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Depressive Symptomatology, Exercise Adherence and Fitness are Associated with Reduced Cognitive Performance in Heart Failure

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Abstract

Objectives—Depression is common in heart failure (HF) and associated with reduced cognitive function. The current study used Structrual Equation Modeling to examine whether depression adversely impacts cognitive function in HF through its adverse affects on exercise adherence and cardiovascular fitness.

Methods—158 HF patients completed neuropsychological testing, physical fitness test, Beck Depression Inventory-II (BDI-II), and measures assessing exercise adherence, and physical exertion.

Results—The model demonstrated excellent model fit and increased scores on the BDI-II negatively affected exercise adherence and cardiovascular fitness. There was a strong inverse association between cardiovascular fitness and cognitive function. Sobel test showed a significant indirect pathway between the BDI-II and cognitive function through cardiovascular fitness.

Discussion—This study suggests depression in HF may adversely impact cognitive function through reduced cardiovascular fitness. Prospective studies are needed to determine whether

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treatment of depression can lead to better lifestyle behaviors and ultimately improve neurocognitive outcomes in HF.

Keywords

Cognitive function; cardiovascular fitness; depression; exercise adherence; heart failure

1. Introduction

Heart failure (HF) affects nearly 6 million Americans and is a major contributor to hospitalizations, elevated rates of mortality, and economic burden (American Heart Association 2010; Roger et al., 2010; Jencks, Williams & Coleman, 2009). HF is associated with poor quality of life and reduced functional independence (Norberg, Bowman, & Lofgren, 2008; Bennet, et al., 2003), and vast evidence indicates cognitive impairment leads to poor outcomes in this population (Alosco, et al., 2012; Zuccala, et al., 2003; Reigel & Weaver, 2009; Kindermann, et al., 2010). Relative to healthy controls, HF patients are at a 4-fold increased risk for cognitive impairment, including deficits in attention, executive function, and memory (Pressler, et al., 2010). The exact mechanisms of cognitive impairment in this population are unclear, though they likely involve cerebral hypoperfusion secondary to cardiac dysfunction combined with the pathological effects of medical comorbidity (i.e., hypertension, diabetes) (Suave, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009; Alosco, et al., 2012; Jefferson, et al., 2007; Vogels, et al., 2007; Zuccala, et al., 2005).

Depression has also recently been shown to be an important contributor to cognitive impairment in this population. Depression is found in nearly 30% of HF patients (Diez-Quevdeo, et al., 2012) and associated with elevated mortality risk, repeated hospitalizations, and adverse cardiac events (Rutledge, Reis, Linke, Greenberg, & Mill, 2006; Kato, et al., 2012). Recent work in this population links increased depressive symptomatology with deficits in attention, executive function, psychomotor speed, and language (Garcia, et al., 2011). Pathophysiological changes (i.e., reduced cerebral blood flow) have also been noted among HF patients with depression relative to their non-depressed counterparts (Alves, et al., 2006).

The mechanisms underlying the association between depression and cognitive impairment in persons with HF may involve reduced cardiovascular fitness. Past work has shown that depression contributes to increased dropout rates of exercise training cardiac rehabilitation programs and reduced physical activity and cardiovascular fitness in people with HF and other cardiovascular diseases (Casey, Hughes, Waechter, Josephson, & Rosneck, 2008; McGrady, McGinnis, Badenhop, Bentle, & Rajput, 2009; Spaderna, et al., 2010; Lysy, Da Costa, & Dasqupta, 2008; Gottlieb, et al., 2009). The links between depression and vascular risk have important consequences, as recent work links reduced cardiovascular fitness to poorer cognitive function among older adults with HF (Alosco, et al., 2011; Steinberg, et al., 2011).

Although past work has examined independent effects of depression, exercise adherence, and cardiovascular fitness on cognitive function in HF, no study to date has explored how these factors may interact in a framework of a hypothesis driven multivariate model. Based on the reviewed findings, we hypothesized that reduced cardiovascular fitness stemming from exercise non-adherence would mediate the relationship between depression and cognitive dysfunction in HF. Our hypothetical relationships among the variables of interest were formalized in a Structural Equations Model (SEM) presented in Figure 1.

2. Methods

2.1 Participants

The sample consisted of 158 consecutively enrolled persons with HF from a large-scale project examining neurocognitive function in older adults with HF. All participants were between the ages of 50-85 years of age, English-speaking, and had an established diagnosis of HF at New York Heart Association (NYHA) class II or III at the time of enrollment. Exclusion criteria included history of significant neurological disorder (e.g. dementia, stroke, multiple sclerosis), head injury with more than 10 minutes loss of consciousness, severe psychiatric disorder, substance abuse and/or dependence, and renal failure. Participants averaged 68.96±9.13 years of age, were 36.7% female, and 82.3% Caucasian. Medical record review indicated the current sample demonstrated an average left ventricular ejection fraction (LVEF) of 40.70 (SD = 14.39). See Table 1 for sample demographic and clinical characteristics.

2.2 Measures

2.2.1. Depressive Symptomatology—The Beck Depression Inventory-II (BDI-II) was administered to assess self-reported depressive symptomatology. The BDI-II is a commonly used checklist of depressive symptoms that exhibits strong psychometric properties in persons with medical conditions (i.e., test-re-test reliability of $r = .93$ to $r = .96$, and an internal consistency of $r = .54$ to $r = .74$) (Amau, Meagher, Norris, & Bramson, 2001; Beck, Steer, & Brown, 1996). BDI-II scores range from 0-63 with increased score indicative of increased symptomatology. The BDI-II score was used as a single manifest predictor in the proposed model.

2.2.2. Exercise Adherence—The Heart Failure Compliance Questionnaire (Evangelista, Berg, & Dracup, 2001) was used to assess treatment adherence in the current sample. This questionnaire asks participants to rate their adherence to different health behaviors (i.e., maintaining doctor appointments, medication management, substance abstinence, following dietary and exercise recommendations). The current study examined participants' responses to the item of the questionnaire assessing exercise adherence. Participants rated their adherence to exercise behaviors based on a scale of 0 (none of the time) to 4 (all of the time). Scores were converted to a 0 to 100 scale with a score of 75% or greater reflecting adherent behaviors (i.e., participants responded adhering to exercise recommendations most or all of the time) (Evangelista, et al., 2001). This exercise adherence item served as a single manifest mediator variable in the proposed model.

2.2.3. Cardiovascular Fitness—Cardiovascular fitness served as a latent construct in the proposed model and was assessed using the 2-Minute Step Test (2MST) and the Duke

Activity Status Index (DASI). The 2MST is an assessment of cardiovascular endurance (Jones & Rikli, 2002). The 2MST has been suggested to be an alternative to the 6-minute walk test, which has been linked with functional work capacity, maximal oxygen uptake, and poor prognosis in patients with HF (Nixon, Joswiak, & Fricker, 1996; Bittner, et al., 1993). Past work has also shown that the 2MST is linked with poorer cognitive function among older adults with heart failure (Alosco, et al., 2011). The 2MST requires the patient to march in place for 2 minutes. The patient is asked to bring each knee up to a marked target set on the wall at the individual's own midpoint between the kneecap and crest of the iliac. The number of times the right knee met the marked target was counted. Increased step count within the 2-minutes was reflective of greater cardiovascular fitness. Average step count for females between the ages of 50-85 ranges from 71-115, while males for this age group range from 60-107 (Jones & Rikli, 2002).

Maximal physical exertion was assessed using the Duke Activity Status Index (DASI), a check-list, in which participants were asked to identify activities they were able to complete, ranging from basic tasks (i.e. walking around the house) to vigorous exercise (i.e. basketball, skiing). The score was a sum of the weighted values for each checked activity. From the composite score, a proxy estimate of peak oxygen uptake in mL/min was computed to serve as an indicator of maximal physical exertion (Hlatky, et al., 1989).

2.2.4. Cognitive Function—A brief neuropsychological battery was administered to all participants to assess multiple domains of cognitive function, including attention, executive function, memory, and language. All tests demonstrate strong psychometric properties including excellent reliability and discriminant and construct validity. Neuropsychological tests administered and used as indicators of the latent construct cognitive function in the proposed model include:

- **Trail Making Test A** (Spreen & Strauss, 1991): Completion time of Trail Making Test A is a reliable and valid measure of attention and complex visual scanning and psychomotor speed (Spreen & Strauss, 1991). Participants are asked to connect a series of letters in sequential order as quickly as possible. Longer time of completion is reflective of worse performance.
- **Trail Making Test B** (Dikmen, Grant, & Tekmin, 2000): Trail Making Test B is a widely used measure of executive function and assesses the ability to shift and maintain cognitive set. Participants are asked to connect a series of numbers and letters in alternating sequential order as quickly as possible. Longer time of completion is indicative of worse performance.
- **Frontal Assessment Battery** (Dubois, Slachevsky, Litvan, & Pillon, 2000): The Frontal Assessment Battery is comprised of six subtests that assess aspects of executive function, including lexical fluency, inhibitory control, sensitivity to interference, higher-ordered motor programming, and abstract reasoning. Scores range from 0-18 with higher scores reflective of better performance.

- **California Verbal Learning Test Delayed Recall** (Delis, Kramer, Kaplan, & Ober, 2000): The California Verbal Learning Test-II (CVLT-II) long delay free recall was used to assess memory functioning in the current sample. Individual are asked to learn a 16-item word list and recall these words after a delay period. This widely used test of verbal memory. Scores on the long delay free recall range from 0-16 and increased score is reflective of better performance.
- **Animals Fluency Test** (Morris, et al., 1989): The animal fluency test was used to assess language abilities. This test has individuals generate as many animal names as possible within a given time limit. Greater number of animals named reflects better performance.

2.2.5. Demographic Characteristics—Medical and demographic characteristics were ascertained through participant self-report and medical record review.

2.3 Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. During a single assessment, participants completed demographic and psychosocial self-report measures, including the BDI-II, DASI, and the Heart Failure Compliance Questionnaire. Participants were also administered a brief neuropsychological test battery to assess cognitive function. Finally, all participants completed the 2MST.

2.4 Statistical Analyses

To test the hypothesis driven model depicted in Figure 1, we used a structural equation modeling (SEM) approach. The model consists of two latent factors: cardiovascular fitness and cognitive function. The 2MST and a proxy measure of peak oxygen uptake served as indicators of cardiovascular fitness. The five neuropsychological measures that assess multiple aspects of cognition contributed to cognitive function. To minimize discrepancy among the scales and maintain directionality, all raw scores of the neuropsychological measures were converted to T-scores (a distribution with a mean of 50 and a standard deviation of 10) using existing normative data adjusting for age, and gender in the case of the California Verbal Learning Test. Additionally, a single indicator variable for each latent construct (i.e., cognitive function and cardiovascular fitness) was fixed at 1 to correct for scaling. The BDI-II and exercise adherence served as a manifest predictor and mediator variable in the current model, respectively. A measurement model was first conducted to examine model fit among the latent variables and their respective indicators. A structural model was then fitted to the data to examine the relationships among the BDI-II, exercise adherence, cardiovascular fitness, and cognitive function. To maintain model parsimony and preserve statistical power, covariates were not included in the model.

The SEM was conducted using EQS software using maximum likelihood approach. Goodness of fit was evaluated by the χ^2 value, comparative fit index (CFI) and the root mean-square error of approximation (RMSEA), recommended as most useful indices of model fit (Thompson, 2000). A non-significant χ^2, CFI ≥ .95, and an RMSEA ≤ .06 indicated good model fit (Hu & Bentler, 1999).

3. Results

Descriptive Statistics

Self-reported depressive symptomatology was prevalent, in this sample of HF patients, with a mean BDI-II score of 7.67 (SD = 7.57). Many of the HF participants reported high rates of exercise non-adherence. Specifically, the sample averaged 56.33 (SD = 33.97) on the exercise adherence composite and 50.6% of the sample reported being non-adherent (i.e., score < 75). Not surprisingly, when compared to normative data accounting for age and gender, both male and female HF patients also performed below the average range on the 2MST, suggesting poorer cardiovascular fitness. See Table 1 for a summary of descriptive statistics.

Consistent with clinical convention, a T-score cutoff of 35 (1.5 SD below the mean) was used to define impairment on neuropsychological measures assessing cognitive function. Many HF participants fell below this cutoff on several of the cognitive tests. Specifically, 26.6% exhibited impairments on the Frontal Assessment Battery, 18.4% on Trail-Making Test B, 10.1% on Trail-Making Test A, and 7.6% on the California Verbal Learning Test Delayed Recall. Impairment on the Animals Fluency Test was less common. See Table 1 for cognitive test T-score means and standard deviations.

Measurement Model

A measurement model was first evaluated to examine fit of the indicators of the latent constructs cardiovascular fitness and cognitive function. The latent factors cardiovascular fitness and cognitive function were allowed to covary. Animals and estimated peak oxygen uptake (as assessed by the DASI) were fixed at 1.0 for cognitive function and cardiovascular fitness, respectively. The measurement model demonstrated excellent fit: χ^2 (13, N = 158) = 13.29, p = .43, *CFI* = 1.00, *RMSEA* = .01 (90% CI = .00, .08). All neuropsychological measures significantly loaded on to cognitive function latent factor (β = .33 to .81, $p < .05$) and the 2MST significantly loaded on to cardiovascular fitness factor (β = .68, $p < .05$). In addition, cognitive function and cardiovascular fitness factors significantly covaried (β = .53, $p < .05$), with greater cardiovascular fitness associated with better cognitive function.

Structural Model

Refer to Table 2 for the observed covariance matrix among the variables analyzed using SEM. The model demonstrated excellent fit: χ^2 (23, N = 158) = 31.39, p = .11, *CFI* = .97: *RMSEA* = .05 (90% CI = .00, .09). Examination of structural pathways revealed that increased depressive symptomatology was associated with reduced exercise adherence and poorer cardiovascular fitness ($p < .05$). Decreased exercise adherence was also significantly associated with worse cardiovascular fitness ($p < .05$).

Finally, the pathways connecting the BDI-II and cardiovascular fitness with cognitive function were also significant with a stronger association noted between cardiovascular fitness and cognitive function ($p < .05$). In each case, increased depressive symptomatology and poorer cardiovascular fitness were associated with decreased cognitive function. The direct pathway between exercise adherence and cognitive function was not significant ($p > .05$). To determine whether cardiovascular fitness demonstrated a statistically stronger relationship with cognitive function relative to the BDI-II, the model was evaluated again after constraining the pathways between the BDI-II and cardiovascular fitness with cognitive function to be equal. This model fit the data significantly worse than the original one ($\Delta \chi^2 (1, N = 158) = 30.90$, $p < .001$), suggesting that cardiovascular fitness exerts greater influence on cognitive function than depressive symptomatology. Sobel test also revealed that there was a significant indirect effect of the BDI-II on cognitive function through cardiovascular fitness ($p < .05$), though not through exercise adherence ($p > .05$). Cardiovascular fitness demonstrated significant indirect effects with all of the individual cognitive variables ($p < .05$ for all). See Figure 1 for standardized parameter estimates.

4. Discussion

Consistent with extant research, HF patients evidenced poor cognitive performance and high prevalence of self-reported depressive symptomatology. In HF patients, depression is associated with poor psychosocial outcomes (Rutledge, et al., 2006; Kato, et al., 2012) and may contribute to cognitive impairment (Garcia, et al., 2011). This study suggests this relationship may stem in part from poor adherence to exercise regimen and reduced cardiovascular fitness.

More than half of the current sample of HF patients reportedly did not follow exercise recommendations, and our findings suggest that depressive symptomatology may contribute to poor adherence. The negative impact of depression on exercise adherence is common among patients with other cardiac problems (Casey, et. al, 2008). There are several potential explanations for the adverse effects of depression on exercise adherence. First, depressed patients may have exaggerated perception of physical symptoms associated with HF (i.e., fatigue, shortness of breath) (Sullivan, LaCroix, & Russo, 1999; Falk, Patel, Swedberg, & Ekman, 2009). Heightened aversion of these symptoms that also accompany normal physical exertion may act as stronger barriers to exercise. Second, motivational factors (i.e., increase self-confidence, enjoyment of exercise) play an important role in exercise adherence among cardiac patients (Marzolini, Mertens, Oh, & Pyley, 2010; Farley, Wade, & Birchmore, 2003; Coghill & Cooper, 2009; Fernandez, Salamonson, Griffiths, Juergens, & Davidson, 2008; Perry & Bennett, 2006) and depression that reduces hedonic value of many activities likely impairs motivational capacities. Lastly, poor self-efficacy is common in depression (Maeda, Shen, Schwarz, Farrell, & Mallon, 2012) and this finding extends to HF patients, particularly regarding their functional ability (Skotzko, et al., 2000). Indeed, poor self-efficacy is a known contributor to treatment adherence (Maeda, et al., 2012) and poor exercise adherence in HF and other cardiovascular disease populations (Maeda, et al., 2012; Oka, DeMarco, & Haskell, 1999; Gardner, et al., 2003). Prospective studies should examine whether treatment of depression (i.e., psychotherapy, anti-depressant medications) improves adherence to exercise regimens in HF patients.

Despite the adverse impact of depression on exercise adherence, a strong relationship also emerged between depressive symptomatology and cardiovascular fitness. The exact reason for this relationship is not entirely clear. Past work among cardiac patients has shown depressive symptoms are associated with reduced exercise capacity (Ruo, Rumsfeld, Pipkin, & Whooley, 2004). It is possible that reduced cardiovascular fitness in depressed HF patients may be a manifestation of a longstanding sedentary lifestyle rather than current exercise adherence (as was assessed in the current study) (Roshanaei-Moghaddam, Katon, & Russo, 2009). In fact, compared to short-term involvement, long-term participation in physical activity is associated with greater and gradual improvements in cardiovascular fitness over time (Bulmenthal, et al., 1991). Depression is also associated with other poor health behaviors that adversely affect cardiovascular fitness, including smoking and obesity (Katon, et al., 2004; Katon W. J., 2003). Indeed, many HF patients are obese (Kapoor & Heidenreich, 2010) and engage in behaviors such as smoking and alcohol use (Kravitz, et al., 1993). Future studies should prospectively examine the association among depression, exercise habits, and cardiovascular fitness in HF patients, as such studies may provide greater insight into the current findings and identify possible intervention strategies.

Our findings indicate that poor cardiovascular fitness may explain the relationship between depression and reduced cognitive function in HF patients. Cardiovascular fitness is strongly influenced by exercise activity and reflective of increased ability of the heart to deliver oxygen throughout the body (American College of Sports Medicine, 2006; Netz, Dwolatzky, Zinker, Argov, & Agmon, 2011). Our findings, in agreement with current literature support the argument that physical fitness rather than current physical activity to be more closely related to cognitive function (Etnier, Sibley, Pomeroy, & Kao, 2003; Netz, Argov, & Inbar, Fitness's moderation of the facilitative effect of acute exercise on cognitive flexibility in older women, 2009). Indeed, cardiovascular fitness is associated with better cognitive test performance in patients with cardiovascular disease (Alosco, et al., 2011; Steinberg, et al., 2011; Gunstad, et al., 2005) and with greater structural and functional integrity of the brain among older adults (Colcombe, et al., 2003; Erickson, et al., 2009). A likely explanation for these findings may involve the beneficial effects of cardiovascular fitness on the vascular system, including endothelial and cardiac functioning (Corvera-Tindel, Doering, Woo, Khan, & Dracup, 2004; Chicco, 2008; Papathanasiou, Tsamis, Georgiadou, & Adamopoulos, 2008; Davison, et al., 2010; Moser, et al., 2004; Jefferson A. L., 2010). Cerebral perfusion also likely plays a critical role, as hypoperfusion is commonly theorized to underlie cognitive deficits in HF patients (Jefferson, et al., 2007; Jefferson, Poppas, Paul, & Cohen, 2007) and this deficiency may be alleviated through improved physical fitness (Stanek, et al., 2011; Rogers, Meyer, & Mortel, 1990). Depressed HF patients appear to be a greater risk for reduced cerebral perfusion (Alves, et al., 2006) and prospective studies should examine whether exercise interventions in HF patients with depression improves cognitive function.

The current study is limited in several ways. First, the present analyses consisted of cross-sectional data and longitudinal studies are needed to clarify the directionality of the relationship between depression and exercise performance and subsequent outcomes. Second, depressive symptomatology, exercise adherence, and estimated oxygen uptake were examined using self-report and future work should examine the relationships among these variables using objective measures (i.e., actigraphy, stress testing). Additionally, the current study also did not examine potential improvements in cognitive function following increased cardiovascular fitness or underlying mechanisms involved. Future studies may benefit from use of functional magnetic resonance imaging (fMRI) to examine the pathophysiological effects of cardiovascular fitness among depressed HF patients. Consistent with this notion, depression has also been associated with increased obesity and diabetes (Ehlert, Gaab, & Heinrichs, 2001; Akil, et al., 1993), and elevations in inflammatory markers (i.e., C-reactive protein) (Panagiotakos, et al., 2004) and future studies should also explore these factors as possible mechanisms for reduced cognitive function as well as poor cardiovascular fitness.

In summary, the current study suggests that reduced cardiovascular fitness may partially explain decreased cognitive function among HF patients with depression. As a frequent morbidity in persons with HF, depression is a potentially important contributor to poor exercise adherence and reduced cardiovascular fitness in this population and thus may impede rehabilitation. Longitudinal studies are needed to elucidate underlying mechanisms and determine whether treatment of depression leads to better neurocognitive outcomes through modification of factors negatively impacting cardiovascular fitness (i.e., physical inactivity).

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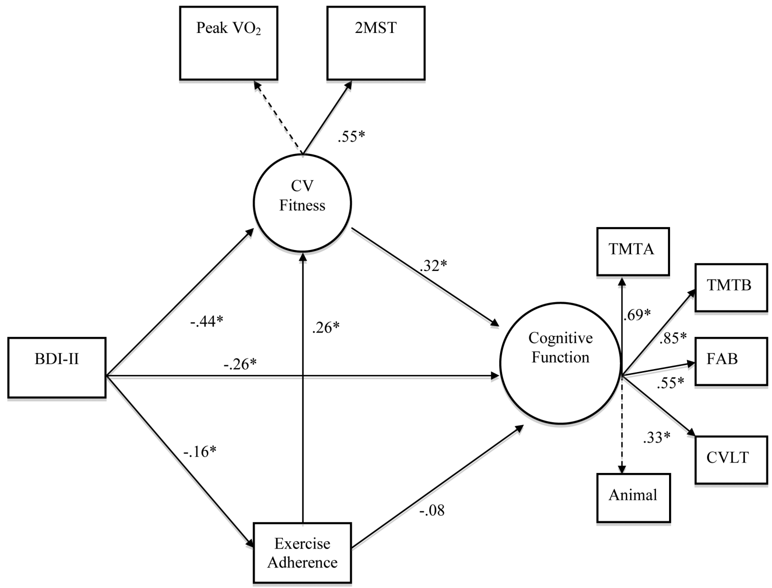

Figure 1. Model Examining the Role of Cardiovascular Fitness and Exercise Adherence in the Relationship Between Depression and Cognitive Function in HF Patients (*N* = 158)

Notes. The pathways between cognitive function and animal was fixed as was the pathway between CV Fitness and Peak VO_2. Standardized parameters estimates are presented in the model; significance levels for these paths are based on the unstandardized estimates. Abbreviations—BDI-II = Beck Depression Inventory-II; TMTA = Trail Making Test A; TMTB = Trail Making Test B; FAB = Frontal Assessment Battery; CVLT= California Verbal Learning Test Delayed Recall; Animal = Animals Fluency Test; 2MST = 2-minute step test; CV = Cardiovascular

$^{*}p < .05$

Table 1

Demographic, Clinical, and Cognitive Characteristics of 158 Older Adults with Heart Failure

Demographic Characteristics	
Age, mean (SD)	68.96 (9.13)
Sex (% Women)	36.7
Race (% Caucasian)	82.3
Years of Education, mean (SD)	13.39 (2.74)
Clinical Characteristics	
Left Ventricular Ejection Fraction, mean (SD)	40.70 (14.39)
Beck Depression Inventory-II, mean (SD)	7.67 (7.57)
Exercise adherence, % non-adherent	50.6
2-Minute Step Test Males	62.90 (24.65)
2-Minute Step Test Females	55.89 (21.14)
2-Minute Step Test Overall Sample	60.32 (23.59)
DASI Peak Oxygen Uptake (mL/min), mean (SD)	24.46 (6.53)
Cognitive Test Performance, T-score mean (SD)	
Trail Making Test A	49.93 (10.56)
Trail Making Test B	43.62 (18.63)
Frontal Assessment Battery	43.08 (21.85)
CVLT Long Delayed Recall	47.12 (10.30)
Animals	54.72 (11.24)

DASI = Duke Activity Status Index; CVLT = California Verbal Learning Test

Table 2

Bivariate Covariance Matrix (*N* = 158)

	2MST	BDI	CVLT	TMTA	TMTB	FAB	Animal	Exercise	Peak
2MST	556.69	--	--	--	--	--	--	--	--
BDI	−35.89	57.37	--	--	--	--	--	--	--
CVLT	−1 .23	−3.82	106.15	--	--	--	--	--	--
TMTA	66.54	−18.64	24.74	111.51	--	--	--	--	--
TMTB	127.53	−56.41	49.65	116.47	346.94	--	--	--	--
FAB	124 .13	−25.50	57.68	88.95	193.34	477.44	--	--	--
Animal	40.05	−9.74	28.28	26.75	64.27	71.08	126.30	--	--
Exercise	132 .82	−41.06	5.60	12.77	25.46	44.86	64.16	1153.96	--
Peak	82 .73	−23.54	3.24	21.57	39.50	35.89	19.02	71.64	42.61

Note. 2MST = 2-minute step test; BDI= Beck Depression Inventory-II; CVLT = California Verbal Learning Test-II Long Delayed Recall; TMTA = Trail Making Test A; TMTB = Trail Making Test B; FAB = Frontal Assessment Battery; Animal = Animals Fluency Test; Peak = Estimate Peak Oxygen Uptake; Exercise = Exercise Adherence