THE LONGITUDINAL EFFECTS OF CARDIAC REHABILITATION
ON COGNITION IN OLDER ADULTS WITH HEART FAILURE

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by

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Introduction

Within the United States, more than five million individuals have HF and an estimated 670,000 new cases are reported each year. With the increasing age of the American population HF has become more prevalent and it is estimated that by 2030 the prevalence of HF will increase by 25% (American Heart Association, 2013). While the incidence of HF in women has declined over recent decades, it remains unchanged among men (Levy, et al., 2002), and despite improved survival rates, the 5-year mortality rate among both genders remains high at 50-60% (Levy, et al., 2002; Rusinaru, et al., 2009).

In addition to being a significant clinical problem, HF produces a significant economic burden, costing an estimated $32 billion annually, and this cost is projected to increase to $70 billion by 2030 (American Heart Association, 2013). A cohort study of Medicare beneficiaries found that over 2.5 million persons were hospitalized with HF from 2001-2005 and of those, 65% were readmitted to the hospital within one year, and nearly 40% were readmitted twice (Curtis et al., 2008).

In contrast to the process of normal cardiovascular aging, HF is a complex clinical syndrome associated with structural and functional damage such that the heart is unable to pump blood sufficiently enough to meet the body’s metabolic needs. The condition of HF usually evolves over time and progresses as the body tries to compensate for the work the damaged heart can no longer perform (Francis, Sonnenblick, Wilson Tang, & Poole-Wilson, 2008). For example, left ventricular dysfunction is a common abnormality in HF and results in a decrease of cardiac output. In response, activation of neurohormonal compensatory mechanisms, such as sympathetic
nervous system activation (e.g., increase in heart rate, peripheral vasoconstriction), occur in an attempt to maintain cardiac output. While this initially maintains cardiac output, chronic sympathetic nervous system activation ultimately leads to further weakening of the heart and is also related to cardiac muscle cell death, hypertrophy, and focal myocardial necrosis (Jackson, Gibbs, Davies, & Lip, 2000). Endothelial dysfunction is also common among individuals with HF, and is implicated in both the pathophysiology and adverse outcomes associated with the disease (Bauersachs & Widder, 2008; Fischer et al., 2005; Bank, Lee, & Kubo, 2000; Katz et al., 2005; de Berrazueta et al., 2010). Increased sympathetic activation has been found to reduce endothelial function in healthy adults (Hijmering et al., 2002), which suggests even further dysfunction is likely among individuals with HF. The compensatory mechanisms recruited ultimately prove to be insufficient and have additional negative effects on the heart, and these initially adaptive responses contribute to the progression of HF (Jackson, Gibbs, Davies, & Lip, 2000; Francis, Sonnenblick, Wilson Tang, & Poole-Wilson, 2008).

In addition to the experience of physical symptoms, cognitive dysfunction is common in HF (Bennett & Sauve, 2003), particularly with increasing HF severity (Vogels, et al., 2007a; Pressler et al., 2010), and the observed deficits are linked to adverse outcomes (Zuccala, et al., 2003; Zuccala, et al., 2001). While the etiology of cognitive dysfunction in this population is not fully understood, several potential mechanisms have been proposed. However, this literature is often mixed and limited by methodological limitations. One potential mechanism that has received limited attention is reduced levels of physical activity. Further examination of the role of physical activity on cognition in HF is warranted as physical inactivity is not only a risk factor for the development of HF (He et al., 2001), but is also implicated in disease progression (Conraads et al., 2012). A greater understanding of the relationship between physical activity and cognition will not only provide insight into the etiology of cognitive deficits in this population, but may
also have implications for reducing the risk for, or even partially reversing, cognitive deficits, as this is a modifiable risk factor.

**The Neuropsychology of Heart Failure**

Cognitive dysfunction is common in HF and is associated with adverse outcomes. The prevalence rates of cognitive dysfunction in HF typically range from approximately 30-50%, though impairment has been found in up to 80% of this population (Bennett & Sauvé, 2003). Moreover, the risk for cognitive dysfunction increases with greater HF severity as measured by the New York Heart Association (NYHA) Functional Class criteria (Vogels, et al., 2007a; Pressler et al., 2010). The risk of cognitive dysfunction in persons with HF is 4-times that of matched controls without HF (Sauvé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009), and individuals with HF are at increased risk for significant cognitive decline over time when compared to healthy controls (Hajduk et al., 2013). Impairment is found in multiple domains including memory, attention, executive function, psychomotor speed, and language (Almeida & Flicker, 2001; Vogels, Scheltens, Schroeder-Tanka, & Weinstein 2007; Vogels, et al., 2007a; Bennett & Sauvé, 2003; Pressler et al., 2010), and recent work has more precisely characterized the cognitive deficits observed in HF by identifying unique cognitive profiles, including those with intact performance, reduced memory, and globally impaired cognition (Miller et al., 2012).

Cognitive impairment in HF is associated with adverse outcomes, including a 5-fold increase in risk for mortality (Zuccala, et al., 2003) and a 6-fold increase in disability (Zuccala, et al., 2001). Non-adherence to medical regimen among HF patients also represents a significant problem (van der Wal, Jaarsma, & van Veldhuisen, 2005) and is likely due, in part, to cognitive deficits. For example, a recent study found that only 34% of HF patients were taking all medications as prescribed and were not taking any unprescribed medications. In addition, more
than half did not adhere to a low sodium diet or were able to calculate sodium content in foods. Moreover, only 16% could name two or more symptoms of worsening HF, and only 9% monitored symptoms for worsening HF (Moser, Doering, & Chung, 2005). Another study examining knowledge of prescribed medication found that only 55% of HF patients could correctly name their medication and only 36% could indicate when they were to take their medication (Cline, Björck-Linné, Israelsson, Willenheimer, & Erhardt, 1999). It appears likely that this poor compliance would extend into the management and monitoring of other medical conditions comorbid in this population, which in turn likely increases the risk for adverse outcomes.

The Etiology of Cognitive Dysfunction in Heart Failure

The etiology of cognitive dysfunction in HF is still being elucidated, though several potential mechanisms have been proposed including structural and functional brain changes and the presence of medical/psychiatric comorbidities. Although each of these factors are associated with adverse neurocognitive outcomes in non-HF populations, the work in addressing their relationship with cognition in HF is scarce, and the available findings are often inconsistent.

Adverse brain changes.

**Structural brain changes.** It is well established that HF is a risk factor for vascular dementia (Roman, 2005) and stroke (Siachos, et al., 2005; Wang et al., 2003). However, prior to the onset of such conditions, adverse brain changes that can negatively affect cognitive functioning emerge on neuroimaging in HF patients. Individuals with HF show cerebral atrophy and infarcts (Schmidt, Fazekas, Offenbacher, Dusleag, & Lechner, 1991; Vogels, et al., 2007b) as well as basal ganglia hyperintensities, deep white matter hyperintensities (WMH), and periventricular hyperintensities (Vogels, et al., 2007b; Almeida et al., 2005). In addition, a
reduction in gray matter volume is seen in areas such as the parahippocampal gyrus, cingulate gyrus, and frontal cortex (Woo, Macey, Fonarow, Hamilton, & Harper, 2003).

Despite these findings, few studies have directly examined the association between structural brain changes and cognitive performance in HF, and those that have report mixed findings and suffer from methodological limitations. For example, temporal lobe atrophy has been found to be associated with decreased performance on tasks of memory and executive function independent of other cardiovascular risk factors (e.g., hypertension). However, no association between WMH (periventricular or total) and cognitive performance was observed (Vogels et al., 2007c). Additional work comparing HF patients to controls found that those with HF performed worse on neuropsychological tests of multiple domains and had significantly worse right medial temporal lobe atrophy. However, those with HF had significantly less severe periventricular WMH than controls (Beer et al., 2009). Both studies are limited by the inclusion of only those without MRI contraindications (e.g., pacemaker) and patients requiring such devices may have more advanced HF and, as a result, different cognitive profiles and patterns of abnormalities on neuroimaging.

Despite methodological limitations, these results also suggest that structural brain changes cannot fully account for the pattern of cognitive impairment seen in HF, as the link is established in other forms of CVD. For example, individuals with hypertension have been found to demonstrate reduced volume and greater WMH when compared to their normotensive peers, and these abnormalities have been found to be associated with deficits on tasks of executive function (Raz, Rodrigue, & Acker, 2003). In addition, whole brain volume has been found to be associated with overall cognitive performance, as well as performance on tasks of attention and executive function among heterogeneous CVD patients, and subcortical hyperintensities have been linked with performance on tasks of attention and executive function (Paul et al., 2005).
**Functional brain changes.** Despite autoregulatory mechanisms that work to maintain adequate blood flow across ranges of cerebral perfusion pressures (Serrador & Milberg, 2010), persons with HF show a 19-30% decrease in cerebral perfusion when compared to healthy controls (Choi et al., 2006; Gruhn, et al., 2001). Moreover, the reduction of global cerebral blood flow (CBF) is associated with the severity and chronicity of HF (Choi et al., 2006). In addition to these generalized reductions, decreased cerebral perfusion is found in specific areas of the brain important for cognitive function including the frontal, temporal, and parietal lobes (Alves, et al., 2005; Burra et al., 2002; Vogels, et al., 2008). A review of the functional imaging literature on HF also found reduced perfusion in posterior cortical regions similar to the pattern of decreased activity seen in Alzheimer's disease (Alves & Busatto, 2006).

The negative impact that even temporary periods of reduced CBF can have on cognition is highlighted by the short-term cognitive dysfunction seen in individuals undergoing coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass. Recent work monitored real-time CBF during cardiopulmonary bypass and found a disruption of CBF in the middle cerebral artery (Brady et al., 2010). Abnormal CBF autoregulation during the re-warming phase of hypothermic cardiopulmonary bypass has also been observed (Joshi et al., 2010). To this end, a review examining neuropsychological outcomes after CABG with cardiopulmonary bypass found cognitive decline in 4-33% of patients 7 days following surgery, with cognitive decline seen in the domains of attention, processing speed, and memory. While it is hypothesized that the etiology of cognitive decline following CABG with cardiopulmonary bypass is multi-factorial, cerebral hypoperfusion is suspected to play an important role (Selnes & Gottesman, 2010).

Based on the above findings, it appears likely that a similar effect of reduced CBF would be found in persons with HF, as the reductions in CBF are more chronic. However, few studies
have directly examined this association in persons with HF, and those that have yielded mixed findings. For example, a positive association between mean blood flow velocity of the right middle cerebral artery (MCA) and performance on the Mini Mental State Exam (MMSE) has been observed. An inverse relationship between MMSE performance and the right MCA pulsatility index (PI), a measure of vascular resistance, has also been observed. However, the initial analyses conducted included individuals with a history of stroke, and when those with stroke history were excluded, only the inverse association between right MCA PI and MMSE performance remained significant (Jesus et al., 2006). While these findings are consistent with what would be expected, the MMSE is a brief, global screening measure of cognitive function and is not equivalent to a comprehensive neuropsychological evaluation.

Additional work examined the associations among CBF and cognitive performance in persons with mild to moderate HF, cardiac controls without HF, and healthy controls. Those with HF had lower mean blood flow velocities and higher PI values for the MCA when compared to healthy controls, but did not differ from cardiac controls. In addition, those with HF performed significantly worse than healthy and cardiac controls on cognitive tasks; however, the reduction in CBF was not related to cognitive performance. While a comprehensive neuropsychological battery was used, the generalizability of these results is limited by the range restriction of cognitive performance. Upon closer inspection, persons in all groups exhibited generally intact cognitive function across all measures (Vogels, et al., 2008).

Work using single-photon emission computed tomography, found that individuals with HF had lower global cognition and poorer performance on tasks of visual and verbal memory, learning, and language, when compared to controls. In addition, individuals with HF showed a reduction in regional CBF in posterior cortical regions of the brain, and total score on a composite cognitive measure was correlated to regional CBF to the posterior cingulate cortex and precuneus.
However, this study is limited by the largely cognitively intact nature of the sample (Alves et al., 2005).

More recently, the associations among cerebral perfusion, cardiac output, and cognition in HF were examined, with a specific focus on cardiac output as a potential moderator. A moderating effect of cardiac output was only observed for the relationship between mean flow velocity of the anterior cerebral artery for memory and executive function performance. However, these results did not exhibit the expected pattern, as higher levels of cardiac output with increasing mean flow velocity of the anterior cerebral artery were associated with decreased performance on tasks of executive function and no change in memory performance. Moreover, CBF velocity was only independently associated with memory performance. However, this study was also limited by the relatively intact nature of the sample (Miller, 2012).

Such findings argue for additional contribution from other mechanisms as the association between CBF and cognition has been demonstrated in other populations. For example, among CVD populations improvements in mean flow velocities in cerebral arteries (Massaro, Dutra, Almeida, Diniz, & Malheiros, 2006) and cognitive function (Bornstein et al., 1995; Deshielids et al., 1996) have been demonstrated following cardiac transplant. In addition, among persons with heterogeneous forms of CVD, systemic hypoperfusion, which likely impacts cerebral perfusion, has been found to be associated with reduced executive function performance (Jefferson, Poppas, Paul & Cohen, 2007).

**Comorbid conditions.** HF is associated with numerous comorbid conditions including hypertension, type-2 diabetes mellitus (T2DM), sleep-disordered breathing, and depression (Metra, et al., 2011). Each condition has been found to be associated with adverse neurocognitive outcomes in older adults, independent of HF, suggesting that those with comorbid HF may be a
particularly vulnerable group. Despite the implicated link between these conditions and cognition in HF, there is limited research examining these potential relationships.

**Hypertension.** Hypertension has been found to be associated with adverse neurocognitive outcomes including cognitive dysfunction, risk of dementia, and structural and functional brain changes in non-HF populations (Birns & Kalra, 2009; Duron & Hannon, 2008a). Although hypertension is a common comorbidity of HF, the extent to which hypertension contributes to the cognitive dysfunction observed in HF remains unclear and understudied. For example, one study found that comorbid hypertension was a risk factor for cognitive dysfunction in HF, but important covariates (e.g., medication status) were not controlled for and a possible additive effect was not examined (Trojano, et al., 2003). A more recent study compared the cognitive performance of HF individuals with and without comorbid hypertension. After controlling for other key demographic/medical variables, hypertension was found to be independently associated with worse cognitive performance in aspects of attention/executive function/psychomotor speed and motor functioning (Alosco, et al., 2012b). Lastly, in a study examining cognitive profiles in HF, individuals who were classified as globally impaired were 10-times more likely to have hypertension than those who demonstrated intact performance. However, group classification based on hypertension status was not better than chance (Miller, et al., 2012).

**Type-2 diabetes mellitus.** It is well established that T2DM is associated with cognitive deficits and risk of dementia in non-HF populations (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009; Allen, Frier, & Strachan, 2004; Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2005). Structural and functional brain changes that can impact cognition have also been demonstrated in T2DM (McCrimmon, Ryan, & Frier, 2012; Hu, et al., 2008;
Vuletic, et al., 2011). T2DM is common in HF, with work finding that 31% of patients with HF had a comorbid diagnosis of diabetes. Moreover, comorbid T2DM was associated with a higher risk of preventable hospitalizations and increased mortality (Braunstein et al., 2003).

Despite these findings, few studies have examined the potential increased risk for cognitive dysfunction when both conditions are present, and the available findings are mixed. A recent study examined the potential additive effect of T2DM on cognitive dysfunction in older adults with HF and after controlling for several important covariates, those with T2DM demonstrated poorer performance on tasks of attention, executive function, and motor functioning, as well as global cognition, than those without T2DM (Alosco et al., 2012a). In contrast, additional work found no difference in the prevalence of T2DM among distinct cognitive profiles (i.e., intact, memory impaired, globally impaired) in HF, suggesting T2DM did not differentially impact cognitive performance (Miller, et al., 2012).

**Sleep-disordered breathing.** Sleep disordered breathing in non-HF populations, particularly obstructive sleep apnea (OSA), has been found to adversely impact performance in numerous cognitive domains and is associated with structural and functional brain changes (Sforza & Roche, 2012; Urbano, Roux, Schindler, & Mohsenin, 2008; Nasr et al., 2009; Ramos, Cabral, Lee, Sacco, & Rundek, 2012). The cognitive deficits in these domains are suspected to result from the recurrence of apnea, sleep fragmentation, daytime sleepiness, and nocturnal hypoxemia that are associated with OSA (Sforza & Roche, 2012). Although no work has exclusively examined cognition in central sleep apnea (CSA), similar findings would likely be observed as CSA also results in sleep fragmentation, excessive daytime sleepiness, and hypoxia/hypoxemia (Eckert, Jordan, Merchia, & Malhotra, 2007).
Sleep disordered breathing is common among individuals with HF, with recent work demonstrating prevalence rates of 76-81% (Oldenburg et al., 2007; Herrscher, Akre, Overland, Sandvik, & Westheim, 2011), and it is also associated with adverse outcomes including an increased risk for disease progression (Bradley & Floras2003a, b). Despite the independent links to adverse neurocognitive outcomes, there is limited work examining the combined relationship. One recent study examined the relationship between sleep apnea and cognition in older adults with HF and found that those with comorbid sleep apnea performed significantly worse on tasks of attention and a measure of global cognition, after controlling for important covariates (Knecht, et al. 2012). Similarly, HF patients who were classified as globally cognitively impaired were 3-times more likely to have sleep apnea than those with intact performance or only reduced memory performance. However, further analyses indicated that the presence of sleep apnea did not classify individuals into their determined groups better than chance (Miller et al., 2012).

Depression. It is well established that late life depression is associated with cognitive dysfunction. While deficits have been observed across numerous cognitive domains, it is important to note that deficits in executive function and processing speed are generally more pronounced and are believed to impact the deficits observed in other cognitive domains (Crocco, Castro, & Loewenstein, 2010; Weisenbach, Boore, & Kales, 2012). In addition, structural brain changes that occur in late-life depression are well documented and occur in regions implicated in cognitive function (Thomas & O’Brien, 2009).

Depression is common in HF, with the prevalence of depression or depressive symptomatology estimated to range from 20 to 60% (Jiang et al., 2001; Rumsfeld et al., 2003; Rutledge, Reis, Linke, Greenberg, & Mills, 2006). However, despite the implicated links few studies have directly examined the relationship with cognition in HF. Trojano and colleagues
(2003) demonstrated that depression was an independent predictor of cognitive dysfunction in HF and that depressed individuals were over 2-times more likely to demonstrate impaired cognitive performance on at least three neuropsychological tests. However, important confounds (e.g., medication status) were not controlled for (Trojano, et al., 2003). In a more recent study, depression was found to be independently associated with cognitive performance, with higher scores on a self-report measure of depressive symptomatology associated with worse performance on tasks of attention, executive function, and language (Garcia et al., 2012).

**Reduced Physical Activity as a Modifiable Risk Factor for Cognitive Dysfunction in HF**

While several mechanisms have been proposed, the etiology of cognitive deficits in HF remains unclear. As such, consideration of additional potential contributors is warranted. One likely risk factor for cognitive dysfunction in this population is reduced physical activity.

**The capacity for physical activity is reduced in heart failure.** The progression of HF is associated with decreasing capacity for physical activity. The NYHA functional class system subjectively quantifies this reduction, with higher NYHA classification indicative of a greater inability to carry out physical activities and the experience of more severe symptoms associated with activity (Swedberg et al., 2005). The inability to carry out exercise seems to be largely related to inadequate peripheral perfusion due to reduced cardiac output. In fact, individuals with HF may achieve less than 50% of the cardiac output healthy controls achieve during peak exercise (Pina et al., 2003). Although cardiac output can be normal when at rest, it does not adequately rise during exercise in HF, thereby impacting functional capacity (Lund & Mancini, 2008). As HF progresses, even minimally exerting activities can result in the experience of significant physical symptoms (Swedberg et al., 2005).
Exercise is considered a safe treatment option in HF for those who are clinically stable and when regimens are made on an individual basis with consideration given to the individual’s HF status, comorbid conditions, and exercise tolerance (Vanhees et al., 2012). Despite recommendations to remain physically active, many individuals with HF do not adhere. For example, one study found that while 80% acknowledged that it was important to engage in physical activity, only 39% actually did (van der Wal et al., 2006). In another study, only 53% of individuals adhered to exercise recommendations and additional analyses were conducted to examine potential variables related to non-compliance. Sixty-one percent of the sample reported that it was more difficult to adhere to exercise recommendations than it was to other adhere to other recommendations, including smoking cessation. Factors that contributed to lack of adherence included lack of self-motivation and energy, and the experience of physical symptoms (Evangilista et al., 2001).

**The benefits of physical activity in heart failure.** Functional capacity is an important prognostic marker in HF, with greater impairment in capacity being related to poorer prognosis. For example, lower peak oxygen consumption, a measure of functional capacity, has been found to be a significant predictor of mortality in HF (Myers et al., 2008; Lund & Mancini, 2008). Given that exercise can readily improve functional capacity, a growing number of studies have shown that structured exercise programs have significant benefit in persons with HF. For example, an increase in peak oxygen consumption by an average of nearly 17% has been observed with structured exercise, with improvements associated with a reduced risk of adverse events including hospitalizations and mortality (Smart & Marwick, 2004; Boudreau, & Genovese, 2007). Exercise training has also been found to reduce sympathetic nervous system activation and endothelial dysfunction (Tabet et al., 2009), which may attenuate the progression of HF. A recent
study also found that involvement in an exercise training program resulted in significant improvements in NYHA classification in HF individuals with preserved ejection fraction, indicating a subjective reduction in the experience of physical symptoms associated with physical activity (Edelmann et al., 2011).

**Benefits of physical activity on cognition.**

*Cognitive benefits of physical activity in non-HF populations.* Numerous studies have examined the possible benefits of physical activity on cognition in older adults. Work with healthy older adults has demonstrated clear benefits of exercise interventions, with gains demonstrated in numerous cognitive domains including executive function, attention/processing speed, memory, and visuospatial abilities. In terms of intervention characteristics, combination programs (i.e., both strength and aerobic exercises) had more benefit than aerobic only; short programs were similar to medium length programs, though neither were as good as long programs; and persons aged 66-70 years benefited the most (Colcombe & Kramer, 2003). Similar findings emerged in a more recent meta-analysis (Smith et al., 2010b).

Studies on the impact of exercise in older adults with CVD have been carried out with similar positive findings, with individuals demonstrating improved cognitive performance. One study assessed CVD patients before and after completion of a cardiac rehabilitation program and found that changes in cognitive performance were related to the gains in fitness (Gunstad et al., 2005). More recent work found improvements in global cognition and in aspects of attention/executive function/psychomotor speed and memory following participation in cardiac rehabilitation (Stanek et al., 2011).

Self-reported levels of physical activity in healthy older adults have also been found to be associated with better performance on tasks of executive function, semantic verbal fluency, and
global cognition, independent of other factors known to impact cognition (Benedict et al., 2013). Prospective work has also demonstrated that when compared to their sedentary peers, the risk of cognitive decline is reduced by 35% and 38% in non-demented individuals who engage in low-moderate and high levels of physical activity, respectively (Sofi, et al., 2011). In fact, based on the rates of decline between different levels of physical activity, research shows that engagement in physical activity that is equivalent to briskly walking 30 minutes per day is comparable to being 5-7 years younger cognitively, among individuals with CVD/vascular risk factors (Vercambre, et al., 2011).

**Benefits of physical activity on cognitive outcomes in HF populations.** There is limited work examining the effect of physical activity on cognitive outcomes in HF, though existing work raises the possibility of cognitive benefits. Studies have shown that reduced levels of functional capacity are related to cognitive dysfunction in HF. Poorer global cognitive function has been found to be independently related to worse performance on a measure of functional capacity (i.e., 6 minute walk test; 6MWT) in older adults with HF. (Baldasseroni, et al., 2010). More recently, Alosco and colleagues (2012c) demonstrated an independent relationship between functional capacity, as measured by the 2-minute step test (2MST), and cognition in HF. After controlling for comorbid conditions, performance on the 2MST was not only significantly predictive of global cognitive function, but also of performance on tasks of executive function and language (Alosco, et al., 2012c). Similarly, performance on the 2MST has been found to be related to cognitive profiles in HF, as individuals categorized as globally impaired demonstrate significantly worse performance on the 2MST than those who are intact or only exhibiting memory impairments (Miller et al., 2012).
Only one study has examined the possible cognitive benefits of an exercise intervention in persons with HF. Tanne and colleagues (2005) detailed the impact of an 18-week exercise training program on functional capacity and cognition in individuals with moderate-severe HF (NYHA class III). The intervention included 50-minutes of aerobic exercise twice per week. Following the intervention, participants demonstrated gains in functional capacity and cognitive improvements were observed on tasks of attention/psychomotor speed and executive function. No such change emerged in HF controls, though performance was not directly compared (Tanne et al., 2005). While these findings are encouraging, the relationship between changes in functional capacity and cognition was not examined, and the neuropsychological battery was relatively brief.

Taken together, these findings suggest that reduced fitness is not only linked to cognitive dysfunction in HF, but may also correspond to the severity of impairment. Moreover, it appears that cognitive deficits may be somewhat reversible following improvements in fitness, arguing for a need of longitudinal work to clarify these possibilities.

The Current Study

Although it is well established that cognitive dysfunction is common in HF, the etiology of these deficits remains unclear. A likely contributor is reduced levels of physical activity. The risk for cognitive dysfunction in HF increases with disease severity and while physical activity is associated with reduced adverse outcomes, many individuals with HF do not adhere to the recommendation to stay active. It is also well established that physical activity is neuroprotective in non-HF populations and it can be postulated that a similar benefit would be found in persons with HF. As described above, recent work has demonstrated positive associations between physical activity/functional capacity and cognition in HF. However, longitudinal work is needed
to clarify the nature of the relationship between functional capacity and cognition in HF. In particular, clarifying the possible impact of exercise intensity is much needed. Although early studies found that the cognitive benefits of physical activity is not highly influenced by exercise intensity (e.g., Smith et al., 2010b; Vercambre, et al., 2011), there is more recent work suggesting that intensity is important (e.g. Brown et al., 2012; Kirk-Sanchez & McGough, 2014).

**Specific Aims**

*Aim 1: Examine the benefits of CR on functional capacity in older adults with HF.*

*Hypothesis 1:* HF patients who complete CR will demonstrate significant improvements in functional capacity over time when compared to HF controls.

*Aim 2: Examine the benefits of CR on cognition in older adults with HF.*

*Hypothesis 2:* HF patients who complete CR will demonstrate significant improvements, or relative stability, in cognitive performance over time when compared to HF controls, who are expected to decline with time.

*Aim 3: Examine the relationship between functional capacity and cognitive performance in older adults with HF.*

*Hypothesis 3:* Functional capacity will be related to cognitive performance such that (a) higher levels of initial functional capacity will lead to higher initial levels of cognitive performance and (b) improvements in functional capacity over time will lead to improvements in cognitive performance over time.

**Secondary Aims**
The current study also aimed to further clarify the above aims, and expand on past work, by examining additional secondary hypotheses. Specifically, the impact of exercise intensity during CR on cognition was examined, as well as the relationship between self-reported levels of physical activity in HF and CR, and the ability of self-reported levels of activity at 9-months to predict cognitive outcomes at 12-months.

**Aim 4: Examine the relationship between exercise intensity during CR and cognitive outcomes in older adults with HF completing CR.**

_Hypothesis 4:_ Higher average exercise intensity over the course of CR will be associated with better cognitive performance at 12-weeks for older adults with HF who complete CR.

**Aim 5: Examine the impact of CR on self-reported levels of physical activity in older adults with HF.**

_Hypothesis 5:_ Older adults with HF who complete CR will self-report higher levels of physical activity than HF controls, and reported levels will increase following completion of CR.

**Aim 6: Examine the relationship between self-reported activity at 9-months and cognitive outcomes at 12-months.**

_Hypothesis 6:_ Higher self-reported physical activity at 9-months will be associated with better 12-month cognitive performance.
Method

Participants

Participants were recruited from outpatient cardiology clinics and were eligible for participation if they were between 50-85 years of age, English-speaking, and had a history of HF. Exclusion criteria included a history of neurological disorder (e.g. stroke, Alzheimer's disease, severe head injury), history of significant psychological problems (e.g. schizophrenia, bipolar disorder, substance abuse), or developmental disability.

Individuals in the CR group self-enrolled in CR based on the recommendation of their healthcare providers. Individuals who were enrolled in CR were required to complete the baseline cognitive testing prior to finishing their ninth CR class. Completion of CR was defined as attending at least 20 CR classes.

The initial sample included 225 older adults with HF. Of this, 81 individuals were enrolled in CR. Fourteen individuals were excluded for having completed fewer than 20 CR classes and an additional 3 were also excluded for having completed more than 8 CR sessions before their baseline cognitive testing. Seventeen additional individuals were excluded for having not completed one or more office visits. The HF control group was initially comprised of 145 individuals, though a total of 22 individuals were excluded for having not completed one or more office visits. Therefore, a total of 170 older adults with HF (47 in CR, 123 HF controls) were included in the preliminary analyses.

Cardiac rehabilitation. CR classes were 1-hour long and were conducted under highly supervised conditions. Exercise regimens were individualized, though all included stretching, a
warm-up, a 40-minute aerobic exercise circuit, and a cool-down period. The aerobic circuit included several different options for training, including a treadmill, elliptical, recumbent and upright stationary cycles, arm ergometer, rowing machine, and stair stepper. For each aerobic exercise, metabolic equivalents (METs) were recorded.

**Measures**

**Cognitive function.** Participants completed a battery of well-established neuropsychological measures that assessed multiple cognitive domains including global cognitive functioning, memory, attention/psychomotor speed, executive function, and language. Specifically, participants completed the following measures:

*Estimated premorbid intelligence.*

*North American Adult Reading Test* (NAART; Blair & Spreen 1989). Individuals are asked to read a list of irregularly pronounced words. This test provides a reliable estimate of IQ in medical populations.

*Global cognitive functioning.*

*Modified Mini Mental Status Examination* (3MS; Teng & Chui, 1987). This test is a brief screening measure of global cognitive function and is an extension of the MMSE (Folstein, Folstein, & McHugh, 1975). Much like the MMSE, the 3MS is comprised of several short tasks, including orientation, learning and brief recall of a short list of target words, and a copy of a simple geometric figure. However, the 3MS also includes a delayed free recall of target words, additional orientation questions, animal fluency, and a measure of executive function (i.e.,
similarities). Previous work has found the 3MS to be better at identifying cognitive impairment and dementia among elderly individuals when compared to the MMSE (McDowell, Newell, Hill, & Hébert, 1997; Bland & Newman, 2001).

**Memory.**

*California Verbal Learning Test-Second Edition* (CVLT; Delis, Kramer, Kaplan, & Ober, 2000). Individuals are asked to learn and recall a 16-item word list. Specifically, indices of Learning (Sum of Trials 1-5), Short Delay Recall, and Long Delay Recall were examined. An alternate form was used at 12-weeks.

**Attention/psychomotor speed.**

*Trail Making Test A* (Reitan, 1958). In the Trail Making A task, participants are asked to connect a series of 25 numbered dots in ascending order as quickly as they can (e.g. 1-2-3, etc.). Time to completion was recorded.

*Letter Number Sequencing* (Wechsler, 1997). This test is a measure of complex attention and auditory working memory. Participants are read strings of numbers and letters of increasing length and asked to reorganize the numbers and letters according to predetermined rules.

*Grooved Pegboard* (Klove, 1963). Individuals are asked to place notched pegs into a 5 X 5 board as quickly as possible. Time to completion for the dominant hand was recorded.

**Executive function.**

*Trail Making Test B* (Reitan, 1958). Trail Making B adds a set-shifting component to Trail Making Test A and requires participants to alternate between numbers and letters in ascending order (e.g. 1-A-2-B, etc.). Time to completion was recorded.
**Frontal Assessment Battery** (Dubois, Slachevsky, Litvan, & Pillon, 2000). This test employs several short tasks to assess frontal system executive function. More specifically, participants are asked to identify similarities among two words (e.g., table, chair), name as many words as they can that start with a target letter, complete frontal-motor hand movements, and tap patterns with their dominant hand.

**Stroop Test** (Golden, 1978). This test measures selective attention and mental flexibility. Participants were asked to first read columns of words spelling out colors printed in black ink (word subtest). They were then asked to identify the color of ink a series of Xs is printed in (color subtest), and finally to indicate the color of the ink a word (which spells out a color) is printed in, regardless of the verbal content (color-word subtest). An interference score was calculated based on word and color subtest performances to determine expected performance on the color-word subtest; this was then compared to actual color-word test performance.

**Language.**

**Animal Naming** (Eslinger, Damasio, & Benton, 1984). This test is a measure of semantic verbal fluency. Participants were asked to name as many different kinds of animals as they could in 60 seconds.

**Boston Naming Test** (Kaplan, Goodglass, & Weintraub, 1983). This test is a measure of confrontation naming and language abilities. Participants were shown pictures and asked to name the depicted item. Item difficulty increases from high-frequency objects (e.g., bed) to lower-frequency objects (e.g., trellis).

**Functional capacity.** While cardiopulmonary testing is the gold standard for assessing functional capacity, it is time consuming and requires numerous resources. Previous work
examining alternative methods to assessing functional capacity has been conducted and there is evidence to suggest that the 2-minute step test (2MST) provides an accurate measurement of functional capacity (Rostagno & Gensini, 2008; Pollentier, et al., 2010; Pedrosa & Holanda, 2009). However, because performance on this test could be impacted by other factors (e.g., effort, orthopedic limitations) and some individuals refused or were unable to complete the 2MST, resting heart rate was included as a second measure of functional capacity, with lower resting heart rate associated with better cardiovascular fitness (Fox et al., 2007).

For the 2MST, participants were asked to march in place for two minutes bringing each knee up to a marked target on the wall set at each individual’s own midpoint between their hip and knee. The participant was allowed to rest if needed, though the timer was not stopped. The number of times the right knee met the target was counted (Rikli & Jones, 1999). Resting heart rate was assessed using an automated oscillometric blood pressure device (Accutor Plus Oscillometric BP Monitor, Datascope Corp, Mahwah, NH). A total of six measurements were averaged to determine resting heart rate.

**Exercise intensity.** METs is a unit used to describe energy expenditure. A MET represents the ratio of the rate of energy used during an activity to the rate of energy used at rest. For example, 1 MET is the rate of energy used by the body while at rest, while an activity that produces 3 METs takes 3-times the amount of energy used by the body when at rest (U.S. Department of Health and Human Services, 2010). METs were recorded during each CR class for each participant. An average individual METs per class score, based on the METs exerted during each aerobic exercise, was computed for every CR class. An overall mean METs value was then calculated by summing the METs for each CR class and dividing by the total number of CR classes completed; this value served as the measure of overall exercise intensity during CR.
METs ranged from 2.10 to 7.09 (M = 4.02 ± 1.27). The lower 10% of the group exerted 2.65 METs and the upper 10% exerted 6.03 METs.

**Self-reported levels of physical activity.** The Community Health Activities Model Program for Seniors Physical Activity Questionnaire (CHAMPS; Stewart et al., 2001) is a self-report questionnaire that consists of 41 items assessing the frequency and duration of various physical activities over the past 4 weeks. There is a formula available that allows for the computation of weekly METs for a subset of 28 of these items (Stewart et al., 2001). There is evidence to suggest that self-report provides valid information regarding physical activity in HF, with significant correlations reported between self-report and prognostic parameters (Jehn et al., 2011).

**Procedure**

All study procedures were approved by the Kent State University Institutional Review Board. Informed consent was provided by all study participants prior to beginning any part of the study. Participants were evaluated at three time points over the course of one year (baseline, 12-weeks, and 12-months). At each time point, the study procedures were completed in one visit. Participants provided medical history information through self-report measures, which was corroborated by medical records whenever possible and updated at subsequent assessments. Participants then completed the neuropsychological test battery, measures of functional capacity, and the CHAMPS. The CHAMPS was also mailed to all participants at 6- and 9-month time points to assess level of physical activity between the 12-week and 12-month assessments.
Statistical Analyses

**Preliminary statistical analyses.** With the exception of the 3MS, raw cognitive test scores were converted into z-scores/scaled scores using well-established normative data based on age, and when possible, education and gender. This was done in order to provide clinical meaning to the data in terms of allowing for qualitative interpretation of scores. These scores were then converted into T-scores to facilitate interpretation. A composite score was created for each cognitive domain (i.e., memory, attention/psychomotor speed, executive function, and language) by averaging the scores of each domain's subtests. If an individual was missing data for a test that made up a cognitive domain, the composite score was not computed and the domain score for that time point was coded as missing. Across the sample, there was a total of 7 missing data points for 7 different individuals. Specifically, within the CR group, there was 1 missing data point for attention/psychomotor speed at baseline, 1 missing data point for language at 12-weeks, and 1 missing data point for attention/psychomotor speed at 12-months. For the HF controls, there were 2 missing data points for attention and 1 missing data point for executive function at 12-weeks, and 1 missing data point for attention at 12-months. These cases remained in the final sample, though the missing time-points were coded as such.

Prior to statistical analyses, the data was examined for group differences in demographic and clinical characteristics between the CR group and the HF controls. Independent samples t-test and chi-square analyses indicated that the groups were demographically and clinically similar (see Table 1) and these variables were therefore not included in further analyses. Prior to testing study hypotheses, the data was examined for outliers and normality. Recent work has found that cognitive profiles in HF are heterogeneous (Miller et al., 2012) with individuals demonstrating a range of performances. As such, deficits in aspects of cognition are likely reflective of true performance and may impact the overall distribution of the data. The data was screened for
univariate outliers and two cases (both HF controls) were identified as having extreme outliers (i.e., > 4 SD), as well as having missing data at other time points, and were dropped from further analyses; extreme outliers were identified for grooved pegboard, TMT-A, and TMT-B, and these cases were also missing data at other time points for these variables. Additional examination of the data distributions revealed adequate normality. Therefore, the final sample was comprised 47 CR completers and 121 HF controls.

Table 1. Demographic and Clinical Characteristics at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CR Group (N=47)</th>
<th>HF Controls (N=121)</th>
<th>Test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.74 ± 8.17</td>
<td>69.47 ± 9.42</td>
<td>1.11</td>
<td>.27</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.28 ± 3.03</td>
<td>13.60 ± 2.60</td>
<td>1.46</td>
<td>.15</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>113.61 ± 9.22</td>
<td>110.20 ± 13.94</td>
<td>1.55</td>
<td>.12</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.10</td>
<td>36.36</td>
<td>1.79</td>
<td>.18</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59.57</td>
<td>70.25</td>
<td>1.75</td>
<td>.19</td>
</tr>
<tr>
<td>Type 2 Diabetes (%)</td>
<td>29.79</td>
<td>32.23</td>
<td>0.09</td>
<td>.76</td>
</tr>
<tr>
<td>Sleep Apnea (%)</td>
<td>19.15</td>
<td>23.97</td>
<td>0.45</td>
<td>.50</td>
</tr>
</tbody>
</table>

*Note. CR = cardiac rehabilitation; HF = heart failure*

The distribution of the total number of CR classes completed, as well as the total number of CR classes completed before the baseline assessment, for the CR group was examined. Most CR participants completed a total of 36 CR classes and there was not extensive variability in the range of total classes completed. The majority of CR participants completed 6 classes prior to baseline cognitive testing, and there was not extensive variability in the range of classes.
completed prior to baseline testing (see Table 2). Given the lack of extensive variability, these variables were not included in further analyses.

Table 2. Cardiac Rehabilitation Class Frequencies.

<table>
<thead>
<tr>
<th>Total Number of CR Classes</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>1 (2.13%)</td>
</tr>
<tr>
<td>22</td>
<td>1 (2.13%)</td>
</tr>
<tr>
<td>27</td>
<td>1 (2.13%)</td>
</tr>
<tr>
<td>34</td>
<td>2 (4.26%)</td>
</tr>
<tr>
<td>36</td>
<td>41 (87.22%)</td>
</tr>
<tr>
<td>37</td>
<td>1 (2.13%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR Classes before Baseline</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (2.13%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (8.51%)</td>
</tr>
<tr>
<td>3</td>
<td>4 (8.51%)</td>
</tr>
<tr>
<td>4</td>
<td>9 (19.15%)</td>
</tr>
<tr>
<td>5</td>
<td>9 (19.15%)</td>
</tr>
<tr>
<td>6</td>
<td>11 (23.40%)</td>
</tr>
<tr>
<td>7</td>
<td>6 (12.77%)</td>
</tr>
<tr>
<td>8</td>
<td>3 (6.38%)</td>
</tr>
</tbody>
</table>

*Note. CR = cardiac rehabilitation.*

**Primary analyses.** Latent growth curve modeling (LCGM) was used to examine the nature of changes in functional capacity and cognitive functioning over time across and between groups. To determine if change in functional capacity was related to participation in CR (Aim 1), an unconditional model grouping of all participants together was first conducted to determine if
functional capacity changed over time. Cardiac rehabilitation status (i.e., CR vs. HF control) was then introduced into the model (see Figure 1) to determine if functional capacity changed over time as a function of CR participation.
Figure 1. Conditional Latent Growth Curve Model for Testing Aim 1.
LGCM was then used to similarly examine if change in cognitive performance was related to participation in CR (Aim 2). First, an unconditional model grouping of all participants together was conducted to determine if cognition changed over time. Cardiac rehabilitation status (i.e., CR vs. HF control) was then introduced into the model (see Figure 2) to determine if cognitive performance changed over time as a function of CR completion. Separate models were conducted for each cognitive domain.
Figure 2. Conditional Latent Growth Curve Model for Testing Aim 2.
The completion of analyses for Aim 3 were contingent upon the results of Aims 1 and 2 being consistent with the hypothesized outcomes. The analysis plan was to use LGCM to examine the relationship between initial levels of functional capacity to cognitive performance for each domain. The interrelated slopes of functional capacity and cognition were also going to be examined to determine if cognition changed as a function of change in functional capacity. CR status was to be included as a covariate to examine group differences.

Hierarchical multiple regression was used to examine the relationship between METs exerted over the course of CR and 12-week cognitive performance (Aim 4). The composite cognitive domain score at the 12-week time point served as the dependent variable in all analyses. Baseline cognitive performance was controlled for in Block 1 and METs was added into Block 2. Since composite cognitive scores were calculated, all missing data was excluded listwise.

LGCM was used to examine the impact of CR on self-reported levels of physical activity (Aim 5). First, an unconditional model grouping of all participants together was conducted to determine if self-reported physical activity changed over time. Cardiac rehabilitation status (i.e., CR vs. HF control) was then introduced into the model (see Figure 3) to determine if self-reported physical activity changed over time as a function of CR completion.
Figure 3. Conditional Latent Growth Curve Model for Testing Aim 5.

Note. CHAMPS = Community Health Activities Model Program for Seniors Physical Activity Questionnaire.
Lastly, linear regression was used to examine the relationship between 9-month CHAMPS and 12-month cognitive performance for each cognitive domain (Aim 6).

**Power considerations for modeling change.** LGCM extends traditional repeated-measures designs by not only modeling change, but by also allowing for the examination of sources and consequences of change. LGCMs also allow for the examination of predictors that are both time-invariant and time-variant (Curran, Obeidat, & Losardo, 2010). Work has also compared LGCMs to repeated-measures MANOVA in ability to detect group differences with sufficient power when considering effect sizes. This work demonstrated that growth curve models consistently had better power in detecting group differences in growth trajectories than repeated-measures MANOVA. In addition, while samples of greater than 500 were needed to detect small group differences \((d = .20)\) with a power of .70 to .80, samples sizes ranging from 100 to 200 were sufficient to detect medium effect sizes \((d = .50)\) at an adequate power level (Fan, 2003). The number of measurements needed to have adequate power has also been examined. LGCM requires a minimum of three time points. When the model converges, power for a three time point model to detect a range of effect sizes is similar to that of models with additional time points (with \(\alpha = .05\)). For example, the power to detect an effect size of \(d = .30\) reaches the maximum with a sample of \(N > 100\) for three, five, seven, and nine time points. As such, adding additional time points does not seem to greatly impact power. However, it is important to note that convergence problems can arise when there are only three time points and the inclusion of additional time points may be of benefit in reducing this possibility (Fan & Fan, 2005).
Results

It is noted that some LGCM produced negative covariance matrices that required the variance of the slope to be constrained at a fixed value (i.e., 0) to allow for interpretation of the model. If the unconditional model required a slope variance constraint, the conditional model was first run without a constraint, and the slope variance was fixed if a negative covariance matrix was produced. Unless otherwise noted, the following results reflect a model that did not require a constraint to be placed on the variance of the slope. For each variable, the overall fit for the unconditional model will be presented first, followed by the parameter estimates of the means and variances of the slope and intercept. The results of the conditional model will then be presented in a similar manner. The conditional model was run for each variable regardless of the results of the unconditional model, given the a priori hypothesis that group differences should emerge.

The fit of the model (i.e., comparing the model’s predictions to the observed data) was evaluated by examining two fit indices, the root mean squared error of approximation (RMSEA) and the comparative fit index (CFI). An RMSEA between 0.08 and 0.05 was considered an adequate fit and an RMSEA < 0.05 was considered a good fit. A CFI ≥ 0.97 was considered a good fit and a CFI ≥ 0.95 was considered an adequate fit (Schermelleh-Engel, Moosbrugger, & Muller, 2003). It is noted that the parameter estimates of a model that has a poor fit should not be interpreted, as it is unlikely to be an accurate reflection of the data; however, all parameter estimates will be reported below.
Primary Aims

**Aim 1: Examine the benefits of CR on functional capacity in older adults with HF.**

**2MST.** The unconditional model required a constraint to be placed on the variance of the slope. Fit indices provided mixed evidence in terms of how well the model fit the data (RMSEA = 0.11, CFI = 0.96). Significant parameter estimates (unstandardized) for the mean of the intercept \( m_{\text{intercept}} = 61.55, \text{S.E.} = 1.85, p < .001 \) and slope \( m_{\text{slope}} = 0.39, \text{S.E.} = 0.15, p = .01 \) were observed, indicating that both values are significantly different from 0, with the slope estimating a mean increase of 0.39 units over time. The parameter estimate for the variance of the intercept was also significant \( \text{var}_{\text{intercept}} = 436.81, \text{S.E.} = 57.80, p < .001 \), suggesting significant variability in 2MST performance at baseline across groups. The variance of the slope is not estimated as this parameter was fixed.

The conditional model produced an adequate fit (RMSEA = 0.06, CFI = 0.99). A significant parameter estimate was observed for the intercept \( \beta = 0.31, \text{S.E.} = 0.08, p < .001 \) indicating individuals in the CR group started off with higher levels of functional capacity as measured by the 2MST at baseline. The parameter estimate for the slope was non-significant \( \beta = 0.11, \text{S.E.} = 0.09, p = .22 \) indicating the rate of change in 2MST performance did not differ between groups. See Table 3 for mean functional capacity and cognitive performance scores.
Table 3. Functional Capacity and Standardized Neuropsychological Test Performance.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>12-week follow-up</th>
<th></th>
<th>12-month follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR Group</td>
<td>HF Controls</td>
<td>CR Group</td>
<td>HF Controls</td>
<td>CR Group</td>
<td>HF Controls</td>
</tr>
<tr>
<td><strong>Functional Capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MST</td>
<td>74.02 ± 20.82</td>
<td>60.11 ± 20.88</td>
<td>79.95 ± 22.83</td>
<td>61.70 ± 24.11</td>
<td>82.07 ± 27.59</td>
<td>61.52 ± 23.67</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>63.94 ± 11.98</td>
<td>65.35 ± 11.65</td>
<td>60.48 ± 9.39</td>
<td>64.27 ± 11.23</td>
<td>62.16 ± 9.70</td>
<td>67.21 ± 10.86</td>
</tr>
<tr>
<td><strong>Cognitive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3MS</td>
<td>94.51 ± 4.36</td>
<td>92.50 ± 5.30</td>
<td>95.06 ± 4.33</td>
<td>93.11 ± 5.33</td>
<td>95.06 ± 5.10</td>
<td>93.40 ± 5.77</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning</td>
<td>50.28 ± 8.75</td>
<td>48.74 ± 11.33</td>
<td>49.15 ± 11.13</td>
<td>50.31 ± 10.98</td>
<td>52.68 ± 10.96</td>
<td>50.19 ± 12.95</td>
</tr>
<tr>
<td>Short Delay</td>
<td>49.36 ± 9.01</td>
<td>47.40 ± 10.37</td>
<td>50.00 ± 11.52</td>
<td>50.17 ± 10.95</td>
<td>52.02 ± 8.89</td>
<td>51.86 ± 11.09</td>
</tr>
<tr>
<td>Long Delay</td>
<td>48.51 ± 9.66</td>
<td>47.19 ± 10.49</td>
<td>48.83 ± 10.74</td>
<td>48.55 ± 11.46</td>
<td>51.60 ± 9.84</td>
<td>51.45 ± 10.81</td>
</tr>
<tr>
<td><strong>Attention/Psychomotor Speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-A</td>
<td>51.64 ± 8.15</td>
<td>50.63 ± 9.84</td>
<td>53.15 ± 7.55</td>
<td>50.90 ± 11.84</td>
<td>52.85 ± 8.06</td>
<td>50.19 ± 12.95</td>
</tr>
<tr>
<td>LNS</td>
<td>52.57 ± 8.07</td>
<td>50.86 ± 9.34</td>
<td>53.17 ± 7.93</td>
<td>51.28 ± 8.07</td>
<td>52.96 ± 7.55</td>
<td>51.51 ± 9.85</td>
</tr>
<tr>
<td>Grooved Pegboard</td>
<td>40.18 ± 25.64</td>
<td>34.20 ± 19.27</td>
<td>43.46 ± 17.73</td>
<td>37.49 ± 16.67</td>
<td>44.38 ± 21.72</td>
<td>35.45 ± 19.47</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-B</td>
<td>46.56 ± 18.03</td>
<td>45.09 ± 15.91</td>
<td>48.89 ± 11.57</td>
<td>46.36 ± 13.47</td>
<td>48.16 ± 13.98</td>
<td>45.80 ± 15.38</td>
</tr>
<tr>
<td>FAB</td>
<td>50.95 ± 16.46</td>
<td>42.65 ± 20.62</td>
<td>53.11 ± 16.00</td>
<td>47.35 ± 16.14</td>
<td>50.86 ± 15.81</td>
<td>43.20 ± 20.10</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>49.79 ± 9.49</td>
<td>50.03 ± 6.96</td>
<td>51.40 ± 7.94</td>
<td>51.13 ± 8.82</td>
<td>51.42 ± 6.59</td>
<td>50.37 ± 7.38</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td>53.57 ± 9.64</td>
<td>49.67 ± 13.45</td>
<td>54.49 ± 9.68</td>
<td>51.91 ± 13.15</td>
<td>54.63 ± 9.39</td>
<td>49.62 ± 17.16</td>
</tr>
<tr>
<td>Animal Fluency</td>
<td>58.17 ± 10.85</td>
<td>53.93 ± 11.83</td>
<td>58.15 ± 12.02</td>
<td>55.69 ± 12.34</td>
<td>59.15 ± 11.65</td>
<td>53.44 ± 11.80</td>
</tr>
</tbody>
</table>

*Note.* CR = cardiac rehabilitation; HF = heart failure; 2MST = 2-Minute Step Test; 3MS = Modified Mini-Mental State Exam; TMT-A = Trail Making Test A; LNS = Letter-Number Sequencing; TMT-B = Trail Making Test-B; FAB = Frontal Assessment Battery; BNT = Boston Naming Test. *CR = 43, Control = 99; *CR = 47, Control = 118; *CR = 45, Control = 119; *CR = 45, Control = 116; *CR = 46, Control = 121.
Resting heart rate. Fit indices provided mixed evidence in terms of how well the model fit the data (RMSEA = 0.21, CFI = 0.95). Significant parameter estimates (unstandardized) for the mean of the intercept ($m_{\text{intercept}} = 63.71$, S.E. = 0.88, $p < .001$) and slope ($m_{\text{slope}} = 0.14$, S.E. = 0.07, $p = .04$) were observed, indicating that both values are significantly different from 0, with the slope estimating a mean increase of 0.14 units over time. The parameter estimate for the variance of the intercept was also significant ($\text{var}_{\text{intercept}} = 84.55$, S.E. = 14.51, $p < .001$), suggesting significant variability in resting heart rate across groups at baseline. The parameter estimate for the variance of the slope was non-significant ($\text{var}_{\text{slope}} = 0.10$, S.E. = 0.29, $p = .72$), indicating no significant variability in how resting heart rate changed over time across groups.

For the conditional model, fit indices provided mixed evidence in terms of how well the model fit the data (RMSEA = 0.15, CFI = 0.96). The parameter estimate for the intercept was non-significant ($\beta = -1.88$, S.E. = 1.91, $p = .33$) indicating there were no significant group differences at baseline in resting heart rate. The parameter estimate for the slope was also non-significant ($\beta = -0.27$, S.E. = 0.15, $p = .06$) indicating the rate of change in resting heart rate over time did not differ between groups.

Aim 2: Examine the benefits of CR on cognition in older adults with HF.

3MS. The unconditional model adequately fit the data (RMSEA = 0.08, CFI = 0.99). Significant parameter estimates (unstandardized) for the mean of the intercept ($m_{\text{intercept}} = 93.21$, S.E. = 0.38, $p < .001$) and slope ($m_{\text{slope}} = 0.06$, S.E. = 0.03, $p = .03$) were observed, indicating that both values are significantly different from 0, with the slope estimating a mean increase of 0.06 units over time across groups. The parameter estimate for the variance of the intercept was also significant ($\text{var}_{\text{intercept}} = 16.58$, S.E. = 2.74, $p < .001$), suggesting significant variability in 3MS scores across groups at baseline. The parameter estimate for the variance of the slope was non-
significant (var_slope = 0.01, S.E. = 0.06, p = .92), indicating no significant variability in how 3MS scores changed over time across groups.

The conditional model fit the data well (RMSEA < 0.001, CFI = 1.0). The parameter estimate for the intercept was significant (β = 0.23, S.E. = 0.09, p = .01) indicating that individuals in the CR group had higher 3MS scores at baseline. However, the parameter estimate for the slope was non-significant (β = -0.18, S.E. = 0.97, p = .86) indicating no difference in the rate of change in 3MS scores over time between groups.

**Memory.** The unconditional model fit the data well (RMSEA < 0.001, CFI = 1.0). Significant parameter estimates (unstandardized) for the mean of the intercept (m_intercept = 47.98, S.E. = 0.71, p < .001) and slope (m_slope = 0.34, S.E. = 0.05, p < .001) were observed, indicating that both values are significantly different from 0, with the slope estimating a mean increase of 0.34 units in memory performance over time. The parameter estimate for the variance of the intercept was also significant (var_intercept = 65.07, S.E. = 10.64, p < .001), suggesting significant variability in memory performance across groups at baseline. The parameter estimate for the variance of the slope was non-significant (var_slope = 0.03, S.E. = 0.20, p = .90), indicating no significant variability in how memory changed over time across groups.

The conditional model also fit the data well (RMSEA < 0.001, CFI = 1.0). The parameter estimate for the intercept was non-significant (β = 0.07, S.E. = 0.09, p = .45) indicating no group differences in memory performance at baseline. The parameter estimate for the slope was also non-significant (β = -0.23, S.E. = 0.88, p = .80) indicating no difference in the rate of change in memory over time between groups.

**Attention/psychomotor speed.** The unconditional model required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.24, CFI = 0.93). A significant parameter estimate (unstandardized) for the mean of the intercept (m_intercept =
47.08, S.E. = 0.71, p < .001) was observed, indicating this value is significantly different from 0. However, the mean of the slope (m_{slope} = 0.02, S.E. = 0.04, p = .73) was non-significant indicating no differences in changes in attention/psychomotor speed over time between groups. The parameter estimate for the variance of the intercept was significant (\text{var}_{intercept} = 66.54, S.E. = 7.97, p < .001), suggesting significant variability in attention/psychomotor speed across groups at baseline. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

The conditional model similarly required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.20, CFI = 0.93). The parameter estimate for the intercept was non-significant (\beta = 0.15, S.E. = 0.08, p = .07) indicating no group differences in attention/psychomotor speed at baseline. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

**Executive function.** The unconditional model required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.23, CFI = 0.91). A significant parameter estimate (unstandardized) for the mean of the intercept (m_{intercept} = 48.30, S.E. = 0.78, p < .001) was observed, indicating this value is significantly different from 0. However, the mean of the slope (m_{slope} = -0.03, S.E. = 0.06, p = .62) was non-significant indicating no differences in change in executive function over time between groups. The parameter estimate for the variance of the intercept was significant (\text{var}_{intercept} = 68.29, S.E. = 8.67, p < .001), suggesting significant variability in executive function across groups at baseline. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

The conditional model similarly required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.19, CFI = 0.92). The parameter estimate
for the intercept was non-significant (β = 0.15, S.E. = 0.09, p = .09) indicating there were no significant group differences in executive function at baseline. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

**Language.** The unconditional model required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.84, CFI < 0.001). A significant parameter estimate (unstandardized) for the mean of the intercept (m_intercept = 55.56, S.E. = 1.23, p < .001) was observed, indicating this value is significantly different from 0. However, the mean of the slope (m_slope = -0.35, S.E. = 0.22, p = .12) was non-significant indicating no difference in changes in language over time between groups. The parameter estimate for the variance of the intercept was significant (var_intercept = 106.70, S.E. = 17.87, p < .001), suggesting significant variability in language across groups at baseline. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

The conditional model similarly required a constraint to be placed on the variance of the slope. This model did not fit the data well (RMSEA = 0.73, CFI = 0.29). The parameter estimate for the intercept was significant (β = 0.92, S.E. = 0.03, p < .001) indicating that individuals in the CR group had higher baseline language performance. The parameter estimate for the variance of the slope was not estimated as the model was constrained.

**Exploratory post-hoc analyses for Aims 1 and 2**

Although LCGM analyses did not support the study hypotheses, additional exploratory post-hoc analyses were conducted in order to clarify the possible benefits of CR on cognitive function in older adults with HF. Repeated measures MANOVA were used to compare functional capacity and neuropsychological test performance of the CR group and HF controls, and pairwise
comparisons were conducted using Bonferroni-corrected post-hoc tests for exploratory purposes only. See Tables 4 and 5 for between and within group differences, respectively.

**2MST.** No group x time interaction \([\lambda = 0.98, F(2, 139) = 1.79, p = .17]\) emerged. However, analyses revealed significant effects of time \([\lambda =0.06, F(2,162) = 5.30, p = .01]\) and group \([F(1,163) = 4.47, p = .04]\). Exploratory examination of between group differences showed that the CR group had better 2MST performance than the HF controls at all time points \((p < .001)\). Within group comparisons showed a trend for the CR group to improve from baseline to 12-weeks \((p = .06)\), and there was a significant improvement from baseline to 12-months \((p = .04)\). The HF controls showed no change in 2MST over time.

**Resting heart rate.** No group x time interaction \([\lambda = 0.98, F(2, 162) = 2.04, p = .13]\) emerged. However, analyses showed a significant effect for time \([\lambda = 0.94, F(2, 162) = 5.30, p = .01]\) and group \([F(1,163) = 4.47, p = .04]\). Exploratory examination of between group differences showed no differences in resting heart rate at baseline, though the CR group had significantly lower resting heart rates than HF controls at 12-weeks \((p = .04)\) and 12-months \((p = .01)\). Within group comparisons showed that the CR group declined in mean resting heart rate from baseline to 12-weeks \((p = .04)\). Mean resting heart rate increased for HF controls from 12-weeks to 12-months \((p < .01)\).

**3MS.** No group x time interaction \([\lambda = 0.97, F(6, 660) = 0.70, p = .65]\) or effect for group \([\lambda = 1.00, F(3,164) = 0.08, p = .97]\) emerged. However, analyses revealed a significant effect of time \([\lambda =0.79, F(6,161) = 7.23, p < .001]\). Exploratory examination of between group differences showed individuals in the CR group had higher scores on the 3MS at baseline \((p = .02)\) and 12-weeks \((p = .03)\); there was a trend for the CR group to have a higher 3MS at 12-months \((p = .09)\). Examination of within group comparisons showed no change in 3MS over time in the CR group.
Within the HF control group, there was a trend for an improvement in 3MS from baseline to 12-months ($p = .06$).

**Memory.** No group x time interaction [$\lambda = 0.97$, $F (6, 660) = 0.70$, $p = .65$] or effect for group [$\lambda = 1.00$, $F (3,164) = 0.08$, $p = .97$] emerged. However, analyses revealed a significant effect of time [$\lambda =0.79$, $F (6,161) = 7.23$, $p < .001$]. Exploratory examination of between group differences showed no differences in performance on any of the memory indices. Examination of within group differences showed individuals in the CR group showed improvements in learning from 12-weeks to 12-months ($p < .01$), and their 12-month performance was better than baseline learning ($p = .02$). The CR group showed no changes in short or long delay recall. The HF controls improved on learning from 12-weeks to 12-months ($p < .001$), and their 12-month performance was better than baseline learning ($p < .01$). On short delay recall, HF controls showed improvement from baseline to 12-weeks ($p < .01$), and their 12-month performance was better than baseline ($p < .001$). On long delay recall, HF controls showed improvement from baseline to 12-months ($p < .001$).

**Attention/psychomotor speed.** No group x time interaction [$\lambda = 0.97$, $F (6, 159) = 0.72$, $p = .64$], effect for group [$\lambda = 0.97$, $F (3,162) = 1.91$, $p = .13$], or effect for time [$\lambda = 0.95$, $F(3,160) = 1.47$, $p = .19$] emerged. Exploratory examination of between group differences showed that the CR group performed better on grooved pegboard at 12-weeks ($p = .04$) and 12-months ($p = .01$). Examination of within group differences showed the HF controls improved on grooved pegboard from baseline to 12-weeks ($p = .04$).

**Executive function.** No group x time interaction [$\lambda = 0.96$, $F (6,160) = 1.12$, $p = .35$] or effect of time [$\lambda = 0.93$, $F (6,160) = 3.03$, $p = .09$] emerged. However, analyses revealed a significant effect of group [$\lambda = 0.95$, $F (3,163) = 3.03$, $p = .03$]. Exploratory examination of between group differences showed that the CR group performed better than HF controls on the
FAB at baseline ($p = .02$), 12-weeks ($p = .04$), and 12-months ($p = .02$). Examination of within group difference showed HF controls improved on the FAB from baseline to 12-weeks ($p = .02$) and declined from 12-weeks to 12-months ($p = .05$) to a mean performance similar to that of their baseline.

**Language.** No significant group x time interaction [$\lambda = 0.96, F (4,162) = 1.77, p = .14$] emerged. However, effects for group [$\lambda = 0.96, F (2,164) = 3.09, p = .05$] and time [$\lambda = 0.93, F (4,162) = 3.27, p = .01$] were observed. Exploratory examination of between group differences showed that the CR group performed better than HF controls on Animal Naming at baseline ($p = .04$) and 12-months ($p = .01$). There were no significant differences in the BNT, though there was a trend for the CR group to perform better at baseline ($p = .07$) and 12-months ($p = .06$). Examination of within group differences showed that the HF control group demonstrated a trend for a decline in Animal Naming from 12-weeks to 12 months ($p = .06$). The HF controls improved on the BNT from baseline to 12-weeks ($p < .001$), though declined from 12-weeks to 12-months ($p < .01$).
Table 4. Post-Hoc Between-Group Differences in Functional Capacity and Standardized Neuropsychological Test Performance.

<table>
<thead>
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<th>Baseline</th>
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<th>12-months</th>
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<tbody>
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<td></td>
</tr>
<tr>
<td>2MST</td>
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<td>CR &gt; Control</td>
<td>CR &gt; Control</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
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<td>CR &lt; Control</td>
<td>CR &lt; Control</td>
</tr>
<tr>
<td><strong>Cognitive Function</strong></td>
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</tr>
<tr>
<td>3MS</td>
<td>CR &gt; Control</td>
<td>CR &gt; Control</td>
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</tr>
<tr>
<td><strong>Memory</strong></td>
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<tr>
<td>Learning</td>
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<tr>
<td>Short Delay</td>
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<tr>
<td>Long Delay</td>
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<tr>
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<td>TMT-A</td>
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<tr>
<td>LNS</td>
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</tr>
<tr>
<td>Grooved Pegboard</td>
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<td>CR &gt; Control</td>
<td>CR &gt; Control</td>
</tr>
<tr>
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<tr>
<td>FAB</td>
<td>CR &gt; Control</td>
<td>CR &gt; Control</td>
<td>CR &gt; Control</td>
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<tr>
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<tr>
<td><strong>Language</strong></td>
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<tr>
<td>BNT</td>
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</tr>
<tr>
<td>Animal Fluency</td>
<td>CR &gt; Control</td>
<td>--</td>
<td>CR &gt; Control</td>
</tr>
</tbody>
</table>

*Note.* CR = cardiac rehabilitation; 2MST = 2-Minute Step Test; 3MS = Modified Mini-Mental State Exam; TMT-A = Trail Making Test A; LNS = Letter-Number Sequencing; TMT-B = Trail Making Test-B; FAB = Frontal Assessment Battery; BNT = Boston Naming Test.
Table 5. Post-Hoc Within-Group Differences in Functional Capacity and Standardized Neuropsychological Test Performance.

<table>
<thead>
<tr>
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<th><strong>CR Group</strong></th>
<th><strong>HF Control</strong></th>
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</thead>
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<tr>
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</tr>
<tr>
<td>2MST</td>
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</tr>
<tr>
<td>Resting Heart Rate</td>
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<td>12wks to 12mos: ↑</td>
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<tr>
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<td></td>
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<tr>
<td><strong>Cognitive Function</strong></td>
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<td></td>
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<tr>
<td>3MS</td>
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<tr>
<td><strong>Memory</strong></td>
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<tr>
<td>Learning</td>
<td>12wks to 12mos: ↑</td>
<td>12wks to 12mos: ↑</td>
</tr>
<tr>
<td></td>
<td>BL to 12mos: ↑</td>
<td>BL to 12mos: ↑</td>
</tr>
<tr>
<td>Short Delay</td>
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<td>BL to 12wks: ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BL to 12mos: ↑</td>
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<tr>
<td>Long Delay</td>
<td>--</td>
<td>BL to 12mos: ↑</td>
</tr>
<tr>
<td><strong>Attention/Psychomotor Speed</strong></td>
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<tr>
<td>TMT-A</td>
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<tr>
<td>LNS</td>
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<tr>
<td>Grooved Pegboard</td>
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<td>BL to 12wks: ↑</td>
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<tr>
<td><strong>Executive Function</strong></td>
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<tr>
<td>TMT-B</td>
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<tr>
<td>FAB</td>
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<td>BL to 12wks: ↑</td>
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<td>12wks to 12mos: ↓</td>
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<tr>
<td>Stroop Interference</td>
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<tr>
<td><strong>Language</strong></td>
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<tr>
<td>BNT</td>
<td>--</td>
<td>BL to 12wks: ↑</td>
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<tr>
<td></td>
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<td>12wks to 12mos: ↓</td>
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<tr>
<td>Animal Fluency</td>
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</tbody>
</table>

*Note. CR = cardiac rehabilitation; HF = heart failure; BL = baseline, 2MST = 2-Minute Step Test; 3MS = Modified Mini-Mental State Exam; TMT-A = Trail Making Test A; LNS = Letter-Number Sequencing; TMT-B = Trail Making Test-B; FAB = Frontal Assessment Battery; BNT = Boston Naming Test.*
Aim 3: Examine the relationship between functional capacity and cognitive performance in older adults with HF. Analyses indicated no group differences in how functional capacity (Aim 1) or cognition (Aim 2) changed over time. The purpose of Aim 3 was to examine the relationship between changes in functional capacity and cognition, with the specific hypothesis that improvements in functional capacity would be related to cognitive gains. Given that study Aims 1 and 2 were not supported, the analyses planned for Aim 3 were not conducted. However, to further understand that data, regression analyses were conducted to determine whether better functional capacity predicted better cognitive performance across groups. See Tables 6 - 8 for regression coefficients.

**CR group.**

**3MS.** The 2MST was a significant predictor of the 3MS at baseline [F (1, 45) = 4.83, p = .03], 12-weeks [F(1,44) = 9.35, p < .01], and 12-months [F(1,42) = 7.37, p = .01], with higher 2MST performance associated with higher 3MS scores. In contrast, resting heart rate was not a significant predictor of the 3MS at baseline [F (1, 45) = 0.34, p = .56], 12-weeks [F (1, 45) = 1.01, p = .32], or 12-months [F (1,45) = 0.04, p = .84].

**Memory.** The 2MST was not a significant predictor of memory performance at baseline [F (1, 46) = 1.64, p = .21], 12-weeks [F (1,45) = 2.46, p = .12], or 12-months [F (1,43) = 0.23, p = .63]. Resting heart rate was also not a significant predictor of memory performance at baseline [F (1,45) = 1.60, p = .21] or 12-weeks [F (1,45) = 0.01, p = .97], but was a significant predictor at 12-months [F (1,45) = 4.09, p = .05], with lower resting heart rate associated with better memory performance.

**Attention/psychomotor speed.** The 2MST was a significant predictor of attention/psychomotor speed performance at 12-months [F (1, 41) = 21.31, p < .001] with higher
2MST performance associated with better attention/psychomotor speed. There was also a similar trend for the relationship between the 2MST and 12-week attention/psychomotor speed \[F (1, 44) = 3.85, p = .06\]. The 2MST was not a significant predictor of attention/psychomotor speed at baseline \[F (1, 44) = 1.20, p = .28\]. Resting heart rate was not a significant predictor of attention/psychomotor speed at baseline \[F (1, 44) = 1.02, p = .32\], 12-weeks \[F (1, 45) = 0.09, p = .77\], or 12-months \[F (1,44) = 0.62, p = .44\].

*Executive function.* The 2MST was a significant predictor of baseline \[F (1, 46) = 3.98, p=.05\], 12-week \[F (1,44) = 12.34, p < .01\], and 12-month \[F (1,42) = 4.26, p = .05\] executive function, with higher 2MST performance associated with better executive function. Resting heart rate was not a significant predictor of executive function at baseline \[F (1, 45) = 2.48, p = .12\], 12-weeks \[F (1, 45) = 0.31, p = .58\], or 12-months \[F (1, 45) = 0.22, p = .64\].

*Language.* The 2MST was a significant predictor of baseline \[F (1, 45) = 9.12, p < .01\], 12-week \[F (1, 43) = 33.51, p < .001\], and 12-month \[F (1,42) = 18.08, p < .001\] language performance, with higher 2MST associated with better language performance. Resting heart rate was not a significant predictor of language at baseline \[F (1, 45) = 0.49, p = .49\], 12-weeks \[F (1,44) = 1.93, p = .17\], or 12-months \[F (1,45) = 0.40, p = .53\].

*HF Controls*

3MS. The 2MST was a significant predictor of the 3MS at baseline \[F (1,107) = 13.11, p < .001\], 12-weeks \[F (1,111) = 7.98, p = .01\], and 12-months \[F (1,105) = 8.98, p < .01\], with higher 2MST performance associated with higher 3MS scores. Resting heart rate was not a significant predictor of the 3MS at baseline \[F (1,119) = 0.01, p = .93\] or 12-weeks \[F (1,118) = 0.47, p = .49\]. However, resting heart rate was a significant predictor of the 3MS at 12-months \[F (1,105) = 8.98, p < .01\].
(1,117) = 4.56, \( p = .04 \), with lower resting heart rate associated with better 3MS performance. See Tables 6-8 for regression coefficients.

Memory. The 2MST was not a significant predictor of memory performance at baseline \([F (1,107) = 0.47, p = .50]\) or 12-weeks \([F (1,111) = 3.01, p = .09]\). However, the 2MST was a significant predictor of memory at 12-months \([F (1,105) = 5.31, p = .02]\), with higher 2MST performance associated with better memory. Resting heart rate was not a significant predictor of memory performance at baseline \([F (1,119) = 0.48, p = .49]\), 12-weeks \([F (1,118) = 1.51, p = .22]\), or 12-months \([F (1,117) = 1.41, p = .24]\).

Attention/psychomotor speed. The 2MST was a significant predictor of attention/psychomotor speed at baseline \([F (1,107) = 23.13, p < .001]\), 12-weeks \([F(1,109) = 10.39, p = .01]\), and 12-months \([F(1,105) = 17.64, p < .001]\), with higher 2MST performance associated with better attention/psychomotor speed. There was a trend for resting heart rate to predict attention/psychomotor speed at 12-months \([F (1,116) = 3.50, p = .06]\), though resting heart rate was not a significant predictor of attention/psychomotor speed performance at baseline \([F (1,119) = 1.76, p = .19]\) or 12-weeks \([F (1,116) = 0.75, p = .39]\).

Executive function. The 2MST was a significant predictor of baseline \([F (1,107) = 8.72, p < .001]\), 12-week \([F (1,110) = 20.89, p < .001]\), and 12-month \([F (1,105) = 4.97, p = .02]\) executive function, with higher 2MST performance associated with better executive function. There was a trend for resting heart rate to predict executive function at 12-months \([F (1,117) = 3.69, p = .06]\), though resting heart rate was not a significant predictor of executive function at baseline \([F (1,119) = 0.81, p = .37]\) or 12-weeks \([F (1,117) = 1.20, p = .28]\).

Language. The 2MST was a significant predictor of baseline \([F (1,107) = 6.25, p = .01]\), 12-week \([F (1,111) = 5.61, p = .02]\), and 12-month \([F (1,105) = 5.78, p = .02]\) language, with higher 2MST performance associated with better language. Resting heart rate was not a
significant predictor of language at baseline $[F (1,119) = 0.21, p = .65]$, 12-weeks $[F (1,118) = 0.13, p = .72]$, or 12-months $[F (1,117) = 2.14, p = .15]$. 
Table 6. Regressions Coefficients for Functional Capacity Predicting Baseline Cognition.

<table>
<thead>
<tr>
<th>Measure</th>
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<tr>
<td>Attention/Psychomotor</td>
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</tr>
<tr>
<td>Speed</td>
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<td>Executive Function</td>
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</table>

*Note.* CR = cardiac rehabilitation; HF = heart failure; 3MS = Modified Mini-Mental State Exam; 2MST = 2-Minute Step Test.
Table 7. Regressions Coefficients for Functional Capacity Predicting 12-week Cognition.

<table>
<thead>
<tr>
<th>Measure</th>
<th>CR Group</th>
<th></th>
<th>HF Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>β</td>
<td>t</td>
</tr>
<tr>
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</tr>
<tr>
<td>2MST</td>
<td>0.08</td>
<td>0.03</td>
<td>0.42</td>
<td>3.06</td>
</tr>
<tr>
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</tr>
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<td>Memory</td>
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</tr>
<tr>
<td>2MST</td>
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<td>0.23</td>
<td>1.57</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
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<tr>
<td>Attention/Psychomotor</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MST</td>
<td>0.09</td>
<td>0.05</td>
<td>0.28</td>
<td>1.96</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>-0.03</td>
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<tr>
<td>Executive Function</td>
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<td>2MST</td>
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<td>Language</td>
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<td>Resting Heart Rate</td>
<td>-0.20</td>
<td>0.14</td>
<td>-0.21</td>
<td>1.39</td>
</tr>
</tbody>
</table>

*Note.* CR = cardiac rehabilitation; HF = heart failure; 3MS = Modified Mini-Mental State Exam; 2MST = 2-Minute Step Test.
Table 8. Regressions Coefficients for Functional Capacity Predicting 12-month Cognition.

<table>
<thead>
<tr>
<th>Measure</th>
<th>CR Group</th>
<th>HF Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td><strong>3MS</strong></td>
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</tr>
<tr>
<td>2MST</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>-0.12</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MST</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>-0.27</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Attention/Psychomotor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MST</td>
<td>0.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>-0.11</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
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<td></td>
</tr>
<tr>
<td>2MST</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MST</td>
<td>0.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>-0.08</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Note.* CR = cardiac rehabilitation; HF = heart failure; 3MS = Modified Mini-Mental State Exam; 2MST = 2-Minute Step Test.
Secondary Aims

**Aim 4:** Examine the relationship between exercise intensity during CR and cognitive outcomes in older adults with HF completing CR.

**3MS.** The full model was a significant predictor of 3MS performance at 12-weeks [F (2, 44) = 36.79, \( p < .001 \)] and accounted for 62.6% of the unique variance in 12-week 3MS performance. After controlling for baseline 3MS, METs during CR was a significant predictor of 3MS performance at 12-weeks [\( \Delta R^2 = 0.05, F (1, 44) = 5.54, p = .02 \)], with greater METs associated with higher 3MS performance. See Table 9 for regression coefficients.

**Memory.** The full model was a significant predictor of memory at 12-weeks [F (2, 44) = 13.59, \( p < .001 \)] and accounted for 38.2% of the unique variance in 12-week memory performance. However, METs during CR was not a significant predictor of memory at 12-weeks after controlling for baseline performance [\( \Delta R^2 < .01, F (1, 44) = 0.14, p = .71 \)].

**Attention/psychomotor speed.** The full model was a significant predictor of attention/psychomotor speed at 12 weeks [F (2, 43) = 87.27, \( p < .001 \)] and accounted for 80.2% of the unique variance in 12-week attention/psychomotor speed performance. There was a trend for METs during CR to predict attention/psychomotor speed at 12-weeks after controlling for baseline performance [\( \Delta R^2 = .02, F (1,43) = 3.59, p = .07 \)], with greater METs associated with better performance.

**Executive function.** The full model was a significant predictor of executive function at 12-weeks [F (2, 44) = 16.76, \( p < .001 \)] and accounted for 43.2% of the unique variance in 12-week executive function performance. However, METs during CR was not a significant predictor of executive function at 12-weeks after controlling for baseline performance [\( \Delta R^2 = .04, F (1, 44) = 2.74, p = .11 \)].
Language. The full model was a significant predictor of language at 12-weeks \( F (2, 43) = 37.45, p < .001 \) and accounted for 63.5\% of the unique variance in 12-week language performance. However, METs during CR was not a significant predictor of language at 12-weeks after controlling for baseline performance \( \Delta R^2 = .02, F (1, 43) = 2.81, p = .10 \).
Table 9. Full Model Results for METs as a Predictor of Cognition at 12-weeks.

<table>
<thead>
<tr>
<th>3MS</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 3MS</td>
<td>0.70</td>
<td>0.09</td>
<td>0.71</td>
<td>7.44</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>METs</td>
<td>0.76</td>
<td>0.33</td>
<td>0.22</td>
<td>2.35</td>
<td>.02</td>
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<tr>
<td>Memory</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Memory</td>
<td>0.76</td>
<td>0.15</td>
<td>0.61</td>
<td>5.15</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>METs</td>
<td>0.37</td>
<td>0.97</td>
<td>0.05</td>
<td>0.38</td>
<td>.71</td>
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<tr>
<td>Attention/Psychomotor Speed</td>
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</tr>
<tr>
<td>Baseline Attention/ Psychomotor</td>
<td>0.59</td>
<td>0.05</td>
<td>0.86</td>
<td>12.52</td>
<td>&lt;.001</td>
</tr>
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<td>Speed</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>METs</td>
<td>0.76</td>
<td>0.40</td>
<td>0.13</td>
<td>1.89</td>
<td>.07</td>
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<tr>
<td>Executive Function</td>
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</tr>
<tr>
<td>Baseline Executive Function</td>
<td>0.44</td>
<td>0.09</td>
<td>0.57</td>
<td>4.80</td>
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</tr>
<tr>
<td>METs</td>
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<td>1.65</td>
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<tr>
<td>Language</td>
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<tr>
<td>Baseline Language</td>
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<td>0.12</td>
<td>0.69</td>
<td>6.35</td>
<td>&lt; .001</td>
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<tr>
<td>METs</td>
<td>1.29</td>
<td>0.77</td>
<td>0.18</td>
<td>1.68</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Note.* METs = Metabolic Equivalents; 3MS = Modified Mini-Mental State Exam.
Aim 5: Examine the impact of CR on self-reported levels of physical activity in older adults with HF. The unconditional model did not fit the data well (RMSEA = 0.12, CFI = 0.86). A significant parameter estimate (unstandardized) for the mean of the intercept (m_intercept = 2.03, S.E. = 0.15, p < .001) was observed, indicating this value is significantly different from 0. The mean of the slope was non-significant (m_slope = -0.02, S.E. = 0.01, p = .13), indicating this value is not significantly different from 0. The parameter estimate for the variance of the intercept was significant (var_intercept = 1.85, S.E. = 0.50, p < .001), suggesting significant variability in self-reported activity across groups at baseline. The parameter estimate for the variance of the slope was non-significant (var_slope = 0.01, S.E. < .01, p = .09), indicating no significant variability in how self-reported levels of physical activity change over time across groups.

The conditional model also did not fit the data well (RMSEA = 0.11, CFI = 0.87). The parameter estimate for the intercept was significant (β = 0.23, S.E. = 0.11, p = .03) indicating individuals in the CR group self-reported higher levels of physical activity at baseline. However, the parameter estimate for the slope was non-significant (β = 0.15, S.E. = 0.16, p = .35) indicating no difference in the rate of change in self-reported physical activity over time between the groups.

Exploratory Post-Hoc Analyses for Aim 5

Although LCGM analyses could not be interpreted due to poor model fit, additional post-hoc analyses were conducted in order to more precisely characterize the nature of the data. Repeated measures ANOVA were used to compare self-reported physical activity of the CR group and HF controls and pairwise comparisons were examined using Bonferroni-corrected post-hoc tests for exploratory purposes only.

No significant group x time interaction [λ = 0.96, F (4,163) = 1.51, p = .20] or effect of time [λ = 0.96, F(4,163) = 1.87, p = .12] emerged. However, a significant effect of group [F
(1,162) = 12.32, \( p = .01 \) was observed. Exploratory examination of between group differences showed that the CR group self-reported greater physical activity at baseline \( (p = .02) \), 12-weeks \( (p = .01) \), 9-months \( (p = .02) \), and 12-months \( (p < .001) \) when compared to controls. Within group comparisons indicated no significant change in reported physical activity across time for either group \( (p > .05 \text{ for all comparisons}) \). See Table 10.

Table 10. Weekly METs for Self-Reported Activity on the CHAMPS.

<table>
<thead>
<tr>
<th>Time point</th>
<th>CR Group</th>
<th>HF Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline*</td>
<td>2.73 ± 2.34</td>
<td>1.81 ± 2.23</td>
</tr>
<tr>
<td>12-weeks*</td>
<td>2.59 ± 2.12</td>
<td>1.60 ± 1.98</td>
</tr>
<tr>
<td>6-months</td>
<td>1.98 ± 1.60</td>
<td>1.69 ± 2.13</td>
</tr>
<tr>
<td>9-months*</td>
<td>2.67 ± 2.66</td>
<td>1.74 ± 2.09</td>
</tr>
<tr>
<td>12-months*</td>
<td>2.62 ± 2.73</td>
<td>1.38 ± 1.46</td>
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</tbody>
</table>

* denotes CR Group > HF Control.

Aim 6: Examine the relationship between self-reported activity at 9-months and cognitive outcomes at 12-months.

**CR group.** Level of physical activity at 9-months as reported on the CHAMPS was not a significant predictor of the 3MS [\( F(1,45) = 0.15, p = .70 \)], memory [\( F(1,45) = 0.46, p = .50 \)],
attention/psychomotor speed \( [F(1,44) = 0.12, \ p = .73] \), executive function \( [F(1,45) = 0.70, \ p = .41] \), or language \( [F(1,45) = 0.74, \ p = .40] \) at 12-months. See Table 11 for regression coefficients.

*HF controls.* Level of physical activity at 9-months as reported on the CHAMPS was not a significant predictor of the 3MS \( [F(1,119) = 0.59, \ p = .45] \), memory \( [F(1,119) = 1.34, \ p = .25] \), attention/psychomotor speed \( [F(1,118) = 0.93, \ p = .34] \), executive function \( [F(1,119) = 0.01, \ p = .94] \), or language \( [F(1,119) = 0.37, \ p = .55] \) at 12-months. See Table 11 for regression coefficients.
Table 11. Regressions Coefficients for 9-month CHAMPS Predicting 12-month Cognition.

<table>
<thead>
<tr>
<th>Measure</th>
<th>CR Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>HF Controls</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>β</td>
<td>t</td>
<td>p</td>
<td>B</td>
<td>SE</td>
<td>β</td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>3MS</td>
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<td>0.29</td>
<td>0.06</td>
<td>0.39</td>
<td>.70</td>
<td>0.19</td>
<td>0.25</td>
<td>0.07</td>
<td>0.77</td>
<td>.45</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.34</td>
<td>0.50</td>
<td>-0.10</td>
<td>0.68</td>
<td>.50</td>
<td>0.53</td>
<td>0.46</td>
<td>0.11</td>
<td>1.16</td>
<td>.25</td>
</tr>
<tr>
<td>Attention/Psychomotor</td>
<td>0.17</td>
<td>0.50</td>
<td>0.05</td>
<td>0.34</td>
<td>.73</td>
<td>0.45</td>
<td>0.47</td>
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<td>Speed</td>
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</tr>
<tr>
<td>Executive Function</td>
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<td>0.83</td>
<td>.41</td>
<td>-0.04</td>
<td>0.50</td>
<td>-0.01</td>
<td>0.08</td>
<td>.94</td>
</tr>
<tr>
<td>Language</td>
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<td>0.86</td>
<td>.40</td>
<td>-0.32</td>
<td>0.53</td>
<td>-0.06</td>
<td>0.61</td>
<td>.55</td>
</tr>
</tbody>
</table>

*Note.* CR = cardiac rehabilitation; HF = heart failure; CHAMPS = Community Health Activities Model Program for Seniors Physical Activity Questionnaire; 3MS = Modified Mini-Mental State Exam.
Discussion

Study Overview

Cognitive dysfunction is common in HF (Bennett & Sauve, 2003) and is associated with many adverse health outcomes (Zuccala, et al., 2003; Zuccala, et al., 2001). The etiology of cognitive dysfunction in HF is still being elucidated, though reduced levels of physical activity is a likely contributor. Exercise is an established treatment option for HF (Boudreau, & Genovese, 2007) and is associated with gains in functional capacity and a reduced risk of adverse clinical outcomes (e.g., Smart & Marwick, 2004; Edelmann et al., 2011; Chien, Lee, Wu, Chen, & Wu, 2008; Oerkild, Frederiksen, Hansen, & Prescott, 2011). The benefits of physical activity on cognitive outcomes in healthy and medical populations (e.g., Colcombe & Kramer, 2003; Smith et al., 2010b; Gunstad et al., 2005; Stanek et al., 2011) is well documented, though less is known about its possible benefits in persons with HF. An initial study (Tanne et al., 2005) suggested that the cognitive benefits of exercise can be observed in HF, though additional work is needed to clarify this possibility.

The current study sought to extend this work by examining the prospective benefits of CR on functional capacity and cognition in older adults with HF. Contrary to expectations, individuals completing CR did not show gains in functional capacity or cognition relative to HF controls. Moreover, exercise intensity during CR was not associated with better cognitive function, there were no differences in self-reported levels of physical activity, and self-reported physical activity was not related to cognitive functioning. Several aspects of these findings warranted further discussion.
Changes in Functional Capacity

Participation in CR was not associated with improvements in cardiovascular fitness in the current study. This finding is in contrast to previous work that has shown improvements in functional capacity following exercise intervention in persons with HF (e.g., Smart & Marwick, 2004; Boudreau, & Genovese, 2007). A likely explanation for this finding is found in the characteristics of the current intervention. As will be addressed in detail below, exercise intensity during CR was low to moderate for this sample of persons with HF, raising the possibility that this level of exercise is insufficient to improve cardiac function at the group level. Previous work in HF has found that improvements in cardiorespiratory fitness correspond to the intensity of exercise (Ismail, McFarlane, Nojoumian, Dieberg, & Smart, 2013). As many individuals engaged in low intensity exercise during CR sessions (e.g. average of 4.02 METs exerted), it is possible that exercise was below the threshold needed to produce clinical improvements in fitness levels. Similarly, the reliance on continuous aerobic activity in the selected CR program may also have limited the opportunity for improved fitness levels in the current sample. Recent work shows that high-intensity interval training (i.e., repetitions of brief, intense exercise followed by a rest period) produces greater improvements in functional capacity than traditional aerobic exercise (Freyssin et al., 2012). Previous work has also shown that combination programs of strength training and interval exercise have greater benefits on functional capacity in HF when compared to interval training alone (Smart, Dieberg, & Giallauria, 2013). Such findings raise the possibility that CR programs could be modified to increase the intensity or type of exercise. Vigorous to high levels of physical activity do not appear to be associated with an increased risk for adverse events in HF, including hospitalization and death (Ismail, McFarlane, Nojoumian, Dieberg, &
Smart, 2013), and future work should employ more intense programs that are mixed and incorporate interval training.

**Changes in Cognitive Function**

Cognitive function remained relatively stable over time for both groups and no cognitive benefit from participation in CR was observed. This finding is in contrast to past work that has demonstrated improvements in attention/psychomotor speed and executive function among older adults with HF following CR (Tanne et al., 2005). One possible explanation for these discrepant findings is likely related to differences in study sample characteristics, as the current sample was comprised of individuals with relatively mild HF. This pattern initially suggests that CR may be more beneficial for improving cognitive dysfunction after surpassing a threshold of disease severity. However, on the other hand, cognitive deficits are more likely in persons with more severe HF (e.g., Vogels, et al., 2007a; Pressler et al., 2010) and such persons are at elevated risk for conditions like Alzheimer’s disease and vascular dementia (Qui et al. 2006; Roman, 2005). The greater levels of cognitive impairment found in persons with more severe HF may not respond to CR, as past work shows minimal cognitive improvement after a 6-month exercise intervention in older adults with known cognitive impairment (Miller et al., 2011).

Taken in combination, this collection of findings argues that the relationship between exercise and cognitive function in HF may be much more complicated than currently hypothesized and that other individual-level factors must be considered. However, findings are further complicated by the lack of improvement in cardiovascular fitness in the current CR sample. Improvement in functional capacity was the postulated mechanism of change for cognition and it is not surprising that cognition remained unchanged for the CR group in the absence of fitness improvement. Additionally, the average cognitive performance for both groups
fell within the normal range on most measures over time, introducing the possibility of range
restriction for cognitive impairment within this generally mild HF sample. Future work with more
heterogeneous samples is needed to better understand the possible effects of CR on cognitive
function in persons with HF.

**Relationship between Functional Capacity and Cognitive Function**

Consistent with past work, higher levels of cardiovascular fitness were positively
associated with cognitive function (e.g., Alosco et al., 2012c; Miller et al., 2012). This is not
surprising given that greater levels of fitness are associated with larger brain volume in important
cortical regions such as the hippocampus (Erickson et al., 2009; Colcombe et al., 2003), as well
as with better cerebrovascular functioning (e.g., endothelial function, cerebral perfusion; Tarumi
& Zhang, 2014). The link between brain pathology and cognition is well-established (e.g., Paul et
al., 2005; Raz, Rodrigue, & Acker, 2003; Jefferson, Poppas, Paul & Cohen, 2007), and although
structural and functional neuroimaging were not examined in the current study, individuals with
better cardiovascular fitness likely had better brain integrity and this likely contributes to
cognitive performance. Given that the CR group started with and maintained higher levels of
functional capacity when compared to HF controls, it is not surprising that they demonstrated
better cognitive performance. It will be important for future prospective work to examine the
relationship between changes in functional capacity and changes in cognitive functioning to
determine the extent to which improvements in fitness promote cognitive gains.

**Impact of Exercise Intensity during CR on Cognitive Function**

With the exception of a global cognitive screener, exercise intensity during CR was not
associated with cognition at 12-weeks. For the vast majority of the sample (72.3%), METs fell
within the light to moderately intense range (Garber et al., 2011), and it appears likely that this level of exercise intensity is not sufficient to provide cognitive benefits in HF. Although past work has shown that the cognitive benefits of physical activity are not influenced by exercise intensity (e.g., Smith et al., 2010b; Vercambre, et al., 2011), there is rapidly growing evidence that intensity may play a key role. For example, more intense physical activity was independently associated with better cognitive performance after controlling for demographic and medical (e.g., CVD) characteristics in healthy older adults (Brown et al., 2012) and a recent review also identified exercise intensity as a crucial factor for cognitive outcomes in older adults (Kirk-Sanchez & McGough, 2014). As outlined above, exercise intensity and program characteristics directly impact functional capacity outcomes in HF (e.g., Ismail, McFarlane, Nojoumian, Dieberg, & Smart, 2013; Freyssin et al., 2012; Smart, Dieberg, & Giallauria, 2013), and it will be important for future work to understand how these aspects of exercise may influence cognitive outcomes in HF.

Though not examined as part of the current study, future studies should also examine the possible cognitive benefits of exercise interventions of longer duration. The CR program utilized in the current study ranged from 20 to 37 sessions, which is typical for many clinical settings. However, there is some evidence that longer interventions (e.g., 6 or more months in duration) are associated with better cognitive outcomes in healthy adults (Colcombe & Kramer, 2003), though this possibility needs to be clarified in the HF population.

**Self-reported Physical Activity in CR and HF Controls**

Self-reported levels physical activity remained stable within both groups over time, suggesting that completion of CR did not increase levels of physical activity. The CR group reported higher levels of physical activity relative to controls at nearly all time points, though
both groups reported activity that fell in the light intensity range (Garber et al., 2011). This suggests that while the observed differences are statistically different, the clinical relevance of this finding may be minimal. One potential explanation for this pattern of findings is that many CR patients reported their initial activity levels after beginning the exercise program and thus their reported baseline levels reflect the exercise completed as part of the CR program rather than additional physical activity levels. However, other factors may also influence these findings. For example, there is evidence to suggest that individuals may be inaccurate in their self-reported levels of activity, as weak correlations between self-reported activity and objective measures of activity (e.g., accelerometer) have been documented (Sabia et al., 2014; Dyrstad, Hansen, Holmes, & Anderssen, 2013). This may be particularly likely in individuals with suspected cognitive impairment, as in persons with HF.

Physical activity is important in HF as higher levels of self-reported activity have been linked to better outcomes, including reduced risk of mortality (Oerkild, Frederiksen, Hansen, & Prescott, 2011). Given the impact that a sedentary lifestyle can have on disease progression and cognition in HF, further understanding the extent to which individuals remain physically active is important, as is identifying potential barriers to adhering to this recommendation. To that end, it will be important for future work to use more objective measurements to assess activity (e.g., accelerometer, actigraphy).

**Self-reported Physical Activity at 9-months and Cognitive Function at 12-months**

Reported level of physical activity at 9-months was not related to cognitive performance at 12-months for the CR group or HF controls. This finding is in contrast to previous work which has demonstrated a positive relationship between self-reported levels of physical activity and cognitive outcomes in both healthy and CVD populations (e.g., Benedict et al., 2013; Sofi, et al.,
2011; Vercambre, et al., 2011). As addressed above, the lack of findings may be in part due to the reliance on self-report, as well as the lack of variability in functional capacity and cognitive measures. Importantly, levels of physical activity did not decline for either group, and remaining at least mildly active over an extended period of time may have an additive effect. A meta-analysis of prospective studies (ranging from 1 to 12 years in duration) found a 38% reduction in risk for cognitive decline for those who engaged in high levels of physical activity when compared to sedentary adults. In addition, even low to moderate levels of physical activity reduced the risk of cognitive decline by 35%. These findings suggest that the effect of physical activity on cognition is not necessarily dose-dependent and argues that any level of physical activity can serve as a protective factor (Sofi, et al., 2011). In fact, engagement in physical activity that is equivalent to briskly walking 30 minutes per day has been found to be comparable to being 5-7 years younger cognitively (Vercambre, et al., 2011). Taken together, these findings argue that any level of exercise is superior to a sedentary life style.

Previous work has also shown that many individuals do not adhere to exercise recommendations after completion of CR (Leong, Molassiotis, & Marsh, 2004; Moore et al., 2003). Self-reported activity remained stable within the current sample which suggests that the current group of CR completers may have better adherence to remaining active, and in turn may have better long-term outcomes. As addressed above, more precise measurements of continued activity after CR are needed to better understand how CR impacts levels of activity.

**Limitations and Future Directions**

The current findings are limited in several ways. The cognitively intact nature of the current sample is also common in the previous work examining the etiology of cognitive deficits in HF (e.g., Vogels, et al., 2008; Alves et al., 2005). Although past work has shown cognitive
impairment in 30-50% of individuals with HF (Bennett & Sauvé, 2003), clinical impairment (i.e., ≤ 1.5 SD below the normative mean) was found in only 23.8% of the current sample. There are several possible explanations for this pattern. First, participants were recruited from outpatient cardiology clinics where they were closely followed by their healthcare providers, suggesting their HF is likely well controlled. The majority (83.9%) of individuals in the current study were classified as NYHA II, suggesting relatively mild physical limitations due to HF (Swedberg et al., 2005). Moreover, mean left ventricular ejection fraction was approximately 42%, which is greater than the observed values of previous work identifying higher rates of cognitive deficits in persons with HF (Vogels et al., 2007a; Pressler et al., 2010). Past studies have shown that greater HF severity leads to greater cognitive impairment, suggesting that the cognitive impact of HF has not yet manifested in this relatively mild group. Another possible explanation for the lower prevalence of impairment could be related to cognitive reserve. Models of cognitive reserve suggest that pre-existing factors, such as education and intellectual ability, can serve as a buffer against cognitive impairment (Stern, 2009). Cognitive reserve has been identified as a protective factor in neurological conditions including dementia (Stern, 2009; Borroni et al., 2009), traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003), stroke (Elkins et al., 2006), and multiple sclerosis (Benedict et al., 2010). Recent work has extended such findings into the HF population, with higher premorbid intellectual functioning attenuating the negative impact of HF on cognition (Alosco, et al., 2012a; Miller et al., 2012). Both groups in the current study were comprised of well-educated individuals with above average levels of intellectual functioning and it therefore appears likely that cognitive reserve is serving as a neuroprotective factor. It will be important for future work to recruit large and heterogeneous samples that include individuals with varying degrees of HF and diverse backgrounds.
Another limitation of the current study is that participation in CR was not randomized, raising the possibility of a selection bias. This possibility is highlighted by individuals in the CR group demonstrating better cardiovascular fitness at baseline, and throughout the duration of the study, when compared to controls. Although no group differences emerged in the current sample, examination of individual factors (e.g., education, occupation, socioeconomic status) that differ between CR enrollers and non-enrollers may be helpful in better understanding the characteristics of individuals who complete CR. While studies that randomize individuals into CR may be unethical, future exercise intervention studies employing randomized controlled methodology would be useful in further understanding the relationship between exercise and cognitive outcomes in this population.

The current study also examined the more immediate effects of CR on cognition and it will be important for future studies to examine more long-term outcomes (e.g., 2, 3, and 5 years). Individuals with HF are at risk for general cognitive decline (Hajduk et al., 2013), as well as for the progression to dementia (Qui et al. 2006; Roman, 2005), and longer follow-up assessments will elucidate the extent to which exercise interventions can attenuate this decline. It is also possible that the measures used in the current study were not sensitive enough to detect changes, particularly after 3 months, and measures of more specific aspects of cognition (e.g., tasks of sustained auditory and visual attention) are needed. Similarly, although the 2MST has been identified as a good estimate for functional capacity (e.g., Rostagno & Gensini, 2008; Pollentier, et al., 2010; Pedrosa & Holanda, 2009), future work employing more precise measurements of functional capacity (e.g., peak oxygen consumption, stress test) will likely be beneficial. In addition, the use of neuroimaging (e.g., functional MRI, arterial spin labeling) to quantify brain changes may also provide greater insight into neurocognitive outcomes in this population.
Clinical Implications

Heart failure represents a significant clinical and economic burden. More than 5 million individuals have HF and approximately 670,000 new cases are reported each year (American Heart Association, 2013). With the increasing proportion of older adults, the number of individuals with HF and the associated costs of care can only be expected to grow (American Heart Association, 2013). Cognitive dysfunction is common in this population (Bennett & Sauve, 2003) and the risk of impairment increases with HF severity (Vogels, et al., 2007a; Pressler et al., 2010). Recent evidence indicates that the pattern of cognitive deficits is heterogeneous (Miller et al., 2012), suggesting a variable degree of limitations in daily activities. Not surprisingly, cognitive dysfunction in this population is associated with adverse outcomes, including increased disability and mortality risks (Zuccala, et al., 2003; Zuccala, et al., 2001). This highlights the importance of interventions aimed at attenuating the progression of HF as well as preventing/stabilizing cognitive decline, as such interventions ultimately impact activities of daily living and quality of life. The current study found that cognitive function was generally intact in a sample of persons with mild HF, though clinically meaningful impairments emerged in a subsample. Given that a traditional CR program did not improve cognitive function, future studies are needed to clarify whether higher intensity exercise can improve neurocognitive outcomes in this high risk population. Finally, cognitive function did not decline over one year which suggests that progression to cognitive impairment is not inevitable in mild HF and encourages further investigation into interventions aimed at maintaining intact cognitive functioning.

Summary

The current study found that participation in CR did not result in improvements in functional capacity or cognitive functioning in older adults with HF. Moreover, the exercise
intensity during CR was unrelated to cognitive performance at follow-up. In addition, CR was not related to an increase in self-reported levels of exercise and self-reported physical activity at 9-months did not predict cognitive performance at 12-months. The lack of findings in the current study are consistent with past work aimed at elucidating mechanisms of cognitive decline in HF, and underscore the importance of further prospective work with large, diverse samples.
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