cytokines have been found to induce alterations in brain function analogous to those in depressed patients, including cognitive impairment, increased activity of the hypothalamus–pituitary–adrenal axis, and altered neurotransmission (Capuron & Dantzer, 2003). Experimentally increasing inflammation (through methods such as injection of a mild, non-sickness inducing vaccine, administration of recombinant human tumor necrosis factor (rH-TNF), or administration of lipopolysaccharide) induces depressive symptoms in humans (Wright et al., 2005; Spriggs et al., 1988; Yirmiya et al., 2000). Clinical evidence shows that cancer patients tend to develop depressive symptoms after being exposed to high doses of inflammatory cytokines as part of their medical treatment, such as radiation or cytokine therapies (Capuron et al., 2000; Musselman et al., 2001).

Depression can also induce inflammation. When exposed to anhedonia-inducing chronic mild stress, rats developed increased plasma levels of IL-1β and TNF-α (Grippo et al., 2005). White blood cells were cultured in vitro with endotoxin to assess the association of depression and inflammatory cytokine production in an infectious challenge with forty-one patients with congestive heart failure (Miller et al., 2005a). Although depressive symptoms were not associated with inflammatory cytokine production, depression was associated with enhanced sensitivity to the anti-inflammatory properties of glucocorticoids, which eventually lead to increases in inflammatory cytokines, such as IL-6 and TNF-α. These results imply that the introduction or presence of depression could potentially hinder an individual’s ability to properly regulate inflammation.
Induction of depressed mood leads to increases in inflammatory markers and inducing inflammation tends to lead to development of depressed mood, or possibly an amplification of pre-existing depressive states (Shimbo et al., 2005). It is also possible that a mutually shared third variable (such as genetic polymorphisms) contributes to both inflammation and depression (Shimbo et al., 2005).

*Depression and inflammation predict cardiovascular disease.* Prospective studies show that depression and inflammation independently predict cardiac events (Arbelaez et al., 2007; Empana et al., 2005; Frasure-Smith et al., 2007; Janszky et al., 2007; Ladwig et al., 2005; Redwine et al., 2007; Vaccarino et al., 2007). However, there is not clear evidence that inflammation explains the relationship between depression and cardiac events (Frasure-Smith et al., 2007; Ladwig et al., 2005). Symptoms of sickness behavior and exhaustion overlap with symptoms of depression, making the relationship between inflammation and depression less clear (Dantzer et al., 2008; Dantzer & Kelley, 2007; Lyness et al., 2001; Charlton, 2000; Ferketich et al., 2000). Some studies support the assertion that the exhaustion and fatigue components of depression, as opposed to symptoms such as demoralization or depressed mood, are associated with cardiovascular disease and inflammation (Appels et al., 2000b; Appels et al., 2000a; Kop et al., 2002; Janszky et al., 2005).

Although studies with humans have not provided consistent evidence for the mediating role of inflammation in the link between depression and cardiovascular disease, there is evidence from animal experiments. Experimentally induced heart failure in rats showed that anhedonia was a by-product of heart failure and mediated by the
presence of pro-inflammatory cytokines (Grippo et al., 2003). Elevated levels of TNF-α and anhedonia, as measured by impaired responding to rewarding electrical brain stimulation, were present in rats that underwent coronary artery litigation to induce heart failure, but not in rats that underwent sham surgery. Additionally, treating the rats with a TNF-α antagonist reduced levels of TNF-α and resulted in normal responses to electrical stimulation. In other words, stopping the inflammatory response also halted development of anhedonia, suggesting that inflammation resulting from heart failure contributes to the development of depression.

*Physical activity reduces inflammation.* The anti-inflammatory effects of exercise may help to explain how physical activity reduces risk of cardiovascular disease and mortality in cardiac patients (Panagiotakos et al., 2004a; Pedersen, 2006; Petersen & Pedersen, 2005; Woods et al., 2006; Pedersen & Saltin, 2006). Physical activity reduces risk for cardiovascular disease, but the exact mechanisms for the protective effects of physical activity are not established. In a recent study on the effects of exercise on risk of cardiovascular disease, 60% of the positive effects of exercise were explained by the effect it has on known risk factors, with inflammation accounting for one-half of the risk factor effect (Mora et al., 2007).

Physically active individuals tend to have lower levels of inflammatory markers compared to physically inactive individuals and participation in exercise programs result in reductions in inflammation (McFarlin et al., 2006; Stewart et al., 2007; King et al., 2003). In a study based on self-report of physical activity, physically active individuals had lower levels of IL-6, IL-1β, TNF-α, and hsCRP compared to inactive individuals.
Physically inactive individuals were placed on a 12-week exercise program and compared to physically active individuals who remained on their normal exercise program (Stewart et al., 2007). At baseline testing, CRP levels were higher in the physically inactive individuals compared to the physically active individuals, but after the 12-week exercise program the physically inactive individuals had marked reductions in CRP levels and no longer differed from the physically active group.

The effect of exercise on inflammation may also depend on the type and intensity of exercise. For example, only individuals who regularly participated in jogging or aerobic dancing were less likely to have elevated levels of inflammatory markers (CRP, fibrinogen, and white blood cell levels) compared to individuals who participated in less intense physical activities (King et al., 2003). It should be noted that although a single bout of exercise is related to a temporary increase in acute inflammation, regular physical activity is associated with a consistent anti-inflammatory effect (Mora et al., 2007; Plaisance et al., 2007; Petersen & Pedersen, 2005; Zaldivar et al., 2006).

Physical activity is also related to a reduction in inflammation among cardiac patients. Physical activity reduced peripheral markers of inflammation, including soluble intercellular adhesion molecule-1, in patients with chronic heart failure (Adamopoulos et al., 2001). Although TNF-α and IL-6 levels were not reduced, physical activity was associated with reduced plasma TNF-α receptor levels in patients with chronic heart failure due to coronary artery disease who participated in four months of endurance and resistant training exercise (Conraads et al., 2002). Exercise is also related to improved
outcomes for individuals with other inflammatory conditions, such as rheumatoid arthritis (Neuberger et al., 2007).

The anti-inflammatory effects of physical activity should lead to associated reductions in depression. However, no known studies have assessed the effects of physical activity on depression and inflammation in cardiac patients. The UPBEAT study could potentially provide evidence for the effect of exercise, physical activity, and physical fitness on depression reduction and inflammatory biomarkers, such as hs-CRP, but the findings and conclusions of this research has yet to be published (Blumenthal et al., 2007b).

*Depression, Inflammation, and Vagal Control*

The associations among depression, inflammation, and exercise in patients with cardiovascular disease could be explained by reduced vagal control. Inflammation leading to atherosclerosis and cardiovascular disease may be due to failure of the nervous system to properly regulate the inflammatory response. Although infection or injuries are the initial causes of chronic inflammation, reduced vagal control interferes with stopping the inflammatory process, resulting in increased inflammation.

*The cholinergic anti-inflammatory pathway.* The cholinergic anti-inflammatory pathway is a physiological mechanism by which the nervous system interacts with the immune system to inhibit potentially damaging inflammation (Tracey, 2002). The central nervous system uses neural input to control cytokine overproduction, much like it coordinates balance for other physiological functions such as heart rate, blood pressure, digestion, body temperature, organ perfusion, and blood glucose levels (Tracey, 2002).
The vagus nerve originates with axons in the medulla oblongata and conducts impulses between the brain and various body structures by extending to organs in the chest and abdomen including the heart, lungs, liver, stomach, pancreas, spleen, kidney, and intestines. In particular, the vagus nerve connects the brain to the visceral organs, such as the spleen and liver, that produce the majority of inflammatory cytokines (Czura et al., 2003), making it the pathway by which the brain controls cytokine overproduction (Metz & Tracey, 2005).

The cholinergic anti-inflammatory pathway is considered the efferent (motor) arm of the “inflammatory reflex,” the neural loop of the immune system and brain’s bidirectional communication. Immune cells secrete cytokines and other molecules that bind to receptors on neurons, activating afferent (sensory) fibers of the vagus nerve. The signal is sent back to the brain with notification of the presence of inflammation. Like a knee-jerk reflex, the brain rapidly sends back an opposing anti-inflammatory signal through the vagus nerve. This opposing response is transmitted by the cholinergic anti-inflammatory pathway to the organs of the reticuloendothelial system where damage is prevented by the inhibition of pro-inflammatory cytokine production and release (Tracey, 2002).

The cholinergic anti-inflammatory pathway includes the term “cholinergic” because the neurotransmitter acetylcholine is used as a chemical signaling agent by nerves in the parasympathetic nervous system, including the vagus nerve. Acetylcholine is released from the nerve ending only when an appropriate signal is transmitted from the brain. After being released, acetylcholine binds to the α7 subunit of the nicotinic
acetylcholine receptor, a specific receptor site on macrophages in the organs of the body. Vagus nerve stimulation causes the brain to “fire,” or transmit the signal through the vagus nerve, resulting in acetylcholine release. When the vagus nerve is not firing, acetylcholine is not released and the inhibitory messages are not conveyed (Tracey, 2006). Through the use of acetylcholine in the vagus nerve, the brain can receive messages regarding the presence of inflammation and send out messages to inhibit inflammation.

_Vagal control and inflammation._ Findings from a variety of experimental studies converge to provide evidence for the role of the vagus nerve in controlling inflammation. The cholinergic anti-inflammatory pathway can be manipulated in a variety of ways, including with acetylcholine (Borovikova et al., 2000), with cholinergic agonists (Pavlov & Tracey, 2005), through electrical stimulation of the vagus nerve (Bernik et al., 2002; Tracey, 2002; Tracey, 2006), or through damage to the vagus nerve (Tracey, 2006).

Vagus nerve stimulation inhibits production of TNF in the liver of rats injected with cytokine-producing lipopolysaccharide (Borovikova et al., 2000). Whereas vagus nerve stimulation suppresses inflammation, decreasing vagus nerve activity results in an overproduction of cytokines. Animal studies have shown the anti-inflammatory effects of vagus nerve stimulation (Bernik et al., 2002; Tracey, 2002; Tracey, 2006). However, studies assessing the effect of vagus nerve stimulation on inflammation in clinical studies with humans with treatment resistant depression are less conclusive (Rado & Janicak, 2007; Marangell et al., 2007; Corcoran et al., 2005).
Further evidence comes from studies on damage to the vagus nerve. If the vagus nerve is not intact, the brain is unable to receive the signal that inflammation needs to be inhibited. Researchers demonstrated this phenomenon by injecting inflammatory cytokines into the organs of rats. The rats with a damaged vagus nerve showed no symptoms or sickness behavior because the brain was unaware of the presence of inflammation (Tracey, 2006).

*Depression, vagal control and cardiovascular disease.* Much of the research assessing vagal control involves the use of heart rate variability (HRV) analysis. The parasympathetic nervous system influences the tonic or resting heart beat through signals from the vagus nerve. The signals from the vagus nerve determine HRV, the degree that beat-to-beat time intervals vary in the heart (Thayer & Lane, 2007). A healthy heart has a more flexible, or variable, rate than an unhealthy heart. High vagal tone is indicated by the heart rate varying considerably (high HRV), whereas poor or low vagal tone occurs when the heart rate is relatively steady with low variability (low HRV). HRV analysis has become an established method to assess autonomic nervous system fluctuations and provides well-defined indicators of cardiac autonomic function (De Meersman & Stein, 2007). Vagal control moderates the risk of arrhythmia conferred by excessive SNS activity, such that people or animals with poor vagal control have higher risk of arrhythmic events. Reduced HRV indicates autonomic imbalance favoring sympathetic tone, which may or may not include reductions in parasympathetic activity.

Previous research provides evidence for a link between depression and vagal functioning as depression is consistently associated with reduced HRV (Carney et al.,
Reduced HRV, as well as other measures of vagal functioning such as resting heart rate, heart rate recovery, and baroreflex sensitivity, are predictors of cardiovascular mortality (Bigger et al., 1992; Klieger et al., 1987; La Rovere et al., 1998; Thayer & Lane, 2007). Indices of vagal function are also related to several established cardiovascular risk factors, as well as the emerging risk factors of depression and inflammation (Thayer & Lane, 2007). HRV also partly explains the relationship between depression and increased risk of mortality in cardiac patients, providing additional support for vagal control as a mediator between depression and cardiovascular disease (Carney et al., 2005a).

*Vagal control, inflammation, and cardiovascular disease.* Reduced vagal control exacerbates the relationship between inflammation and cardiovascular disease by interfering with halting the inflammatory process. Reduced levels of HRV indices tend to be associated with elevated levels of inflammatory markers in non-cardiac samples (Sajadieh et al., 2004; Sloan et al., 2007; Sajadieh et al., 2006; Dawood et al., 2007; Marsland, et al., 2007). Contrary to expectations, no or weak associations between HRV indices and inflammatory markers were present in cross-sectional and repeated measures studies of patients with cardiovascular disease (Hamaad et al., 2005; Janszky et al., 2004; Yue et al., 2007; Carney et al., 2007; Lanza et al., 2006; Malave et al., 2003; Aronson et al., 2001).

The mediating or moderating effect of HRV on the prognostic value of inflammatory markers in predicting cardiovascular disease was assessed in only one
known study (Sajadieh et al., 2006). Elevated levels of inflammatory marker CRP and reduced levels of HRV indices were independently related to an increased risk of death or acute myocardial infarction five years later. A combination of CRP and any of the HRV or heart rate measurements was more predictive of cardiovascular outcomes compared to any of the measurements alone (Sajadieh et al., 2006). However, because inflammation and HRV were assessed at the same time point, this study was unable to address if one variable preceded the other. Autonomic imbalance may affect inflammation, as both bone marrow and lymphatic systems are innervated by the autonomic system.

Alternatively, inflammation may influence the autonomic balance of the brain by affecting hypothalamic-pituitary-adrenal (HPA) axis at the pituitary and adrenal gland (Fruchart, 2003). Although there is strong empirical support for the association between the vagus nerve and inflammation, the relationship between vagal control of the heart (as measured by HRV) and inflammatory markers is less clear.

One crucial piece of missing information is the extent of the relationship between the vagal control of the cholinergic anti-inflammatory pathway and vagal control of the heart. The extent to which vagus nerve activity in the heart correlates with the activation of the cholinergic anti-inflammatory pathway in humans is not established (Tracey, 2005). It is not currently known if the vagus nerve affects the heart in the same way it affects other organs, such as the liver or spleen. It is known that the threshold of vagus nerve activity that activates the cholinergic anti-inflammatory pathway is significantly lower than required to activate a change in HRV (Tracey, 2005). Since a greater amount of vagus nerve activity is needed to change HRV than is needed activate the cholinergic
anti-inflammatory pathway and change inflammation, any small change in HRV should be reflected in more pronounced changes in inflammation.

Evidence for an association between vagal control of the heart and vagal control of the cholinergic anti-inflammatory pathway comes from clinical research studies. As expected, patients with diseases characterized by elevated levels of pro-inflammatory cytokines, such as severe sepsis, rheumatoid arthritis, lupus, and inflammatory bowel disease have reduced levels of various HRV indices (Tracey, 2005). Vagus nerve activity also appears to have cardioprotective effects (Prystowsky et al., 1981). For example, dogs susceptible to ventricular fibrillation exhibited greater reductions in vagal tone when exercising compared to dogs who were resistant to ventricular fibrillation (Billman & Hoskins, 1989). Although not assessed, if vagal tone is related to controlling inflammation, elevated levels of pro-inflammatory cytokines could be expected in the dogs susceptible to ventricular fibrillation.

_Depression, inflammation and vagal control._ Increased inflammatory processes and dysregulation of the autonomic nervous system are both proposed mechanisms for explaining the relationship between depression and increased risk of cardiac mortality (Carney et al., 2002b). Although clinical evidence shows that individuals with conditions associated with elevated levels of pro-inflammatory cytokines and decreased vagal activity, such as rheumatoid arthritis, also tend to be at higher risk for depression compared to healthy individuals, inflammation and vagal control have not been examined extensively in cardiac populations (Dickens et al., 2002).
Reduced vagal control, increased inflammation, and depression each independently predict cardiovascular disease, but have been simultaneously examined in relatively few studies with mixed results. Higher levels of fibrinogen (a marker of inflammation and coagulation) were moderately correlated to lower levels on four HRV indices (TP, VLF, LF, and HF) in a sample of 44 depressed patients with coronary heart disease (Carney et al., 2007). IL-6 was also moderately negatively related to TP, VLF, and LF. However, neither CRP nor TNF-α were related to any of the HRV indices, which could be explained by lack of statistical power due to the small sample size. Although this study assessed inflammation and vagal functioning in a depressed cardiac sample, conclusions could not be drawn regarding the role of depression due to lack of a non-depressed control group.

Inflammation and vagal function were also assessed in at least one depressed non-cardiac sample. Several measures of vagal functioning (HRV, cardiac baroflex sensitivity, and pulse pressure) were unrelated to hs-CRP in 25 individuals with major depressive disorder and 15 healthy individuals without depression (Dawood et al., 2007). There were also no differences between depressed and non-depressed individuals in blood pressure, heart rate, baroreflex sensitivity, or HRV. Consistent with prior research suggesting a relationship between depression and inflammation, depressed individuals had higher hs-CRP levels compared to their non-depressed counterparts. In addition, patients with major depressive disorder had higher pulse pressure (determined by the left ventricular ejection rate, the distensibility of large arteries, heart rate and, total peripheral vascular resistance) compared to non-depressed individuals. The lack of difference in
HRV was unanticipated given the expectation that reduced HRV should accompany both depression and inflammation. Differences in HRV between depressed and non-depressed individuals could exist but perhaps were undetected due to the small sample size.

In the same study, a 12-week treatment of selective serotonin reuptake inhibitors (SSRIs) alleviated depressive symptoms for the depressed individuals in the sample, but also potentially increased cardiac risk by reducing cardiac baroreflex sensitivity and HRV, in addition to increasing pulse pressure and hsCRP. This result was also surprising, given the expectation that reductions in depressive symptoms should be accompanied by reductions in inflammation and increased HRV. The unexpected findings could be a result of a small sample size or selection bias.

These two studies (Carney et al., 2007; Dawood et al., 2007) were limited due to small sizes (of 44 and 40 patients, respectively) which likely contributed to the lack of associations between depression, indexes of vagal control, and inflammation. Another study with a larger sample size (N = 682) also investigated the relationships among inflammatory markers, heart rate variability, and depression in a group of patients with coronary heart disease (Frasure-Smith, et al., 2009). Although there were no differences in heart rate variability between individuals with and without depression (as measured by the Beck Depression Inventory-II), elevated inflammatory markers (IL-6 and CRP) were associated with reduced measures of heart rate variability. In addition, higher levels of depressive symptomology were associated with elevated CRP, but there was no associated between depression and IL-6. A particularly notable finding in this study was that the relationship between heart rate variability and CRP was stronger among patients
with elevated depressive symptomology compared to patients without depression, providing potential support for the role of depression in the relationship between autonomic imbalance and inflammatory response.

In addition to assessing whether associations between autonomic dysfunction and inflammation are stronger in depressed versus non-depressed patients, another study also examined the extent to which autonomic nervous system dysfunction and inflammation contributed to the relationship between depression and cardiovascular mortality (Kop, et al., 2010). Analysis of 907 patients without cardiovascular disease in the Cardiovascular Health Study showed that depression was associated with lower measures of HRV indices and elevated markers of inflammation (white blood cell count and fibrinogen). HRV-based indices of autonomic dysfunction were also associated with higher levels of inflammation. Follow-up analysis of approximately 13 years showed that before and after adjusting for covariates, depression was related to increased risk of cardiovascular mortality (hazard ratio = 1.88). Inclusion of HRV and inflammatory markers in the analysis reduced the predictive value of depression by 13.9%, but depression remained an independent predictor of cardiovascular mortality. These results indicate that the relationship between depression and cardiovascular mortality may be partially explained by autonomic dysfunction and inflammation, but that much of the predictive value of depression remains unexplained by these neuroimmunological variables.

Additional studies assessing depression, inflammation, and autonomic functioning are needed to clarify these relationships, particularly given inconsistent findings across studies and the range of indices used to measure autonomic dysfunction and
inflammation. Attention should also be given to other physical and psychological characteristics that may be related to depression and contribute to autonomic balance and inflammatory processes. For example, examining the role of physical fitness may also help to determine the role of vagal functioning in the relationship between depression and inflammation.

*Exercise improves vagal control.* Improved vagal activity may help to explain how exercise and physical activity reduce depression and inflammation. As evidence by increases in HRV and improved heart rate recovery, exercise is associated with improved vagal tone, increases parasympathetic activity, and decreases in sympathetic activity (Rosenwinkel et al., 2001; Carter et al., 2003). Exercise and stress management training each reduced emotional distress and improved markers of vagal functioning (HRV and baroreflex sensitivity) compared to usual medical care alone (Blumenthal et al., 2005). High vagal modulation is associated with a greater improvement in exercise capacity in healthy sedentary populations and may help explain high HRV in trained athletes (De Meersman & Stein, 2007).

Physical activity also may protect against the decline in vagal activity associated with aging. For example, older adults who participated in a 12-month supervised exercise program had increased levels of HRV as measured by Holter monitoring compared to no changes in HRV for a matched control group not involved in the exercise program (Stein et al., 1999). Improvements in vagal modulation were also associated with intensive interval training in elderly men (Pichot et al., 2005). These findings
provide support for increasing or maintaining fitness in order to slow the decline of vagal modulation that comes with aging.

In a study of 300 patients enrolled in cardiac rehabilitation, patients with more depression symptoms on a self-report depression inventory exhibited reduced HR recovery following a ramped-protocol treadmill stress test (Hughes, et al., 2006). The relationship between depression symptoms and heart rate recovery appeared to be partly attributable to lower levels of physical fitness among more depressed patients, suggesting that fitness is involved in the relationship between depression and ANS functioning.

Therefore, physical fitness promotes vagal control, which in turn activates the cholinergic anti-inflammatory pathway. The pathway regulates inflammation by inhibiting production of pro-inflammatory cytokines. Properly regulated inflammation can limit the atherosclerotic effects that lead to cardiovascular disease. No known studies have simultaneously assessed the effect of physical fitness on depression and markers of inflammation and vagal functioning.

The Present Study

Although previous studies have investigated relationships among depression, indexes of vagal control, and inflammation, findings were somewhat inconsistent (Carney et al., 2007; Dawood et al., 2007; Frasure-Smith, et al., 2009; Kop, et al., 2010). The present study investigated these relationships in a sample of patients enrolled in cardiac rehabilitation. In addition, none of these studies included an investigation of the effect that physical fitness may play in the relationships among depression, inflammation, and vagal control. Given that exercise is associated with improvements in depression,
inflammation, and vagal control, physical fitness may play a crucial role in the interaction of these variables. In the present study, we sought to include physical fitness as a factor in evaluating the relationship between depression and inflammation.

Two of our previous studies demonstrated that depression is related to reduced autonomic nervous system activity (as measured by HRV and heart rate recovery), but that physical fitness attenuates this relationship (Hughes et al., 2006; Hughes et al., 2008). With vagal functioning influencing the inhibition of inflammation through the cholinergic anti-inflammatory pathway, altered autonomic nervous system functioning is related to increased levels of inflammation. Therefore, we expected that physical fitness would also attenuate the relationship between depression and inflammation. We hypothesized that physical fitness would account for much of the variance in the depression-inflammation relationship. We expected elevated levels of depressive symptomology would be related to reductions in physical fitness and vagal control, and subsequent elevations in inflammation. The primary purpose of the present study was to examine if physical fitness, through improved vagal control, attenuated the relationship between depression and inflammation in cardiac rehabilitation patients (Figure 1).
Hypotheses

**Aim 1.** The first aim of the present study was to examine the association between depression and inflammation in cardiac rehabilitation patients with coronary artery disease or coronary heart disease.

_Hypothesis 1:_ Depression would be positively associated with higher stimulated production of inflammatory cytokines IL-6 and TNF-α. In other words, higher levels of depressive symptomology would be related to higher stimulated production of inflammatory markers.
Hypothesis 2: Patients with a current or past diagnosis of depression would have higher stimulated production of inflammatory markers compared to non-depressed patients. Prior studies have shown that inflammatory markers were significantly elevated in individuals with a history of major depression, indicating that proinflammatory states may be related to past, as well as current diagnosis of depression (Kling et al., 2007).

Aim 2. The second, and central, aim of the present study was to examine physical fitness as a mediator of depression and inflammation when examined in conjunction with heart rate recovery.

Hypothesis 3. In order to support the multiple mediator model and consistent with prior research, it was hypothesized that depression would be related to lower levels of physical fitness, depression would be related to reduced heart rate recovery, and physical fitness would be positively correlated with heart rate recovery (Ruo et al., 2004; Hughes et al., 2006).

Hypothesis 4. Physical fitness would be inversely related to stimulated production of inflammatory markers IL-6 and TNF-α. Lower levels of physical fitness would be related to higher production of inflammatory cytokines.

Hypothesis 5. Physical fitness would mediate the relationship between depression and inflammation. It was expected that even after controlling for heart rate recovery, physical fitness would account for a significant amount of variance in the relationship between depression and inflammation. The relationship between depression and inflammation would be reduced when physical activity was included.
METHOD

Participants

Participants were 96 patients enrolled in Summa Health System’s phase II cardiac rehabilitation program at Akron City Hospital between August 2009 and August 2010. Patients were recruited for the study during their intake visit or within their first week of classes at cardiac rehabilitation. Demographic and medical characteristics can be found in Table 1. The patient sample was 70% men, 90% Caucasian, and range in age from 28-98 years old. Participants were predominantly white (90), with far fewer reporting their race to be black (5), and “Alaska native/American Indian” (1).

In order to expand on prior studies assessing the relationships among depression (Carney et al., 2007; Dawood et al., 2007; Frasure-Smith, et al., 2009; Kop, et al., 2010), vagal functioning, and inflammation in cardiac patients, the present study compared depressed and non-depressed patients with coronary heart disease on indices of inflammation and vagal control. Patients included in the study were diagnosed with coronary heart disease or coronary artery disease. Patients treated for these conditions with coronary bypass graft surgery or percutaneous coronary intervention were included, as well as patients that have diagnoses subsumed under these conditions (e.g. myocardial infarction, angina).

The present study focused on depression in post-myocardial infarction and coronary artery disease patients, consistent with patient samples in previous research (Carney et al., 1988; Frasure-Smith et al., 1993; Frasure-Smith et al., 1995; Frasure-Smith et al., 1999; Lesperance et al., 2002; van Melle et al., 2004). Patients with
diagnoses hierarchically above coronary artery disease or coronary heart disease were excluded. For example, patients with heart failure, which is often considered the “endpoint” of many types of cardiovascular disease, were excluded. In addition, patients with myocardial infarction within the previous 48 hours were excluded.

Patients who did not complete the Beck Depression Inventory (BDI) or who did not complete an exercise stress test were excluded from hypothesis testing. Three patients did not complete the BDI, but all patients completed a diagnostic interview assessing depression. Five patients did not complete or produce valid results for exercise stress testing.

Procedure

Prior to the beginning of data collection, the protocol of this study was approved by both the Kent State University and SUMMA Health System institutional review boards (IRBs).

The cardiac rehabilitation program at Summa Health System’s Akron City Hospital enrolls over 400 patients in cardiac rehabilitation each year. The phase II outpatient EKG-monitored exercise and education program was designed to help cardiac patients with recuperation and also to allow patients to develop a personal heart disease prevention program. The program has attained national certification by the AACVPR through adherence to and documentation of a high level of clinical standards of patient care (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004) and was most recently recertified in August 2006. As of 1997, Medicare provided coverage for cardiac rehabilitation for patients who have had a documented diagnosis of acute MI
within the preceding 12 months, have had coronary bypass surgery, or have stable angina pectoris and are considered to have a medical need for cardiac rehabilitation (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004).

Patients were recruited during their intake visit at cardiac rehabilitation and participated in the research protocol during their two weeks of cardiac rehabilitation. An intake appointment, conducted by a case manager (registered nurse or exercise physiologist), included an exercise stress test, cognitive functioning assessment, and completion of psychosocial, daily functioning, and cognitive questionnaires by the patient. Physicians occasionally waived an entry stress test for patients who had orthopedic or other limitations, but approximately 87% of patients participate in a treadmill exercise stress test before starting cardiac rehab.

Participants who enrolled in the study signed a consent form agreeing to take part in a larger study entitled IGNITE Rehab (Integrating Growth, Neurocognitive, and Inflammation research To Enhance Rehabilitation) assessing the effects of psychosocial factors, physical functioning, and cognitive abilities on inflammation in cardiac rehabilitation patients. For the purposes of the present study, participants agreed to take part in a clinical diagnostic interview and blood draw, complete questionnaire packets, and granted the researchers permission to gather information from medical records and treadmill exercise stress test data. Participants received monetary compensation for participation. Resting heart rate, maximum heart rate during exercise, exercise capacity, and heart rate recovery at two minutes after peak exercise were obtained from a ramped-protocol treadmill exercise stress test. The patients participated in a clinical diagnostic
interview and blood draw prior to participating in their regularly scheduled cardiac rehabilitation session. The clinical diagnostic interview took place before the blood draw, allowing the patient to be seated for a minimum of 20 minutes prior to the blood draw ensuring a resting blood draw. However, data on patient’s most recent exercise or physical activity was not gathered.

Medical chart review was conducted to obtain patient diagnoses, medical history, and medications. Medications were classified into the following categories: beta-blockers, alpha-blockers, diuretics, statins, anti-anxieties, anti-depressants, anti-coagulants, ACE inhibitors, ASAs, and NSAIDS.

**Measures**

*Depression.* The Beck Depression Inventory (BDI) (Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961) was used to assess depressive symptomatology during the previous two weeks. Each of the twenty-one items on the BDI consisted of four statements representing increasing degrees of severity with scores ranging from 0 to 3. The total score on the BDI can range from zero (no depression) to a maximum score of 63 (severe state of depression). Patients with a BDI score of 10 or greater were considered to show at least mild to moderate symptoms of depression. Using a cutoff score of 10, the BDI has a sensitivity of 82% and specificity for 79% for diagnosing major depression in patients diagnosed with MI (Strik et al., 2001).

The BDI included cognitive-affective and somatic symptom items. The cognitive-affective items consisted of questions assessing sadness, hopelessness about the future, feelings of failure and punishment, satisfaction and enjoyment in pleasurable
activities, irritability, decision making, guilt, disappointment, suicidal thoughts. The somatic items of the measure assessed physical and somatic symptoms, such as sleep, fatigue, appetite, weight, worries about health problems, and interest in sex.

Patients enrolled in Summa Health System’s cardiac rehabilitation program completed the BDI upon entry to the program and prior to discharge. Cardiac rehabilitation staff members notified the primary care or the referring physician of potential depression by attaching a note to the patient’s entry report for patients with BDI scores of 19-29, indicating moderate to severe depression. Cardiac rehabilitation case managers immediately telephoned the primary care or referring physician for patients with scores of 30-63, indicative of severe depression, or for patients who respond positively to an item indicating suicidal ideation or intent.

Depression was also assessed in the present study with the mood module of the Structured Clinical Interview for DSM-IV (SCID). The SCID is a semistuctured interview for making the major DSM-IV Axis I diagnoses. The mood module included assessment of current and past history of depression, dysthymia, and bipolar disorders. For purposes of the proposed study, patients with a diagnosis of current or history of Major Depressive Disorder or Dysthymic Disorder were considered depressed. Prior studies have shown that inflammatory markers were significantly elevated in individuals with a history of major depression, indicating that proinflammatory states may be related to past, as well as current diagnosis of depression (Kling et al., 2007). The SCID has high reliability for Major Depressive Disorder (Kappa = .80) and Dysthymic Disorder (Kappa = .76) (Zanarini, et al., 2000). Whereas the BDI consisted of a continuous
variable indicating level of depressive symptomology, the SCID provided a categorical variable indicating the absence or presence of depression. For data analysis, depression was used as a continuous variable as indicated by the total BDI score. Depression was used as a categorical variable for illustrative purposes to show differences between patients who qualified for a depressive disorder based on the SCID.

**Exercise stress testing.** Resting heart rate, maximum heart rate, exercise capacity, and heart rate recovery scores for each patient were recorded from a treadmill exercise test. The treadmill exercise test was conducted according to a modified ramp protocol using a Quinton Medtrack ST55 treadmill (Quinton Cardiology, Deerfield, WI). The test was terminated at the patient’s request, or if the patient showed clinical signs of ischemia, malignant arrhythmias, severe hypertension (SBP > 240) or hypotension (20 mm Hg decrease in SBP). The electrocardiogram (ECG) was continuously recorded from rest until 6 minutes following the cessation of exercise using a Burdick ECG management system (Quinton Cardiology, Deerfield, WI). A standard 12-lead ECG was used to measure heart rate at rest before the initiation of exercise, at each exercise stage, at maximum peak of exercise (the point of exercise termination), within one minute following termination, and at two minutes, four minutes, and six minutes following termination.

**Physical fitness.** Exercise capacity was used as an indicator of physical fitness. Exercise capacity was estimated at the time point that maximum heart rate was attained in metabolic equivalents (METS) according to the American College of Sports Medicine's Guidelines for Exercise Testing (American College of Sports Medicine, 2000b). METS
is a multiple of oxygen consumption at rest, such that 1 MET equals 3.5ml/kg/min, which is the amount of oxygen that a person needs at rest (Pollock & Schmidt, 1995). For example, 13 METS as a result of an exercise test meant that the patient is estimated to exceed his resting oxygen consumption by a multiplier of 13. A person's maximal MET value equals his/her maximal oxygen consumption in ml (ml/kg/min) (American College of Sports Medicine, 2000a). Prior studies estimating exercise capacity using METS in patients with cardiovascular disease averaged ranges of between 6 and 7 METS (Ruo et al., 2004; Hughes et al., 2006; Myers et al., 2002) and categorized patients into having poor exercise capacity (METS < 5) and normal exercise capacity (METS ≥ 5) (Ruo et al., 2004). Estimated METS is a widely used measure of physical fitness and frequently coincides with typical activities that are measured by the number of METS required. For example, light physical activity is less than three METS (slow walking, light stretching), moderate physical activity requires anywhere from three to six METS (brisk walking, cycling), and greater than six METS would include vigorous physical activities such as running in healthy individuals. A previous study showed that individuals with METS below five had twice the risk of mortality compared to individuals with METS above eight in samples of patient with cardiovascular disease and healthy subjects (Myers et al., 2002).

Heart rate recovery. Heart rate recovery, a measure of vagal control, was defined as the difference in heart rate from maximum heart rate (heart rate at exercise termination) to heart rate two minutes later (Cole et al., 2000; Lipinski et al., 2004). All heart rate values were verified by reading the EKG strips. Based on previous treadmill
exercise stress tests at the same site, test-retest reliability ranged from .93 to .99 for resting, maximum, and 2 minute recovery heart rate and inter-scorer reliability ranged from .97 to .99 for resting, maximum, and 2 minute recovery heart rate.

*Resting heart rate.* Resting heart rate prior to the treadmill exercise stress test was also assessed. Reduced resting heart rate is an indicator of altered autonomic nervous system functioning and found among depressed cardiac patients (Carney et al., 1999). Reduced resting heart rate was also associated with increased risk of mortality among coronary heart disease patients in prior research (Dyer et al., 1980).

*Inflammation.* Inflammation was assessed through blood draws conducted by the blood laboratory at Summa Health System. The blood draws took place prior to exercise sessions to ensure that measures of inflammation were unaffected by recent physical activity. Participants were asked not to exercise before the blood draw, but extent of physical activity prior to blood draw was not recorded. Patients were allowed to eat prior to blood draw.

Whole blood stimulation assay was utilized as described by Marsland et al. (2007) to determine IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, INF gamma, TNF-α, and P-selectin. For each participant a 4cc blood sample was collected in citrate-treated vacutainer tubes. The whole blood was stimulated with Lipopolysaccharide and incubated at 37 degrees Celsius with 5% CO₂ humidified atmosphere for 24 hours. Parallel comparison tubes without Lipopolysaccharide treatment were used to control for spontaneous production of cytokines. The tubes were then centrifuged for 10 minutes. To avoid variation of assay conditions, all supernatants were collected, stored, and frozen at -80 degrees Celsius until
the study was complete. Upon study completion, plasma was analyzed through the use of the multiplex analysis system. Stimulated production of cytokines were determined using Luminex (Luminex Corporation, Austin, TX). Samples were assayed in duplicate and levels of stimulated cytokine production were derived from a standard curve.

The inflammatory markers assessed included IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, INF gamma, TNF-α, and P-selectin. IL-6 and TNF-α were used for the purposes of the present study. These specific inflammatory markers were selected based on findings from previous studies linking these inflammatory markers with depression (Parissis et al., 2004; Anisman et al., 2005; Dantzer, 2001; Miller et al., 2005a; Grippo et al., 2003; Grippo et al., 2005). IL-6 (interleukin-6) is a lymphokine produced by T cells, fibroblasts, macrophages, and various other cells. One of its main functions is synthesizing plasma proteins. IL-6 was previously proposed to be one of the major cytokines related to psychosocial factors and increased risk of cardiovascular disease (Sjogren et al., 2006; Suarez, 2003). TNF-α (tumor necrosis factor-alpha) is a pro-inflammatory cytokine that helps to stimulate the acute phase reaction. Prior research showed that TNF-α was associated with a three-fold risk of recurrent cardiovascular events (Ridker et al., 2000b) and higher levels of depression in healthy men (Suarez et al., 2003).

**Sociodemographics.** Five demographic characteristics were assessed: age, gender, race, education level, and employment status. Psychosocial covariates examined included: age, gender, race, education level, employment status, and marital status. Age was recorded at the date of intake and was represented as a continuous variable. Gender
consisted of two categories: male and female. *Race* included the categories of non-Hispanic White, African-American, Asian, Native Hawaiian or Pacific Islander, Native American or Alaska Native, and Hispanic. *Education level* was based on the number of completed years of formal education and was represented as a continuous variable.

*Employment status* consisted of two categories: employed and retired/not employed.

*Marital status* consisted of four categories: married, divorced, widowed, unmarried.

**Medical characteristics.** Additional medical characteristics relevant to the patient’s condition were gathered from intake appointment data including weight, body mass index, diagnosis, medications, and other risk factor information. *Weight* was a continuous variable measured by balance scale in pounds. *Body mass index* (BMI) was a continuous variable calculated from the patient’s height and weight (BMI = (Weight in Pounds / (Height in inches)^2) x 703). *Diagnosis* was categorized into the six following categories: coronary artery bypass grafting (CABG), myocardial infarction (MI) & percutaneous coronary intervention (PCI), PCI, MI, angina, and other. The diagnosis list was hierarchical, as the diagnoses listed first included patients with that diagnosis and possibly one or more of the subsequent diagnoses. Additional medical conditions that might be related to inflammation were also assessed, including fibromyalgia, hay fever, kidney disease/dysfunction, rheumatoid arthritis, osteoarthritis, tendonitis or bursitis, and other related medical conditions.

*Medication* was represented by nine classes: beta-blockers, alpha-blockers, diuretics, statins, selective serotonin reuptake inhibitor (SSRI), anti-anxiety medication, other anti-depressants, anti-coagulants, and anti-arrhythmias. Patients were coded as
taking or not currently taking medications in each of the nine classes at the time of intake. If covariates are significantly correlated with the variables of interest (depression, inflammation, physical fitness, heart rate recovery) they were included in subsequent analyses.

Analytic strategy

Initial Analysis. Descriptive analyses (frequencies and percentages, means and standard deviations) were used to assess the characteristics of the total sample, depressed, and non-depressed patients. Values of stimulated production of inflammatory markers were log normal (base e) transformed before analysis to better approximate normal distributions.

Bivariate correlations were conducted to assess the relationship among the study variables. Specifically, higher scores on the BDI were expected to be positively correlated with stimulated production of inflammatory markers and negatively correlated with physical fitness, heart rate recovery, and resting heart rate. Independent sample t-tests were used to compare depressed and non-depressed patients (as based on the diagnostic interview) on stimulated production of inflammatory markers, physical fitness, heart rate recovery, resting heart rate, and covariates.

Mediation. In order to determine if physical fitness attenuates the relationship between levels of depression (as a continuous variable) and inflammation, a mediational model will be used. Multiple linear regression analyses were conducted to determine the statistical associations among BDI scores, stimulated production of inflammatory
markers, and physical fitness. All variables must be statistically associated with the other variables in order to test for mediation (Baron & Kenny, 1986).

To determine whether physical fitness mediated the relationship between depression and inflammation a series of regression analyses were performed according to the method outlined by Baron and Kenny (1986). These analyses required estimating the following three regression equations (i) regressing the mediator variable (physical fitness) on the independent variable (depression); (ii) regressing the dependent variable (inflammation) on the independent variable (depression); and (iii) regressing the dependent variable (inflammation) on both the independent variable (depression) and the mediator variable (physical fitness). To establish mediation the following conditions were needed: 1) the independent variable (depression) must correlate significantly with the mediator variable (physical fitness); 2) the mediator variable (physical fitness) must correlate significantly with the dependent variable (inflammation); and 3) when the effects of the mediator (physical fitness) are controlled for, a previously significant correlation between the independent variable (depression) and dependent variable (inflammation) is greatly attenuated (Baron & Kenny, 1986).

The Sobel test could have been conducted in conjunction with all meditational tests to determine if the change in relationship between depression and inflammation was significantly different when the effect of the mediator was included (MacKinnon et al., 1995). The Sobel test uses unstandardized coefficients and standard errors of the independent variable-mediator and the mediator-dependent variable relationships to determine statistical significance.
In addition to assessing physical fitness as mediator, heart rate recovery was also assessed simultaneously as a mediator in order to assess for the mediating role of reduced autonomic functioning. Preacher and Hayes (2008) proposed that simultaneous multiple mediation should be conducted to determine if an overall effect exists for all mediators (indirect effect of both physical fitness and heart rate recovery combined) and the effect of each mediator (specific indirect effect of physical fitness and specific indirect effect of heart rate recovery). In accordance with recommendations from Preacher and Hayes (2008) the multiple mediation analysis included two parts: (1) investigation of the total indirect mediation effect of the set of mediators (physical fitness and heart rate recovery) on the effect of depression to inflammation; and (2) testing hypotheses regarding individual mediators in the context of a multiple mediator model (specific indirect effects of physical activity and heart rate recovery in the context of the other mediator included). Therefore, the unique effects of physical fitness when controlling for heart rate recovery were determined.

Using the meditational model allowed for the identification of potential mechanisms (i.e. physical fitness; heart rate recovery) to explain the relationship between depression and inflammation. However, it should be noted that due to the cross-sectional nature of this study, temporal precedence could not be established among the variables and true mediation cannot be determined. However, examining the relationships among depression, inflammation, and physical activity can lay the groundwork for a future prospective examination with assessments at multiple time points in which true mediation can be examined.
RESULTS

Description of the sample

The sample included 96 patients (71 men and 25 women) who enrolled in CR between August 2009 and August 2010.

Depression. Patients were divided into “depressed” (N = 19, 19.8%) and “non-depressed” (N = 77, 80.2%) categories according to their clinical diagnostic interviews. Among the “depressed” group, patient diagnoses included Major Depressive Disorder single episode (N = 6, 6.3%), Major Depressive Disorder recurrent (N = 9, 9.4%), and Major Depressive Disorder in remission (N = 4, 4.2%). BDI scores ranged from 0 – 34 with an average of 6.3 ± 6.5.

As shown in Table 1, patients with a depression diagnosis had significantly greater BDI scores (M = 12.8, SD = 9.2) compared to patients without a depression diagnosis (M = 4.5, SD = 4.1), t (91) = -5.78, p < .01, indicating that on average patients with a depression diagnosis according to the clinical interview reported higher levels of depressive symptoms compared to those without a diagnosis of depression.

Three patients did not complete the BDI, but participated in the clinical interview. Two patients without the BDI were diagnosed with Major Depressive Disorder single episode and one had no depression diagnosis.

Notable differences between depressed and non-depressed patients from treadmill stress testing are also shown in Table 1. Estimated exercise capacity (METS) ranged from 3 to 17.5 (M = 8.4, SD = 3.6). Heart rate at rest ranged from 46 beats per minute to 101 beats per minute (M = 8.4, SD = 3.6), whereas maximum heart rate ranged
from 74 beats per minute to 171 beats per minute ($M = 125.2, SD = 22.9$). Heart rate recovery at 2 minutes following maximum heart rate averaged 36.4 ($SD = 13.7$).

Patients diagnosed with depression during the clinical interview differed from patients without depression in physical fitness and maximum heart rate. Patients without depression ($M = 8.8, SD = 3.7$) had significantly higher estimated exercise capacity (as measured in METS) compared to patients with depression ($M = 6.9, SD = 3.0$), $t (90) = 2.0, p < .05$, indicating that patients without depression were more physically fit than patients with depression. Patients without depression ($M = 128, SD = 23$) had significantly higher maximum heart rate on the treadmill exercise stress test compared to patients with depression ($M = 116, SD = 19$), $t (90) = 2.0, p < .01$, which is another possible indicator of greater fitness in non-depressed patients. However, there was no significant difference between depressed and non-depressed patients in resting heart rate.
Table 1. *Clinical and Demographic Characteristics of All, Depressed, and Non-Depressed Patients based on SCID Diagnosis*

Values represent the mean ± 1 S.D.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>96</td>
<td>19</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62±10</td>
<td>58±10</td>
<td>63±10</td>
<td>.08</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>71%</td>
<td>73%</td>
<td>74%</td>
<td>.97</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>90%</td>
<td>96%</td>
<td>84%</td>
<td>.06</td>
</tr>
<tr>
<td>Employed (% employed)</td>
<td>51%</td>
<td>40%</td>
<td>47%</td>
<td>.58</td>
</tr>
<tr>
<td>Education</td>
<td>14.1±2.5</td>
<td>14.4±2.4</td>
<td>14.1±2.5</td>
<td>.60</td>
</tr>
<tr>
<td>BDI</td>
<td>6.3±6.5</td>
<td>12.8±9.2</td>
<td>4.5±4.1</td>
<td>.00</td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td>211±47</td>
<td>235.6±41.8</td>
<td>201.3±41.7</td>
<td>.00</td>
</tr>
<tr>
<td>Body mass index</td>
<td>32±6</td>
<td>35.1±6.7</td>
<td>30.6±6.0</td>
<td>.00</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>124±17</td>
<td>124±19</td>
<td>124±15</td>
<td>.84</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>71±11</td>
<td>70±10</td>
<td>71±11</td>
<td>.89</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>8.4±3.6</td>
<td>6.9±3.0</td>
<td>8.8±3.7</td>
<td>.04</td>
</tr>
<tr>
<td>Resting heart rate (N = 91)</td>
<td>69.5±12.2</td>
<td>66±9</td>
<td>70±13</td>
<td>.17</td>
</tr>
<tr>
<td>Maximum heart rate (N = 91)</td>
<td>125.2±22.9</td>
<td>116±19</td>
<td>128±23</td>
<td>.04</td>
</tr>
<tr>
<td>Heart rate recovery (N = 91)</td>
<td>36.4±13.8</td>
<td>35.4±12.5</td>
<td>36.8±14.1</td>
<td>.70</td>
</tr>
</tbody>
</table>
Patients’ cardiovascular diagnoses were also recorded. As shown in Table 2, the most common cardiovascular diagnosis was percutaneous coronary intervention (PCI), which constituted 64% of the overall sample. Patients diagnosed with depression during the clinical interview did not significantly differ in cardiovascular diagnosis from patients without a depression diagnosis.

Table 2. Cardiovascular Diagnoses of All, Depressed, and Non-Depressed Patients based on SCID Diagnosis

<table>
<thead>
<tr>
<th>Cardiovascular Diagnoses</th>
<th>All Patients</th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
<td>.84</td>
</tr>
<tr>
<td>MI &amp; PCI</td>
<td>22%</td>
<td>16%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>64%</td>
<td>68%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>8%</td>
<td>11%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>2%</td>
<td>0%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

*Note:* The diagnosis list is hierarchical, as the diagnoses listed first include patients with that diagnosis and one of the subsequent diagnoses.

Other medical diagnoses that could potentially affect inflammation were also compared between depressed and non-depressed patients. Patients diagnosed with depression did not significantly differ from those without a depression diagnosis in these medical conditions, as listed in Table 3. Although the difference was not statistically significant, 16% of depressed patients were also diagnosed with rheumatoid arthritis, compared to only 5% of non-depressed patients with rheumatoid arthritis.

Table 3. *Other Medical Diagnoses of All, Depressed, and Non-Depressed Patients based on SCID Diagnosis*

<table>
<thead>
<tr>
<th>Other Medical Diagnoses</th>
<th>All Patients</th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>p   value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>.99</td>
</tr>
<tr>
<td>Hay Fever</td>
<td>15%</td>
<td>11%</td>
<td>17%</td>
<td>.49</td>
</tr>
<tr>
<td>Kidney Disease/Dysfunction</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
<td>.38</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>7%</td>
<td>16%</td>
<td>5%</td>
<td>.11</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>11%</td>
<td>11%</td>
<td>10%</td>
<td>.99</td>
</tr>
<tr>
<td>Tendonitis/Bursitis</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>.99</td>
</tr>
<tr>
<td>Other</td>
<td>51%</td>
<td>37%</td>
<td>51%</td>
<td>.28</td>
</tr>
</tbody>
</table>

As shown in Table 4, there was a significant difference in the percentage of depressed patients taking antidepressants (42%) compared to patients with depression
taking antidepressants (10%). There were no other statistically significant differences in medications between depressed and non-depressed patients.

Table 4. Medications of All, Depressed, and Non-Depressed Patients based on SCID Diagnosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>All Patients</th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>85%</td>
<td>95%</td>
<td>83%</td>
<td>.19</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>27%</td>
<td>26%</td>
<td>27%</td>
<td>.93</td>
</tr>
<tr>
<td>Diuretics</td>
<td>29%</td>
<td>37%</td>
<td>27%</td>
<td>.41</td>
</tr>
<tr>
<td>Statins</td>
<td>94%</td>
<td>95%</td>
<td>94%</td>
<td>.84</td>
</tr>
<tr>
<td>Anti-depressants/SSRI</td>
<td>17%</td>
<td>42%</td>
<td>10%</td>
<td>.00</td>
</tr>
<tr>
<td>Anti-anxieties</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>.62</td>
</tr>
<tr>
<td>Anti-coagulants</td>
<td>79%</td>
<td>90%</td>
<td>77%</td>
<td>.22</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>76%</td>
<td>90%</td>
<td>73%</td>
<td>.13</td>
</tr>
<tr>
<td>ASA</td>
<td>91%</td>
<td>100%</td>
<td>88%</td>
<td>.12</td>
</tr>
<tr>
<td>NSAID</td>
<td>6%</td>
<td>16%</td>
<td>4%</td>
<td>.06</td>
</tr>
</tbody>
</table>

Table 5 summarizes untransformed minimum and maximum values as well as the means and standard deviations of stimulated and unstimulated inflammatory markers assessed for the more expansive study. The control (unstimulated) and LPS (stimulated) values are listed for each cytokine. The final stimulated production value for each inflammatory cytokine for each patient was derived by the control value subtracted from the LPS value. The inflammatory cytokines of interest for this specific study were IL-6 ($M = 53,404.27$, $SD = 36,143.98$) and TNF-α ($M = 13,941.54$, $SD = 8,669.59$).

Table 5. Untransformed Values for Inflammatory Cytokines

Values reported as pg/ml

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>96</td>
<td>.00</td>
<td>260.94</td>
<td>79.18</td>
<td>63.62</td>
</tr>
<tr>
<td>IL-2ctl</td>
<td>96</td>
<td>.00</td>
<td>79.88</td>
<td>5.71</td>
<td>11.68</td>
</tr>
<tr>
<td>IL-2LPS</td>
<td>96</td>
<td>.00</td>
<td>340.82</td>
<td>84.87</td>
<td>66.63</td>
</tr>
<tr>
<td>IL-4</td>
<td>96</td>
<td>.14</td>
<td>192.27</td>
<td>46.67</td>
<td>38.59</td>
</tr>
<tr>
<td>IL-4ctl</td>
<td>96</td>
<td>.00</td>
<td>91.34</td>
<td>8.07</td>
<td>53.69</td>
</tr>
<tr>
<td>IL-4LPS</td>
<td>95</td>
<td>10.53</td>
<td>219.25</td>
<td>54.25</td>
<td>43.69</td>
</tr>
<tr>
<td>IL-6</td>
<td>96</td>
<td>4.30</td>
<td>143059.40</td>
<td>53404.23</td>
<td>36143.98</td>
</tr>
<tr>
<td>IL-6ctl</td>
<td>96</td>
<td>.00</td>
<td>109850.16</td>
<td>1521.19</td>
<td>11202.23</td>
</tr>
<tr>
<td>IL-6LPS</td>
<td>85</td>
<td>14.06</td>
<td>143217.14</td>
<td>49402.30</td>
<td>35388.17</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>--------</td>
<td>----</td>
<td>---------</td>
<td>-----------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>IL-8</td>
<td>96</td>
<td>0.00</td>
<td>113034.95</td>
<td>57128.61</td>
<td>37133.22</td>
</tr>
<tr>
<td>IL-8ctl</td>
<td>96</td>
<td>0.00</td>
<td>60059.05</td>
<td>8258.81</td>
<td>10800.27</td>
</tr>
<tr>
<td>IL-8LPS</td>
<td>67</td>
<td>55.42</td>
<td>116261.27</td>
<td>48953.76</td>
<td>42228.41</td>
</tr>
<tr>
<td>IL-10</td>
<td>96</td>
<td>82.57</td>
<td>4235.24</td>
<td>1385.58</td>
<td>848.91</td>
</tr>
<tr>
<td>IL-10ctl</td>
<td>96</td>
<td>0.00</td>
<td>881.28</td>
<td>43.77</td>
<td>103.21</td>
</tr>
<tr>
<td>IL-10LPS</td>
<td>96</td>
<td>102.87</td>
<td>4333.76</td>
<td>1426.61</td>
<td>849.02</td>
</tr>
<tr>
<td>GCMSF</td>
<td>96</td>
<td>0.00</td>
<td>26369.22</td>
<td>4223.33</td>
<td>6714.64</td>
</tr>
<tr>
<td>GCMSFctl</td>
<td>96</td>
<td>0.00</td>
<td>1574.72</td>
<td>141.59</td>
<td>209.94</td>
</tr>
<tr>
<td>GCMSFLPS</td>
<td>96</td>
<td>41.87</td>
<td>26391.60</td>
<td>4272.68</td>
<td>6604.15</td>
</tr>
<tr>
<td>IFN</td>
<td>96</td>
<td>0.00</td>
<td>39763.90</td>
<td>5455.71</td>
<td>7912.68</td>
</tr>
<tr>
<td>IFNctl</td>
<td>96</td>
<td>0.00</td>
<td>32434.75</td>
<td>1004.25</td>
<td>3933.08</td>
</tr>
<tr>
<td>IFNLP</td>
<td>96</td>
<td>172.70</td>
<td>56840.39</td>
<td>6185.13</td>
<td>9496.18</td>
</tr>
<tr>
<td>TNF</td>
<td>96</td>
<td>1096.63</td>
<td>52488.37</td>
<td>13941.54</td>
<td>8669.59</td>
</tr>
<tr>
<td>TNFctl</td>
<td>96</td>
<td>0.00</td>
<td>6228.96</td>
<td>276.79</td>
<td>816.84</td>
</tr>
<tr>
<td>TNFLPS</td>
<td>94</td>
<td>1283.34</td>
<td>52570.12</td>
<td>14143.39</td>
<td>9134.32</td>
</tr>
<tr>
<td>P-selectin</td>
<td>94</td>
<td>.53</td>
<td>20.57</td>
<td>5.72</td>
<td>4.89</td>
</tr>
</tbody>
</table>
After being log normal (base e) transformed to better approximate normal distributions, the final stimulated production values were used and are reported throughout analysis of the results of the present study. Table 6 shows the log transformed means for all inflammatory cytokines assessed. Additional analysis was based on log transformed values of stimulated production of cytokines for IL-6 ($M = 10.29$, $SD = 1.72$) and TNF-α ($M = 9.32$, $SD = .74$).

Table 6. Log Transformed Values for Stimulated Inflammatory Cytokines

Values reported as pg/ml

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>96</td>
<td>.00</td>
<td>5.57</td>
<td>3.74</td>
<td>1.49</td>
</tr>
<tr>
<td>IL-4</td>
<td>96</td>
<td>-1.97</td>
<td>5.26</td>
<td>3.51</td>
<td>.95</td>
</tr>
<tr>
<td>IL-6</td>
<td>96</td>
<td>1.46</td>
<td>11.87</td>
<td>10.29</td>
<td>1.72</td>
</tr>
<tr>
<td>IL-8</td>
<td>96</td>
<td>.00</td>
<td>11.64</td>
<td>10.35</td>
<td>1.70</td>
</tr>
<tr>
<td>IL-10</td>
<td>96</td>
<td>4.41</td>
<td>8.35</td>
<td>7.02</td>
<td>.74</td>
</tr>
<tr>
<td>GCMSF</td>
<td>96</td>
<td>1.24</td>
<td>10.18</td>
<td>6.33</td>
<td>2.29</td>
</tr>
<tr>
<td>IFN</td>
<td>96</td>
<td>.00</td>
<td>10.59</td>
<td>7.71</td>
<td>1.55</td>
</tr>
<tr>
<td>TNF</td>
<td>96</td>
<td>7.00</td>
<td>10.87</td>
<td>9.32</td>
<td>.74</td>
</tr>
<tr>
<td>P-selectin</td>
<td>94</td>
<td>-.63</td>
<td>3.02</td>
<td>1.36</td>
<td>.92</td>
</tr>
</tbody>
</table>
Depression and inflammation

The first aim of the present study was to examine the association between depression and inflammation in cardiac rehabilitation patients with coronary artery disease or coronary heart disease.

Hypothesis 1 & 2. Contrary to expectations, depression was not positively associated with higher stimulated production of inflammatory markers IL-6 and TNF-α. Table 7 summarizes correlations among BDI scores, exercise capacity in METS, heart rate variables, and stimulated production of inflammatory cytokines. As shown in Table 7, initial bivariate correlational analysis showed that depressive symptomology as assessed by the BDI was not significantly related to stimulated production levels of IL-6 ($r = .04$, $p = .72$) or TNF-α ($r = -.01$, $p = .35$). However, BDI scores were significantly negatively correlated with exercise capacity as measured in METS ($r = -.27$, $p < .05$), indicating that higher levels of depressive symptomology were associated with reduced physical fitness.
Table 7. *Beck Depression Inventory (BDI)* score, *Exercise Capacity (METS)*, *Resting Heart Rate (HR)*, *Maximum HR*, *HR Recovery (HRR)*, *IL-6*, and *TNF-α*: Correlations and Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>BDI</th>
<th>METS</th>
<th>Resting HR</th>
<th>Maximum HR</th>
<th>HR Recovery</th>
<th>IL-6</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>93</td>
<td>91</td>
<td>91</td>
<td>91</td>
<td>91</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>BDI (N = 93)</td>
<td>-</td>
<td>-.27*</td>
<td>.01</td>
<td>.02</td>
<td>.08</td>
<td>.04</td>
<td>-.01</td>
</tr>
<tr>
<td>METS (N = 91)</td>
<td>-</td>
<td>-.14</td>
<td>.55**</td>
<td>.53**</td>
<td>.07</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Resting HR (N = 91)</td>
<td>-</td>
<td>.40**</td>
<td>-.18</td>
<td>-.07</td>
<td>-.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum HR (N = 91)</td>
<td>-</td>
<td></td>
<td>.63**</td>
<td>.09</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Recovery (N = 91)</td>
<td>-</td>
<td></td>
<td></td>
<td>.09</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (N = 96)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>6.30</td>
<td>8.36</td>
<td>69.52</td>
<td>125.21</td>
<td>36.4</td>
<td>10.29</td>
<td>9.32</td>
</tr>
<tr>
<td>SD</td>
<td>6.53</td>
<td>3.64</td>
<td>12.16</td>
<td>22.93</td>
<td>13.77</td>
<td>1.72</td>
<td>.74</td>
</tr>
<tr>
<td>Range</td>
<td>0 – 42</td>
<td>3 – 17.5</td>
<td>46 – 101</td>
<td>74 – 171</td>
<td>0 – 80</td>
<td>1.46 – 7.00</td>
<td>11.87</td>
</tr>
</tbody>
</table>

* *p < .05. **p < .01.

**Note:** Abbreviations: METS: metabolic equivalents. *M*: mean. *SD*: 1 standard deviation.

IL-6 and TNF-α are log transformed.
Likewise, patients with a depression diagnosis based on the SCID did not differ in stimulated production levels of IL-6 or TNF-\(\alpha\) (*Hypothesis 2*). There was no statistically significant difference in stimulated IL-6 between patients diagnosed with current or past history of depression \(M = 10.56 \pm 1.04\) and no depression \(M = 10.22, SD = 1.85\), t(94) = -.753, \(p > .05\). There was also no statistically significant difference in stimulated TNF-\(\alpha\) between patients diagnosed with current or past history of depression \(M = 9.26, SD = .71\) and no depression \(M = 9.34, SD = 9.74\), t(94) = .389, \(p > .05\).

Table 8 shows comparisons of patients with depression diagnosis and patients with no depression diagnosis on all measured cytokines for the more expansive study. None of the cytokines assessed significantly differed between depressed and non-depressed patients. In addition, there were no significant correlations between levels of depressive symptomology as assessed by the BDI and stimulated production of other cytokines analyzed including IL-2 \((r = .003, p = .98)\), IL-4 \((r = -.10, p = .34)\), IL-8 \((r = .02, p = .86)\), IL-10 \((r = -.03, p = .77)\), GCMSF \((r = -.02, p = .83)\), IFN \((r = -.06, p = .56)\), and p-selectin \((r = .14, p = .18)\).
Table 8. **Stimulated production of inflammatory cytokines for depressed vs. non-depressed patients**

Values represent the mean ± 1 S.D. reported as pg/ml

<table>
<thead>
<tr>
<th>Cytokine*</th>
<th>N</th>
<th>Depressed (N = 19)</th>
<th>Non-Depressed (N = 77)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>96</td>
<td>3.93 ± 1.48</td>
<td>3.69 ± 1.50</td>
<td>.54</td>
</tr>
<tr>
<td>IL-4</td>
<td>96</td>
<td>3.64 ± .87</td>
<td>3.47 ± .97</td>
<td>.49</td>
</tr>
<tr>
<td>IL-6</td>
<td>96</td>
<td>10.56 ± 1.04</td>
<td>10.22 ± 1.85</td>
<td>.45</td>
</tr>
<tr>
<td>IL-8</td>
<td>96</td>
<td>10.63 ± 1.13</td>
<td>10.28 ± 1.81</td>
<td>.43</td>
</tr>
<tr>
<td>IL-10</td>
<td>96</td>
<td>7.00 ± .84</td>
<td>7.02 ± .72</td>
<td>.95</td>
</tr>
<tr>
<td>GCMSF</td>
<td>96</td>
<td>6.02 ± 2.70</td>
<td>6.41 ± 2.19</td>
<td>.52</td>
</tr>
<tr>
<td>IFN</td>
<td>96</td>
<td>7.83 ± 1.65</td>
<td>7.67 ± 1.54</td>
<td>.69</td>
</tr>
<tr>
<td>TNF</td>
<td>96</td>
<td>9.26 ± .71</td>
<td>9.34 ± .74</td>
<td>.70</td>
</tr>
<tr>
<td>P-selectin</td>
<td>94**</td>
<td>1.35 ± .93</td>
<td>1.36 ± .93</td>
<td>.97</td>
</tr>
</tbody>
</table>

*Cytokine production values are log-transformed.

**2 participants with missing data for p-selectin. Depressed N = 17, Non-depressed N = 77

When accounting for physical fitness and heart rate recovery, there was no significant relationship between depression and IL-6 when controlling for physical fitness and heart rate recovery (Table 9). Likewise, as shown in Table 10, there was no significant relationship between depression and TNF-α after controlling for physical fitness and heart rate recovery.
Table 9. *Linear Regression Analysis Predicting Stimulated IL-6 from Depression (BDI), Exercise Capacity (METS), and Heart Rate Recovery*

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>$t$</th>
<th>$p$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>10.18 (.28)</td>
<td>38.06</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>BDI</td>
<td>.01 (.03)</td>
<td>.04</td>
<td>.34</td>
<td>.74</td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.011</td>
</tr>
<tr>
<td>Constant</td>
<td>9.60 (.65)</td>
<td>14.67</td>
<td>.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>.01 (.03)</td>
<td>.05</td>
<td>.43</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.03 (.07)</td>
<td>.07</td>
<td>.49</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>HR Recovery</td>
<td>.01 (.02)</td>
<td>.06</td>
<td>.43</td>
<td>.67</td>
<td></td>
</tr>
</tbody>
</table>

$R^2$ change: F (2, 83) = .478, $p > .05$

Table 10. *Linear Regression Analysis Predicting Stimulated TNF-α from Depression (BDI), Exercise Capacity (METS), and Heart Rate Recovery*

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>$t$</th>
<th>$p$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.008</td>
</tr>
<tr>
<td>Constant</td>
<td>9.37 (.11)</td>
<td>84.09</td>
<td>.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>-.01 (.01)</td>
<td>-.09</td>
<td>-.82</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.013</td>
</tr>
<tr>
<td>Constant</td>
<td>9.12 (.27)</td>
<td>33.49</td>
<td>.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>-.01 (.01)</td>
<td>-.06</td>
<td>-.53</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.02 (.03)</td>
<td>.08</td>
<td>.77</td>
<td>.44</td>
<td></td>
</tr>
<tr>
<td>HR Recovery</td>
<td>.01 (.01)</td>
<td>.02</td>
<td>.18</td>
<td>.86</td>
<td></td>
</tr>
</tbody>
</table>

$R^2$ change: F (2, 83) = .566, $p > .05$
Depression and physical fitness.

Hypothesis 3. Consistent with expectations, depression scores were negatively associated with lower exercise capacity \((r = -.27, p < .01)\), indicating that higher levels of depressive symptomology were related to lower levels of physical fitness. Physical fitness was positively related with heart rate recovery \((r = .53, p < .01)\), indicating that more physically fit patients achieved greater decreases in HR at two minutes post-exercise. However, higher levels of depressive symptomology were not significantly related to resting heart rate \((r = .01, p > .05)\), maximum heart rate \((r = -.02, p > .05)\), or heart rate recovery \((r = .08, p > .05)\).

Hypothesis 4. Physical fitness as assessed by estimated exercise capacity was unrelated to stimulated production of TNF-\(\alpha\) \((r = .14, p > .05)\) or stimulated production of IL-6 \((r = .07, p = .72)\). In the regression model, exercise capacity was not a significant contributor to explaining variance in stimulated production of IL-6 (as shown in Table 9) or TNF-\(\alpha\) (as shown in Table 10). Heart rate recovery was not significantly related to stimulated production of IL-6 \((r = .09, p > .05)\) or TNF-\(\alpha\) \((r = .08, p > .05)\). Heart rate recovery was not a significant contributor to explaining variance in stimulated production of IL-6 (as shown in Table 9) or TNF-\(\alpha\) (as shown in Table 10) when evaluated as part of the proposed regression model.

Hypothesis 5. Overall models for physical fitness mediating the relationship between depression and inflammation were not significant for stimulated production of IL-6 (Table 9) or TNF-\(\alpha\) (Table 10). Depression, physical fitness, or heart rate recovery
were not significant contributors in explaining variance in stimulated production of IL-6 or TNF-α.

Additional variables: Antidepressant use, Gender, Age and Body Mass Index

Antidepressant use. Antidepressant use was more prevalent in patients diagnosed with depression (42%) compared to patients without a depression diagnosis (10%), \( \chi^2 (1) = 11.04, p < .01 \). Patients who endorsed taking antidepressants (\( M = 8.82, SD = .81 \)) had significantly lower stimulated production of TNF-α compared to patients who did not endorse taking antidepressants (\( M = 9.4, SD = .68 \)), \( t (94) = 3.12, p < .01 \). Patients who endorsed taking antidepressants did not differ from those who did not endorse taking anti-depressants in production of IL-6.

Gender. There was a trend toward a gender difference in levels of depressive symptomology. Women (\( M = 8.20, SD = 7.34 \)) had significantly higher BDI scores compared to men (\( M = 5.23, SD = 5.61 \)), \( t(91) = -2.07, p < .05 \), suggesting higher levels of depressive symptomology in women compared to men. However, there was no difference in percentage of women who qualified for a depression diagnoses (20.0%) and men who qualified for a depressive diagnosis (19.7%), \( \chi^2 (1) = .001, p > .05 \). There were no significant differences between men and women in stimulated production of TNF-α or IL-6.

Age. In addition, age was negatively correlated with depressive symptomology (\( r = -.32, p < .01 \)), indicating that younger individuals endorsed a greater number of depressive symptoms. There was no significant relationship between age and stimulated production of inflammatory cytokines.
**Body mass index.** There were significant differences between patients with a depression diagnosis and patients without a depression diagnosis in weight and body mass index. Patients with depression ($M = 235.6$, $SD = 41.8$) weighed significantly more than patients without depression ($M = 201.3$, $SD = 41.7$), $t(91) = -3.2$, $p < .01$. Likewise, patients with depression ($M = 35.1$, $SD = 6.7$) had significantly greater body mass index compared to patients without depression ($M = 30.6$, $SD = 6.0$), $t(91) = -2.28$, $p < .01$. Weight and body mass index were highly correlated ($r = .86$, $p < .01$), so in order to avoid multi-collinearity only body mass index was used in additional analyses.

Depressive symptomology was positively correlated with body mass index ($r = .36$, $p < .01$), indicating that greater depressive symptomology was associated with greater body mass index. There was also a negative correlation between stimulated production of TNF-α and body mass index ($r = -.25$, $p < .05$), indicating that higher body mass index was associated with lower TNF-α production. Physical fitness was negatively correlated with body mass index ($r = -.34$, $p < .01$), indicating that greater physical fitness was associated with lower body mass index.

Body mass index, anti-depressant use, gender, and age were not significant predictors of stimulated production of IL-6 in regression analysis (see Table 11). Body mass index ($B = -.04$, $p < .01$) and anti-depressant use ($B = -.50$, $p < .05$) were all significant predictors of TNF-α production (see Table 12), indicating that reduced body mass index and lack of anti-depressant use were associated with higher stimulated production of TNF-α.
Table 11. *Linear Regression Analysis Predicting IL-6 from Age, Gender, Body Mass Index, and Anti-depressant Use*

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (S.E.)</td>
<td>Beta</td>
</tr>
<tr>
<td>Constant</td>
<td>13.12 (.71)</td>
<td>7.67</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>-.03 (.03)</td>
<td>-.18</td>
</tr>
<tr>
<td>Anti-depressant use</td>
<td>-.53 (.49)</td>
<td>-.07</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-.28 (.42)</td>
<td>-.10</td>
</tr>
<tr>
<td>Age</td>
<td>-.02 (.02)</td>
<td>-.01</td>
</tr>
</tbody>
</table>

R² change: F (4, 88) = 1.05, p > .05

** p < .01, * p < .05

Table 12. *Linear Regression Analysis Predicting TNF-α from Age, Gender, Body Mass Index, and Anti-depressant Use*

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (S.E.)</td>
<td>Beta</td>
</tr>
<tr>
<td>Constant</td>
<td>11.15 (.67)</td>
<td>16.53</td>
</tr>
<tr>
<td>Body Mass Index*</td>
<td>-.04 (.01)</td>
<td>-.31</td>
</tr>
<tr>
<td>Anti-depressant use*</td>
<td>-.50 (.19)</td>
<td>-.26</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>.09 (.17)</td>
<td>.05</td>
</tr>
<tr>
<td>Age</td>
<td>-.01 (.01)</td>
<td>-.17</td>
</tr>
</tbody>
</table>

R² change: F (4, 88) = 4.78, p < .01

** p < .01, * p < .05
Another regression was conducted to examine if the covariates that significantly predicted stimulated production of TNF-α (anti-depressant use and body mass index) would impact the relationships among depression, physical fitness, heart rate recovery. As shown in Table 13, anti-depressant use was a significant predictor of lower TNF-α production (B = -0.70, p < .01) indicating that anti-depressant use was associated with lower stimulated production of TNF-α. Body mass index was significantly related to stimulated production of TNF-α (B = -0.30, p < .05), indicating that lower body mass index was related to higher TNF-α production. None of the other variables included in the regression (BDI score, exercise capacity, or heart rate recovery) were significant predictors of TNF-α production.

Other variables investigated, including employment status, blood pressure, race, cardiac diagnosis, non-cardiac medical conditions, and other medications were not significantly related to depression or inflammation and were not further analyzed.

Table 13. Linear Regression Analysis Predicting TNF-α from Body Mass Index, Anti-depressant Use, Depression (BDI), Exercise Capacity (METS), and Heart Rate Recovery

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (S.E.)</td>
<td>Beta</td>
</tr>
<tr>
<td>Constant</td>
<td>10.18 (.51)</td>
<td>20.00</td>
</tr>
<tr>
<td>Body Mass Index*</td>
<td>-.03 (.01)</td>
<td>-.29</td>
</tr>
<tr>
<td>Anti-depressant use**</td>
<td>-.70 (.28)</td>
<td>-.34</td>
</tr>
<tr>
<td>BDI</td>
<td>.02 (.01)</td>
<td>.16</td>
</tr>
<tr>
<td>Heart rate recovery</td>
<td>-.01 (.01)</td>
<td>-.02</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.02 (.03)</td>
<td>.09</td>
</tr>
</tbody>
</table>

R² change: F (5, 78) = 4.17, p < .01
** p < .01, * p < .05
**Exploratory analyses**

*Moderation Model.* Exploratory regressions testing a moderation model were conducted assessing the effect of depression, physical fitness, and the interaction of depression and physical fitness on stimulated production of TNF-α (Table 14) and IL-6 (Table 15).

A step-wise regression was conducted to predict stimulated production of TNF-α from depression, physical fitness, and the interaction between depression and physical fitness (Table 14). When the interaction term (depression x exercise capacity) was added to depression and physical fitness, the model did not significantly explain variance in TNF-α production. Physical fitness, depression, and the depression-physical fitness interaction were not significant predictors of TNF-α production.

**Table 14. Linear Regression Analysis Predicting TNF-α from Depression (BDI), Exercise Capacity (METS) and Depression-Exercise Capacity Interaction**

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (S.E.)</td>
<td>Beta</td>
</tr>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>9.15 (.24)</td>
<td>38.48 .00</td>
</tr>
<tr>
<td>BDI</td>
<td>-.01 (.013)</td>
<td>-.07 -.67 .51</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.02 (.02)</td>
<td>.16 1.05 .30</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>9.13 (.24)</td>
<td>38.27</td>
</tr>
<tr>
<td>BDI</td>
<td>-.01 (.01)</td>
<td>-.04 -.32 .75</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.03 (.02)</td>
<td>.13 1.18 .24</td>
</tr>
<tr>
<td>BDI x METS interaction</td>
<td>.10 (.09)</td>
<td>.13 1.16 .25</td>
</tr>
</tbody>
</table>

R² change: F (1, 86) = 1.35, p > .05
** p < .01, * p < .05
Table 15. *Linear Regression Analysis Predicting IL-6 from Depression (BDI), Exercise Capacity (METS) and Depression-Exercise Capacity Interaction*

<table>
<thead>
<tr>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>10.263 (.19)</td>
</tr>
<tr>
<td>BDI</td>
<td>.02 (.03)</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.04 (.05)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>10.16 (.19)</td>
</tr>
<tr>
<td>BDI</td>
<td>.01 (.20)</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.11 (.20)</td>
</tr>
<tr>
<td>BDI x METS interaction*</td>
<td>-.40 (.20)</td>
</tr>
</tbody>
</table>

R² change: F (1, 86) = 3.96, p = .05
** p < .01, * p < .05

As shown in Table 15 a step-wise regression was conducted to predict stimulated production of IL-6 from depression, physical fitness, and the interaction between depression and physical fitness. In order to assess a moderator effect the interaction of depression and exercise capacity on IL-6 production was examined through the use of standardized z-scores for depressive symptomology based on the BDI and standardized z-scores for estimated exercise capacity in METS. Although the main effects for depression or physical fitness predicting IL-6 production were not significant, there was a significant interaction effect (depression x physical fitness) on IL-6 (B = -.40, p = .05).

For illustrative purposes, estimated exercise capacity was divided into high exercise capacity (METS > 8) and lower exercise capacity (METS ≤ 8) as shown in Table 16 and Figure 2. Although the main effects for depression or physical fitness predicting IL-6 production were not significant, there was a significant interaction effect (depression x physical fitness) on IL-6 (B = -.41, p < .05), as shown in Table 13.
Table 16. Linear Regression Analysis Predicting IL-6 from Depression (BDI), Categorical Exercise Capacity (METS ≤ 8 or METS > 8) and Depression-Exercise Capacity Interaction

<table>
<thead>
<tr>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (S.E.)</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>10.20 (.26)</td>
</tr>
<tr>
<td>BDI</td>
<td>.09 (.19)</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.13 (.38)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>.057*</td>
</tr>
<tr>
<td>Constant</td>
<td>10.13 (.26)</td>
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<tr>
<td>BDI</td>
<td>.38 (.23)</td>
</tr>
<tr>
<td>Exercise capacity (METS)</td>
<td>.06 (.38)</td>
</tr>
<tr>
<td>BDI x METS interaction*</td>
<td>-.89 (.40)</td>
</tr>
</tbody>
</table>

R² change: F (1, 86) = 4.88, p < .05

** p < .01, * p < .05

Figure 2. The Effect of the Interaction of Depressive Symptoms (BDI) and Exercise Capacity (METS) on Stimulated Production of IL-6
Although the interaction was significant, as illustrated in Figure 2, correlations between BDI score and stimulated production of IL-6 were not significant for individuals with an exercise capacity of eight METS or below \((r = .243, p = .09)\) or for individuals with an exercise capacity of eight METS or above \((r = -.230, p = .14)\).

Additional analyses were conducted using BDI as a categorical variable rather than a continuous variable. Independent-samples t-tests were conducted to compare stimulated production of IL-6 for individuals with low levels of depressive symptomology \((BDI < 10)\) and high levels of depressive symptomology \((BDI \geq 10)\) in conjunction with low \((METS \leq 8)\) and high \((METS > 8)\) levels of physical fitness, as depicted in Figure 3. Among the 47 individuals with low levels of physical fitness \((METS \leq 8)\), there was a significant difference in production of IL-6 between individuals who had low levels of depressive symptomology \((M = 9.89, SD = 1.96)\) and high levels of depressive symptomology \((M = 11.00, SD = .73)\), \(t(45) = -2.031, p < .05\). These results indicate that among individuals with low physical fitness, greater levels of depressive symptoms are associated with elevated production of IL-6. However, for the 43 individuals with high levels of physical fitness \((METS > 8)\), there was no significant difference in production of IL-6 between individuals with low levels of depressive symptomology \((M = 10.32, SD = 1.88)\) and high levels of depressive symptomology \((M = 10.18, SD = .89)\), \(t(41) = .151, p > .05\).
For exploratory purposes, the regression with physical fitness as a moderating variable was conducted using different cut points for categorizing high and low levels of physical fitness. A significant interaction (B = -.811, p = .047) was also found using seven METS as a cut point (individuals equal to or below seven METS were considered low physical fitness vs. individuals above seven METS were considered high physical fitness). There was no significant interaction using six METS as a cut point (B = -.658, p = .093), indicating that above seven METS could be considered a point at which the level of physical fitness influences the depression-inflammation relationship.
Body mass index. Given that body mass appeared to be a significant predictor of inflammation and depression in initial analyses, the relationships between body mass index and variables of interest were further examined. In a step-wise regression, physical fitness was associated with lower levels of depressive symptomology (B = -.479, SE = .182, p < .05). Body mass index was added to the regression and was positively related to depressive symptomology (B = .286, SE = .105, p < .01), indicating that an elevated body mass was related to elevated depressive symptoms. In addition, when body mass index was included in the regression, the relationship between physical fitness and depressive symptoms was no longer significant (B = -.297, SE = .188, p > .05). Therefore, when body mass index was included, the amount of variance in depression explained by physical fitness was greatly reduced, indicating that body mass index likely accounts for much of the relationship between physical fitness and depression.

Similarly, body mass index appeared to account for a significant amount of variance in production of TNF-α, whereas physical fitness did not. Regression analysis indicated that physical fitness was not significantly associated with TNF-α (B = .009, SE = .022, p > .05). Body mass index was negatively related to TNF-α (B = -.035, SE = .012, p < .01), indicating that an elevated body mass was related to lower TNF-α. There was no significant relationship between body mass index and IL-6 or between physical fitness and IL-6.
DISCUSSION

Summary

Descriptive statistics indicated that elevated depressive symptomology was present in 20% of our sample. Results did not support the hypothesis that depression would be positively related to stimulated production of inflammatory cytokines IL-6 and TNF-α. Given that the relationship between depression and inflammation was not significant, the original model proposing that physical fitness is a mediator of the depression-inflammation relationship could not be supported. Although results did not yield the expected positive relationship between depression and stimulated production of IL-6 or TNF-α, the interaction of physical fitness and depression significantly predicted IL-6 production. Among individuals with lower levels of physical fitness (estimated exercise capacity of 8 METS and below), there was a negative relationship between elevated depressive symptomology and elevated production of IL-6. Among individuals with higher levels of physical fitness (estimated exercise capacity of 8 METS and above), there was no significant relationship between depressive symptomology and IL-6 production. Depression was also significantly related to lower physical fitness and elevated body mass index, which may have implications for poorer health outcomes among patients with depression. Given the lack of support for treatment of depression leading to reduced risk of mortality among patients with cardiovascular disease, the inclusion of exercise targeting improved physical fitness should be emphasized in treatment plans as a way to reduce mortality rates in patients with cardiovascular disease and depression.
Rate of Depression

The rates of major depression or elevated depressive symptoms reported for cardiac samples in other studies range from 22% to 41% (Frasure-Smith et al, 1993; Frasure-Smith et al, 1999; Hance et al, 1996; Lespérance et al, 2000; Jiang et al, 2001; Connerney et al, 2001). In our study, the rate fell slightly below this range, as approximately 20% of the patients had a diagnosis of current or past depression. Likewise, approximately 19% of patients had BDI scores of 10 or greater, indicative of elevated levels of depressive symptomology. Other studies conducted in the same cardiac rehabilitation program yielded similar rates of depression (Hughes, et al., 2006; Josephson et al., 2006; Casey, et al., 2008).

The lower percentage of depressed patients in our sample of cardiac patients compared to higher rates of depression among other samples may potentially be due to the present study including only patients enrolled in cardiac rehabilitation. The 20% prevalence rate of depression in the present study was similar to rates ranging from 15-31% among other studies in the same cardiac rehabilitation program, as well as cardiac rehabilitation programs in other areas (Todaro et al., 2005; Sanderson & Bittner, 2005; Lavie & Milani, 2006; Hughes, et al., 2006; Josephson et al., 2006; Casey, et al., 2008). Since depressed cardiac patients are more likely to dropout after a cardiac rehabilitation program shortly after starting the program, fewer depressed patients may have been available for our recruitment by virtue of the lower likelihood that depressed patients were engaged in cardiac rehabilitation long enough to participate in the study (Casey, et al., 2008).
Another potential reason for the low rate of depression is the length of time from the cardiac event to start of cardiac rehabilitation when the patients were enrolled in the present study. Depression tends to remit over time, even for patients who are not treated with psychotherapy or antidepressants (Glassman et al., 2002; Berkman et al., 2003). Lauzon et al. (2003) used the BDI to evaluate 550 patients during an initial myocardial infarction and found a 34.7% prevalence rate of clinically significant depressive symptomology (BDI ≥ 10). Of 466 patients re-evaluated 30 days later, 70% of those depressed at baseline were still depressed, whereas 30% no longer had clinically significant depressive symptoms. Reduction of depressive symptomology also tends to occur during cardiac rehabilitation, with women exhibiting the greatest reduction (Josephson et al., 2006). Therefore, it is likely that the rate of depression among patients in the present study was lower than the rate of depression among patients with cardiovascular disease overall.

Diagnosing Depression

One potential improvement over several previous studies is that the present study consisted of a more thorough depression assessment. The present study utilized a self-report questionnaire to evaluate depressive symptomology as well as a more extensive diagnostic interview. The BDI cutoff scores that indicate the possibility of clinically significant depression are widely used (typically a score equal to or greater than 10), particularly with research in cardiac samples (Frasure-Smith et al, 1995; Frasure-Smith et al, 1999; Lespérance et al, 2002; Grace et al., 2004). Using this cutoff, there was 83.9% consistency between the clinical interview diagnosis and clinically significant levels of
depressive symptomology (10.8% of sample had both elevated levels of depressive symptomology on the BDI and a depression diagnosis, whereas 73.1% of the sample did not have elevated levels and were not diagnosed as depressed).

Despite the thoroughness of depression assessment in the present study, there were a few discrepancies between the number of patients qualifying for depression diagnosis based on clinical interview and the number of patients qualifying for potential depression based on the BDI self-report questionnaire. Among the 93 patients completing the BDI and the diagnostic interview, 7.5% had a BDI score less than 10 and were diagnosed with a depressive disorder, while 8.6% had a BDI score equal to or greater than 10 and did not qualify for a depression diagnosis based on clinical interview.

An advantage of utilizing clinical interview in addition to a self-report questionnaire is obtaining information for specific depression diagnoses. In a previous study by the same researchers, 44 cardiac rehabilitation patients who completed the BDI also participated in a Structured Clinical Interview for the DSM-IV. None of the 22 patients with BDI scores below 5 were diagnosed with any type of depression. Of the 22 patients with BDI scores above 12, eleven were diagnosed with current major depression, four with major depression in remission, two with minor depression, three with dysthymia, and two had no diagnosis of depression (Hughes, et al., 2010). Similarly, among the 22 patients with BDI scores above 10 in the present study, eleven were diagnosed with current major depression, four with major depression in remission, two with minor depression, three with dysthymia, and two had no diagnosis of depression. Utilizing both the BDI and diagnostic interviews allows for the most complete
assessment of depression and future research studies should include the simultaneous use of both assessment methods.

One likely explanation for the discrepancy between BDI and clinical interview is that depression is partly characterized by multiple somatic symptoms. Elevated BDI scores without a depression diagnosis may be a product of the overlap of somatic symptoms of depression (changes in sleep, weight, and energy) and symptoms of cardiovascular disease. Silverstein (1999) distinguished ‘somatic depression’ as characterized by sleep disturbance, fatigue, and appetite disturbance from ‘pure depression’ that does not include these somatic symptoms. Differences in the endorsement of somatic symptoms compared to cognitive-affective symptoms on the BDI were not compared in this study. During a clinical interview, the timeline and cause of somatic symptoms may allow symptoms to be more accurately attributed to either depression or medical causes.

Previous studies conducted in the same cardiac rehabilitation program showed that somatic symptoms of depression were more likely endorsed compared to cognitive-affective symptoms (Casey, et al., 2008). Somatic symptoms, such as fatigue, appetite problems, and sleep difficulties, are more strongly predictive of cardiovascular events compared to cognitive symptoms of depression (Hoen, et al., 2010). Other research showed that compared to psychiatric patients, post-myocardial infarction patients had a relative lack of depressive cognitions, but an equal or greater endorsement of somatic symptoms (Martens et al., 2006).
The overlap of symptoms could lead to either fewer or a greater number of depression diagnoses in cardiac patients. On one hand, cardiac patients may have elevated depression rates due to endorsement of several of the somatic components of depression that overlap with cardiac symptoms. On the other hand, as suggested by Martens et al. (2006), cardiac patients may be less likely to consider emotional causes for their symptoms or health care providers may attribute symptoms of depression to the cardiovascular disease, resulting in failure to diagnosis existing depression. Alternative depression measures, such as the Cardiac Depression Scale (Di Benedetto et al., 2006), may be more suitable for the cardiac population than the BDI. Whichever screening tool is used, a clinical interview is likely to help provide a more specific depression diagnosis and account for multiple causes of symptoms.

Although the present study obtained specific depression diagnoses, the small sample size and limited number of patients with a depression diagnoses were not conducive to analyzing differences between different depression diagnoses. Therefore, patients with a diagnosis of current major depressive disorder were grouped together with patients with a diagnosis of major depressive disorder in remission. There were no significant differences in BDI score, physical fitness, heart rate recovery, or inflammation among the different depression diagnoses. The lack of significant differences may be due to no actual differences among diagnoses, or may be the product of sample sizes too small to result in significant differences. Taylor (2010) suggests that focusing on subgroups of depression (such as individuals with severe depression, long-standing
depression, or groups with comorbid anxiety disorders) might yield more specific and significant results compared to focusing on patients with depression in general.

There have been few known studies that empirically examined differences in inflammation between individuals with current and past depression. However, prior studies have shown that inflammatory markers were elevated in individuals with a history of major depression, suggesting that elevated inflammatory cytokines could be related to past diagnoses of depression (Kling et al., 2007). Although the results of the present study did not support the hypothesis that depression is related to elevated inflammatory cytokines, it is possible that patients with a previous episode of depression could also be susceptible to reduced levels of physical fitness, reduced vagal control, and subsequently higher inflammation.

Depression and Inflammation

The hypothesis that higher levels of depressive symptomology would be related to higher stimulated production of inflammatory markers IL-6 and TNF-α (Hypothesis 1) was not supported in the present study. In addition, the hypothesis that patients with current or past diagnosis of depression will have higher stimulated production of inflammatory markers compared to non-depressed (Hypothesis 2) was also not supported. Depressive symptomology was also unrelated to inflammation after controlling for additional variables including physical fitness, heart rate recovery, age, gender, body mass index, and anti-depressant use.
The primary aim of the study was to evaluate the hypothesis that physical fitness mediates the relationship between depression and inflammation (Hypothesis 5). It was expected that even after controlling for heart rate recovery, physical fitness would account for a significant amount of variance in the relationship between depression and inflammation. It was expected that the relationship between depression and inflammation would be reduced when physical fitness is included. The relationships necessary to test the proposed model (a relationship between depression and inflammation and a relationship between inflammation and physical fitness) were not significant. Without a significant relationship between depression and inflammation it was not possible to assess potential mediators of this relationship, such as physical fitness and heart rate recovery.

The lack of significant results in this study is not completely surprising given that other studies of cardiac patients have failed to find a relationship between depression and inflammation (Whooley et al., 2007; Glassman & Miller, 2007). In particular, the results of previous studies suggest that the relationship between depression and inflammation may be greatly attenuated when other variables are taken into account, such as body mass index, age, smoking status, medications, or gender (Tiemeier et al., 2003; Kop et al., 2002; Miller et al., 2002; Steptoe et al., 2003; Whooley et al., 2007; Glassman & Miller, 2007; Lesperance et al., 2004; Raison et al., 2006). Positive relationships between depression and inflammation were not significant with or without inclusion of covariates in the present study. Findings, and lack of significant findings, from the present study and past studies, show the importance of including relevant covariates in depression and
inflammation research. Particularly with inflammation, multiple factors could potentially influence levels of inflammatory markers.

Another reason for the lack of consistent results among studies on the relationship between depression and inflammation is the variety of inflammatory markers assessed in depression and inflammation research studies. The cytokines assessed in the present study (IL-6 and TNF-α) were selected based on associations of these cytokines with both depression and cardiovascular disease in previous research (Parissis et al., 2004; Anisman et al., 2005; Dantzer, 2001; Miller et al., 2005a; Grippo et al., 2003; Grippo et al., 2005; Sjogren et al., 2006; Suarez, 2003; Ridker, et al., 2000b). Other markers not assessed in the present study, such as C-reactive protein, have been assessed in previous studies in regard to depression and cardiovascular disease (Ladwig, et al., 2005; Empana, et al., 2005; Vaccarino, et al., 2007; Janszky, et al., 2007; Frasure-Smith, et al., 2007; Arbelaez et al., 2007). With no current “gold standard” measurement for inflammation, future research should include assessment of a variety of inflammatory markers and be aimed at identifying markers that can be consistently and accurately measured.

Another possibility for the lack of consistent findings regarding the relationship between depression and inflammation are the various methodologies used to assess inflammation. The present study utilized a whole blood assay designed to simulate the actions of a variety of immune cells in their in vivo environment (Marsland, et al., 2007). Other studies have measured cytokine production by activated monocytes or mononuclear cells, which may provide more specificity but are less likely to replicate the overall immune response (Suarez, et al., 2003). There is evidence from immunology
research showing that using different methods can yield different results (De Groote et al., 1992). However, further research should be conducted to determine if inconsistent findings in the relationship between depression and inflammation are due to the various methods of assessments used in research studies.

*Depression, physical fitness, and HR recovery*

The second aim of the present study was to evaluate the extent to which physical fitness mediates the relationship between depression and inflammation when examined in conjunction with heart rate recovery. Given that the relationship between depression and inflammation was not significant, a model in which physical fitness is a mediator of the depression-inflammation relationship cannot be supported. However, the relationships among depression, physical fitness, and heart rate recovery were assessed in order to evaluate these relationships that might potentially provide more information about the mechanistic processes taking place.

Based on previous research, it was expected that depression would be related to lower levels of physical fitness, depression would be related to reduced heart rate recovery, and physical fitness would be positively correlated with heart rate recovery (*Hypothesis 3*). Results were somewhat consistent with these expectations and previous studies (Ruo et al., 2004; Hughes et al., 2006). Depression scores were negatively associated with lower estimated exercise capacity, indicating that patients with higher levels of depressive symptomology had lower levels of physical fitness. Likewise, patients without depression (based on clinical interview) had significantly higher
estimated exercise capacity compared to patients with depression indicating that patients without depression were more physically fit than patients with depression.

This finding was consistent with the results of previous studies showing that depression is related to lower levels of physical fitness (Ruo et al., 2004; Hughes et al., 2006). However, these studies are not conclusive in determining directionality. Depression may lead to reductions in physical fitness, but it is also possible that reduced physical fitness contributes to depression, or that other variables influence both physical fitness and depression. Although clinical trials have shown that exercise has anti-depressive effects (Blumenthal et al., 1999; Babyak et al., 2000), it should be noted that participation in exercise or an exercise program is not synonymous with increases in physical fitness. Further research should be conducted to investigate the mechanisms by which depression is related to reduced physical fitness.

Physical fitness was positively related with heart rate recovery in the present study, indicating that more physically fit patients had had larger decreases in heart rate recovery at two minutes post-exercise. As heart rate recovery is an indicator of vagal functioning, these results are consistent with previous research suggesting that greater physical fitness is associated with better vagal functioning (Hughes et al., 2006).

However, contrary to expectations, higher levels of depressive symptomology were not significantly related to resting heart rate, maximum heart rate, or heart rate recovery. The lack of significant relationship between depression and resting heart rate, maximum heart rate, and heart rate recovery is surprising given significant relationships in previous studies in the same cardiac rehabilitation program (Hughes et al., 2006). The
lack of significant results in the present study may be due to a smaller sample size (93 participants) compared to 300 participants in previous studies. The lack of significant results may also be due to the utilization of resting heart rate and heart rate recovery as measures of vagal control, as opposed to analysis of heart rate variability. Previous studies have consistently shown that depression is associated with reduced heart rate variability (Carney et al., 1988; Carney et al., 1995; Carney et al., 2001; Hughes & Stoney, 2000; Hughes et al., 2006; Stein et al., 2000). Heart rate variability may be more accurate given that heart rate recovery relies heavily on maximum heart rate achieved during a treadmill exercise stress test (Hughes, et al., 2006). Differences in vagal control between depression and non-depressed patients may have been detected in the present study with different assessment methods. Although more burdensome and costly, it may be necessary for future studies to utilize heart rate variability analysis in order to more clearly elucidate the relationships among depression, vagal control, and inflammation.

**Physical fitness and inflammation**

In order for physical fitness to mediate the depression-inflammation relationship, it was expected that physical fitness would be negatively related to stimulated production of IL-6 and TNF-α (*Hypothesis 4*). Contrary to predictions, physical fitness was not significantly related to IL-6 and TNF-α production. In addition, the hypothesis that heart rate recovery would be negatively related to inflammatory markers was not supported. There was no statistically significant relationship between heart rate recovery and IL-6 or TNF-α production.
These results were somewhat surprising given that other studies showed that exercise is related to reductions in inflammation (McFarlin et al., 2006; Stewart et al., 2007; King et al., 2003), leading to the expectation that physical fitness is also related to reductions in inflammation. However, physical activity may not translate directly into physical fitness. Although prior studies have shown that physical activity (measured in energy expenditure) is related to physical fitness levels, the amount of activity, type of activity, and other individual health characteristics, all contribute to variance in physical fitness level (Stofan, et al., 1998).

The discrepant results between previous studies and the present study in the inflammation-physical fitness relationship may be due to some lack of consistency in measuring inflammation. Participants in the present study were instructed not to exercise the day of the blood draw and steps were taken to ensure a resting blood draw, but most recent exercise and physical activity levels were not monitored or recorded as part of the study. Although regular physical activity is associated with reduced systemic inflammation, a single bout of exercise is related to a temporary increase in acute inflammation (Mora et al., 2007; Plaisance et al., 2007; Petersen & Pedersen, 2005; Zaldivar et al., 2006). Particularly given that participants were recently enrolled in a cardiac rehabilitation program in which exercise is strongly encouraged, the possibility of increased physical activity near the time of the blood draw cannot fully be ruled out.
**Exploratory Analysis**

*Additional variables: Antidepressant use, Gender, Age, and Body Mass Index*

*Antidepressant use.* Other variables, such as antidepressant use, gender, age, and body mass index, were also examined. As expected, antidepressant use was more common in patients with a depression diagnosis compared to patients without a depression diagnosis. Antidepressant use was quite common among depressed patients (42%) in the present study. Patients who endorsed taking antidepressants had significantly lower TNF-α compared to patients who did not endorse taking antidepressants, indicating antidepressant use was associated with reduced inflammation as indicated by lower stimulated production of TNF-α. This finding is consistent with previous animal model studies that showed antidepressants use is related to reduced production of TNF-α and IL-10 (Maes & Kenis, 2002). An association between antidepressant use and reduced inflammation may also partly explain the lack of significant findings between depression and inflammation in the present study as antidepressant use could potentially mask the inflammatory effects of depression. Future studies should include analysis of inflammation in depressed patients with and without antidepressant use.

*Gender.* Although there were no gender differences in diagnosis of depression, women in the present study reported significantly higher levels of depressive symptomology compared to males. This finding is consistent with previous studies showing that women enrolled in cardiac rehabilitation have higher levels of depressive symptomology compared to men (Josephson et al., 2006; Todaro et al., 2005). Despite
differences in depressive symptomology, there was no significant relationship between gender and inflammation. Previous research has shown a relationship between CRP and depression in men, but not women (Danner et al., 2003; Ford & Erlinger, 2004). One potential explanation for differences in inflammation between men and women could be differences in cardiac vagal control. Previous studies show cardiac vagal control appears to be greater in depressed women compared to depressed men (Thayer et al., 1998; Chambers & Allen, 2007). Additional studies should be conducted with larger sample sizes to determine if gender has a moderating effect on the relationships among depression, vagal control, and inflammation.

*Age.* There was no significant relationship between age and inflammation. This is somewhat surprising given that elevated levels of pro-inflammatory cytokines play a role in disorders associated with aging, such as Alzheimer’s disease (Leonard, 2007). In addition, research has shown that aging is associated with enhanced production of pro-inflammatory cytokines, such as IL-6, and decreased production of anti-inflammatory cytokines, including IL-10 (Dantzer et al., 2008). However, age was negatively related to depressive symptomology in the present study, indicating that younger individuals endorsed a greater number of depressive symptoms.

*Body mass index.* Body mass index was not related to inflammation, but was significantly related to depression in the present study. Given that body mass appeared to be a significant predictor of depression in initial analyses, additional exploratory analyses were conducted to examine the relationships among body mass index, physical fitness, depression, and inflammation. Body mass index was positively related to depressive
symptomology, indicating that an elevated body mass was related to higher levels of depressive symptoms. This significant positive relationship is consistent with prior findings from the CARDIA (Coronary Artery Risk Development in Young Adults) study showing that depressive symptomology influences change in body mass index over time (Needham, et al., 2010). In addition, body mass index attenuated the relationship between physical fitness and depression in the present study. In other words, when body mass index was included, the amount of variance in depression explained by physical fitness was greatly reduced, indicating that body mass index likely accounts for much of the relationship between physical fitness and depression.

These findings are somewhat surprising in light of recent research on body mass index and physical fitness. In a recent prospective study of 14,345 men, researchers found that maintaining or improving physical fitness (as measured by METS on a treadmill stress test) was associated with reduced risk of mortality, even after controlling for body mass index. The researchers also found that body mass index was not associated with mortality risk (Lee, et al., 2011). Further research should be conducted on the influence of both body mass index and physical fitness on depression and inflammation, and more importantly, how these interactions may influence mortality risk.

Physical Fitness as a Moderating Variable

Additional analyses were conducted to examine another model that could explain the potential relationships among depression, physical fitness, vagal control, and inflammation. Physical fitness and vagal control were proposed to be mediators for the expected positive relationship between depression and inflammation. A mediator is a
variable that explains the mechanism by which there is a relation between a predictor and an outcome (Baron & Kenny, 1986). This proposed model suggests that depression and inflammation could be related due to reduced physical fitness and vagal control.

Another model to potentially explain the role of physical fitness in the relationship between depression and inflammation is a moderation model. A moderator is a variable that alters the direction or strength of the relation between a predictor and an outcome in which the effect of the predictor on the outcome depends on the level of the moderator (Baron & Kenny, 1986). According to this model, the level of physical fitness would alter the relationship between depression and inflammation. Specifically, a high level of physical fitness would result in reduced strength in a relationship between depression and inflammation, whereas a low level of physical fitness would result in a stronger relationship between depression and inflammation. Therefore, the level of physical fitness would dictate the effect that depression would have on inflammation.

In exploratory analysis, the interaction of depression and physical fitness significantly predicted IL-6. According to the results, for lower levels of physical fitness (METS ≤ 8) there was a positive relationship between level of depressive symptomology and production of inflammatory marker IL-6. Among less physically fit individuals, patients with elevated depressive symptoms (BDI ≥ 10) had significantly greater production of IL-6 compared to individuals without elevated depressive symptomology (BDI < 10). However, for individuals with higher levels of physical fitness (METS > 8), there was no significant relationship between depression and IL-6 production. This interaction suggests that physical fitness potentially serves as a protective factor that
weakens the likelihood that individuals with depression will have higher levels of chronic inflammation.

The cutoff point of low (METS \( \leq 8 \)) and high (METS > 8) physical fitness was based on previous findings that individuals with an exercise capacity of METS below five had twice the risk of mortality compared to individuals with METS above eight (Myers et al., 2002). A significant interaction was found using seven METS as a cut point, but no significant interaction using six METS as a cutoff point. These results indicate that an exercise capacity of approximately seven or eight METS is a point at which physical fitness influences the depression-inflammation relationship.

These results are consistent with recent findings in suggesting the importance of physical fitness in reducing risk of mortality. In a recent study in which physical fitness was associated with reduced risk of mortality even after controlling for body mass index, researchers found that every increase in one MET was associated with a 19% lower risk of heart disease and a 15% lower risk of all-cause mortality (Lee, et al., 2011). In another study of patients with heart failure, depressed individuals who improved in exercise capacity during an exercise training program had substantially lower risk of mortality compared to their counterparts who did not improve in exercise capacity during the exercise training program (Milani, et al., 2011). Additional studies should be conducted in the future to further elucidate the role of physical fitness in the effects of depression and health outcomes. Based on the findings of the present study, physical fitness should be promoted, particularly given that physical fitness is not only associated with reduced
mortality, but could also potentially serve as a protective factor in preventing elevated inflammation among individuals with depression.

**Limitations**

There are several limitations within the present study. First, the cross-sectional nature of the study design did not allow for causality or directionality to be shown. Other studies, particularly animal models, show that inflammation leads to depression rather than depression leading to inflammation (Anisman et al., 2005; Dantzer, 2001). Other studies show that artificial injections of inflammatory proteins and cells in healthy people reliably produces transient depressive symptoms and behaviors (Kop & Gottdiener, 2005). Additionally, inflammation was not measured at multiple time points. Additional time points of measuring inflammation may have provided more accurate assessment of chronic inflammatory processes. Multiple time points would also allow for evaluation of changes in inflammation coinciding with changes in depression.

Additional limitations included restrictions on measurement techniques utilized in the present study. For example, the assay used in the present study assessed a limited number of inflammatory markers. Other markers, such as C-reactive protein, which has been widely used in conjunction with studies on cardiovascular disease was not assessed (Ladwig, et al., 2005; Empana, et al., 2005; Vaccarino, et al., 2007; Janszky, et al., 2007; Frasure-Smith, et al., 2007; Arbelaez et al., 2007). In addition, vagal control was measured by assessing resting heart rate and heart rate recovery, whereas heart rate variability is more widely accepted and used as a measure of vagal control (De Meersman & Stein, 2007).
Another general limitation was a relatively small sample size in the current study. Although over 500 patients were screened to potentially participate in the study, only 96 participated after ruling out patients who did not meet exclusion criteria. In addition, as shown by the sample sizes in Table 4, 5 participants were missing exercise stress test date, reducing these analyses to 91 participants. The small sample size may have led to lack of significant findings. For example, a difference was not detected among depressed and non-depressed individuals in heart rate recovery in the present study, whereas a difference was detected in a previous study assessing heart rate recovery and depression in a sample of 300 patients from the same site (Hughes, et al., 2006). If possible, future research should include larger sample sizes in order to detect small differences that might exist.

Implications for Treatment for Patients with Depression and Cardiovascular Disease

Despite lack of significant findings in the present study, examination of the roles of autonomic dysfunction, inflammation, and physical activity likely has important implications for the treatment of patients with depression and cardiovascular disease. Although research indicates that cardiac patients experience significant levels of depression, interventions addressing depression have been unsuccessful. Previous attempts at treating depression through psychotherapy (ENRICHD), antidepressants (SADHART and MIND-IT), or both (CREATE) had little impact on reducing risk of mortality among cardiac patients (Glassman et al., 2002; Berkman et al., 2003; Lesperance et al., 2007; van Melle, et al., 2007). Recent findings have shown that depression interventions, such as medication and therapy, may be more protective if they
are implemented prior to the onset of clinical cardiovascular disease (Stewart, Perkins, & Callahan, 2012).

Although current research is not conclusive, the possibility remains that multiple physiological correlates of depression, such as changes in inflammation, physical fitness, or autonomic nervous system functioning, could be at least partially responsible for the link between depression and increased risk of mortality. Therefore, focusing on these physiological correlates in treatment may effectively contribute to reductions in mortality risk as well as reductions in depressive symptoms.

Antidepressant use, and its effects on depressive symptoms and inflammation, in cardiac patients with depression, is a treatment that warrants further investigation. There are mixed findings regarding whether antidepressants exacerbate or reduce inflammatory effects (Maes & Kenis, 2002; Pizzi, et al., 2009). Antidepressant use is associated with lower re-hospitalization rates in patients recovering from acute coronary syndromes (Mazza, et al., 2010). Additional research should be conducted to determine the effects of antidepressant use with this specific patient group. Issues such as interactions with other medications, potential side effects, and combining medication with other forms of therapy and treatment should be further considered.

Promoting exercise and physical fitness may be just as important as psychotherapy or antidepressants in treating cardiac patient with depression. In a study of over 66,000 adults, physical fitness, as measured by exercise capacity, substantially improved predictions of all-cause and cardiovascular mortality, even after controlling for numerous other risk factors, suggesting that perhaps exercise capacity warrants more
attention in prevention and treatment of cardiovascular disease (Gupta, et al., 2011; Lauer, 2011). The Heart and Soul study showed that the relationship between depressive symptoms and cardiovascular events was attenuated when physical activity was included, suggesting that exercise training may improve morality risk related to depression (Whooley, et al., 2008). Evidence has shown that programs that promote physical fitness, such as cardiac rehabilitation, are beneficial in reducing cardiac mortality (Wenger et al., 1995; Taylor et al., 2004; Leon et al., 2005). There is also evidence that depressed cardiac patients may even benefit more from physical activity programs than non-depressed cardiac patients (Milani et al., 1996; Taylor et al., 2004; Ruo et al., 2004; Carels, 2004). Engaging in physical activity allows for behavioral activation and changing maladaptive cognitions that would typically occur in traditional psychotherapy (Hays, 1999). The present study assessed physical fitness, but it is unclear if physical activity may also impact the depression-inflammation relationship independent of physical fitness level. A meta-analysis showed that both physical activity and physical fitness are related to reduced all-cause mortality, but it is unclear which is more important in determining health benefits (Blair, Cheng, & Holder, 2001).

Further research on depression, physical activity, physical fitness, neuroimmunological functioning (such as inflammation and vagal control) should be conducted to better inform health professionals on the most effective focus of treatment. For example, a patient may be encouraged to focus on reducing depression cognitions, adhere to a medication regimen, pay more attention to their heart rate, improve their physical fitness, and stay physically active. Given that any patient has a limited amount
of time, energy, and attention, it would be helpful to determine which strategies are most
effective in attaining positive health outcomes. Programs that include a comprehensive
focus, such as cardiac rehabilitation, are likely the most effective, but further research on
the mechanisms underlying these treatments should be conducted to determine the ways
in which patients can benefit most.

Conclusions

The present study extended previous findings by examining the effect that
physical fitness may play in the relationships among depression, inflammation, and vagal
control. Depression was prevalent in this sample as 20% qualified for a depression
diagnosis according to clinical interview. The results did not show an overall positive
relationship between depression and inflammation (IL-6 or TNF-α). However, additional
analysis showed that there was a positive relationship between depressive
symptomology and production of IL-6 among individuals with lower levels of physical
fitness, whereas there was no relationship between depression and IL-6 production
among individuals with higher levels of physical fitness. Depression was related to lower
physical fitness and elevated body mass index. These results suggest that individuals with
higher levels of physical fitness may be protected from depression leading to elevated
inflammation. Consequently, interventions should be implemented that target improving
physical fitness, particularly for depressed patients. Improved physical fitness could
potentially be related to reductions in depression as well as potentially reducing cardiac
mortality among depressed patients.
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