HHS Public Access
Author manuscript
Appl Physiol Nutr Metab. Author manuscript; available in PMC 2015 August 19.

Published in final edited form as:
Appl Physiol Nutr Metab. 2014 June ; 39(6): 724–729. doi:10.1139/apnm-2013-0380.

Relationship between exercise behavior, cardiorespiratory fitness, and cognitive function in early breast cancer patients treated with doxorubicin-containing chemotherapy: a pilot study[1]

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Abstract

The purpose of this study was to examine the relationship between self-reported exercise behavior, cardiorespiratory fitness (CRF), and cognitive function in early breast cancer patients. Thirty-seven breast cancer patients following completion of chemotherapy (median 16 months) and 14 controls were studied. Cognitive function was assessed using the Central Nervous System (CNS) Vital Signs software (CNS Vital Signs, LLC, Morrisville, N.C., USA), a computerized test battery consisting of 9 cognitive subtests. Exercise behavior was evaluated using the Godin Leisure Time

[1]This paper is a part of a Special Issue entitled The role of diet, body composition, and physical activity on cancer prevention, treatment, and survivorship.

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Conflict of interest statement
The authors declare no conflicts of interest.

Exercise Questionnaire, and CRF was assessed via a cardiopulmonary exercise test to assess peak oxygen consumption. Patients' mean total exercise was 184 ± 141 $min \cdot week^{-1}$ compared with 442 ± 315 $min \cdot week^{-1}$ in controls ($p < 0.001$). Significantly fewer patients (32%) were meeting exercise guidelines (i.e., ≥150 min of moderate-intensity or vigorous exercise per week) compared with 57% of controls ($p = 0.014$). Patients' peak oxygen consumption averaged 23.5 ± 6.3 $mL \cdot kg^{-1} \cdot min^{-1}$ compared with 30.6 ± 7.0 $mL \cdot kg^{-1} \cdot min^{-1}$ in controls ($p < 0.01$). Scores on the cognitive subdomains were generally lower in patients compared with controls, although only the difference in verbal memory was significant (unadjusted $p = 0.041$). In patients, weak to moderate correlations were indicated between exercise, peak oxygen consumption, and the majority of cognitive subdomain scores; however, there was a significant positive correlation between exercise and visual memory ($r = 0.47$, $p = 0.004$). In conclusion, breast cancer patients following the completion of primary adjuvant chemotherapy exhibit, in general, worse cognitive performance than healthy women from the general population, and such performance may be related to their level of exercise behavior.

Keywords

neurocognition; breast cancer; adjuvant therapy; late effects

Introduction

Significant improvements in early detection and adjuvant therapy have resulted in a dramatic reduction in the risk of cancer-specific mortality in women diagnosed with early breast cancer (Siegel et al. 2013). As a result, approximately 2.5 million women are alive today in the United States with a history of breast cancer (Siegel et al. 2013). However, these patients now have sufficient longevity to be at risk for the chronic and late effects of adjuvant therapy (Scott et al. 2013). Research in this domain has traditionally focused on the chronic psychosocial late effects, such as impairments in quality of life, persistent fatigue, depression, and anxiety (Day et al. 1999; Ganz et al. 1995, 1998; Goodwin et al. 2003; Land et al. 2006). More recent research endeavors have broadened to include investigation of long-term cognitive impairments in early breast cancer patients (Ahles et al. 2002; Jim et al. 2012; Phillips et al. 2012; Kesler et al. 2013). This work has demonstrated that standard breast cancer adjuvant therapy, particularly treatment with chemotherapy, is associated with adverse cognitive functioning, including impairments in memory, processing speed, and executive function (Ahles et al. 2002; Jim et al. 2012; Phillips et al. 2012), which may persist up to 20 years following the completion of primary adjuvant therapy (Koppelmans et al. 2012).

A meta-analysis of 17 studies involving 807 early breast cancer patients demonstrated small but statistically significant impairments in several cognitive domains, including verbal and visuospatial function (Jim et al. 2012). Cognitive impairments identified using neuropsychological test performance correlate with structural brain differences detected with functional imaging (Deprez et al. 2012). While the underlying biopsychosocial mechanisms remain to be elucidated (Ahles et al. 2002), the development and testing of effective therapeutic strategies to attenuate and (or) prevent adjuvant therapy-induced cognitive deficits in women with early breast cancer is emerging as a high priority in breast cancer survivorship research.

A growing evidence base indicates that higher levels of self-reported exercise behavior are associated with significant reductions in the risk of dementia, Alzheimer's Disease (AD), and cerebrovascular disease (Laurin et al. 2001; Scarmeas et al. 2009; Schmidt et al. 2013). In a meta-analysis of 16 prospective epidemiologic studies involving 163 797 nonclinical adults, exercise was associated with a 28% and 45% reduced risk of dementia and AD, respectively (Hamer and Chida 2009). In addition, higher cardio-respiratory fitness (CRF), an objective measure of exercise exposure, is also a significant predictor of cognitive function in adults. For example, in a recent prospective study of 19 458 community-dwelling individuals, those in the highest quartile of CRF had a ~30% reduction in the risk of all-cause dementia, relative to adults in the lowest CRF quartile (DeFina et al. 2013). Finally, structured exercise training improves various domains of cognitive function in previously sedentary adults (Angevaren et al. 2008).

Of importance, a diagnosis of early breast cancer and associated therapeutic management is associated with significant declines in exercise behavior and CRF (Irwin et al. 2003; Jones et al. 2012*a*; Lakoski et al. 2013), while low levels of exercise and CRF are associated with impairments in quality of life, fatigue, and other patient reported outcomes (PROs) (Herrero et al. 2007; Milne et al. 2007). Conversely, systematic reviews and meta-analyses conclude that aerobic training following standard prescription guidelines (i.e., 3–5 times$\cdot$week^{-1}, for 30–45 min$\cdot$session^{-1}, at 60%–80% of baseline exercise capacity for 12 to 24 weeks) (American College of Sports Medicine 2013) is not only safe and feasible but associated with maintenance and improvement in CRF and PROs in early breast cancer patients during and following the completion of primary adjuvant therapy, respectively (Schmitz and Speck 2010; Schmitz et al. 2010). However, whether exercise training is an effective strategy to prevent and (or) treat cognitive impairment in breast cancer patients has not been investigated.

As an initial step into this line of investigation, we conducted a cross-sectional pilot study to examine the relationship between self-reported exercise behavior, CRF, and cognitive function in early breast cancer patients previously treated with anthracycline-containing chemotherapy. We hypothesized that (*i*) cognitive function would be impaired in breast cancer patients compared with normative age–sex matched healthy controls; and (*ii*) higher exercise behavior and CRF would be associated with higher cognitive function in breast cancer patients.

Materials and methods

Study population and procedures

Thirty-seven (n = 37) asymptomatic women with histologically confirmed estrogen-receptor positive (ER^+) and human epidermal growth factor receptor 2 (HER-2) negative breast adenocarcinoma (stage IA–IIIC) that was previously treated with doxorubicin-containing chemotherapy (median 16 months; interquartile range, 6 to 32 months) were enrolled between January 2011 and January 2012 at Duke University Medical Center (DUMC).

Additional major eligibility criteria were (*i*) no recent documented cardiac disease, and (*ii*) no contraindications to a cardiopulmonary exercise test (CPET) (American Thoracic Society/American College of Chest Physicians (ATS/ACCP) 2003; Jones et al. 2009). Fourteen age–sex-matched controls were also recruited for comparison purposes. The control subjects were recruited from a convenience sample of nursing staff at the DUMC. Major eligibility for control subjects were (*i*) no recent documented cardiac disease, and (*ii*) no contraindications to a CPET (ATS/ACCP 2003; Jones et al. 2009). The DUMC Institutional Review Board approved the study and all participants provided written consent prior to the commencement to any study-related procedures.

Cognitive function testing

Cognitive function was assessed using the Central Nervous System (CNS) Vital Signs software (CNS Vital Signs, LLC, Morrisville, N.C., USA), which is a computerized test battery comprising the following cognitive subtests: psychomotor speed (Finger Tapping and Symbol Digit Coding); reaction time (Stroop Test); complex attention, cognitive flexibility, processing speed (Symbol Digit Coding); executive function (Shifting Attention); verbal memory, visual memory, composite memory (Four Part Continuous Performance Test). Age-adjusted standardized scores for each test domain (mean = 100; SD = 15) were obtained from CNS Vital Signs. Standardized scores less than 20 were truncated at 20. CNS Vital Signs has well-established reliability and validity in healthy and clinical subjects (Gualtieri and Johnson 2006).

Exercise behavior

Exercise behavior was assessed by self-report using the leisure score index (LSI) of the Godin Leisure-Time Exercise Questionnaire (Godin and Shephard 1985). The LSI contains 3 questions that assess the average frequency of mild (minimal effort, no perspiration), moderate (not exhausting, light perspiration), and vigorous-intensity (heart beats rapidly, sweating) exercise during free time in a typical week. In the present study, patients reported their average weekly exercise over the past month. We also asked for average duration within each intensity category. The weekly minutes (frequency × average duration) of exercise in each intensity category was summed to calculate total exercise minutes per week, moderate- plus vigorous-intensity exercise as well as the proportion meeting current national cancer exercise guidelines (i.e., at least 150 min of moderate-intensity or vigorous exercise per week) (Schmitz et al. 2010) was determined.

Incremental exercise testing

To determine CRF, a CPET with 12-lead electrocardiography monitoring (Mac 5000, GE Healthcare, USA) was performed by certified exercise physiologists to determine peak oxygen consumption ($\dot{V}O_{2peak}$). The specific protocol for this test has previously been reported in detail (Jones et al. 2012*b*). In brief, all tests were performed on a motorized treadmill (GE series 2000 Treadmill, GE Healthcare) with expired gas analysis (ParvoMedics TrueOne 2400, Sandy, Utah, USA) to determine $\dot{V}O_{2peak}$ (ATS/ACCP 2003; Jones et al. 2009). All cardiopulmonary exercise testing data was recorded as the highest 30-s value elicited during the exercise test.

Clinical parameters

Demographic and medical characteristics were abstracted from electronic medical chart review. Performance status was assessed by the attending oncologist at the time of study enrollment using the Karnofsky Performance Scale.

Statistical analyses

Descriptive analyses are presented for the demographic/medical characteristics, cognitive function domains, exercise behavior, and CRF. ANOVA was used to examine differences between patients and controls on continuous variables, while Fisher's exact test was used for categorical variables. We also conducted analysis of covariance (ANCOVA) to assess differences between patients and controls on cognitive function, adjusting for age, exercise behavior, and $\dot{V}O_{2peak}$. Bivariate Pearson product-moment correlations were used to examine the relationship between exercise behavior, CRF, and cognitive function. A 2-sided significance level of 0.05 was used for all statistical tests. No adjustments were made for multiple comparisons. All statistical calculations were performed using SAS version 9.2 (SAS Institute, Cary, N.C., USA).

Results

Participant characteristics

Patients' mean ± SD age and weight were 52 ± 12 years (range, 28–72 years) and 77 ± 20 kg, respectively. The median (interquartile range, IQR) months since diagnosis and since chemotherapy completion were 22 months (IQR, 9 to 43 months) and 16 months (IQR, 6 to 32 months), respectively. Control subjects' mean age and weight were 58 ± 5 years (range, 36–69 years) and 68 ± 9 kg, respectively. There were no significant differences between groups on any medical or demographic variables (Table 1).

Exercise behavior and CRF data are presented in Table 1. Patients' mean total exercise and moderate plus vigorous exercise were 184 ± 141 min·week^{-1} and 108 ± 109 min·week^{-1} compared with 442 ± 315 min·week^{-1} and 359 ± 302 min·week^{-1} in controls ($p < 0.001$). Thirty-two percent of patients met exercise guidelines (i.e., ≥150 min of moderate-intensity or vigorous exercise per week) compared with 57% of controls ($p = 0.014$). Similarly, patients' mean $\dot{V}O_{2peak}$ was 23.5 ± 6.3 mL·kg^{-1}·min^{-1} and 1.7 ± 0.4 L·min^{-1} compared with 30.6 ± 7.0 mL·kg^{-1}·min^{-1} and 2.1 ± 0.4 L·min^{-1} in controls ($p \leq 0.015$). Overall, mean $\dot{V}O_{2peak}$ in patients was 23% lower compared with controls.

Cognitive function

Cognitive data are presented in Table 2. In comparison with age-adjusted standardized scores for each test domain (mean = 100; SD = 15), cognitive subdomain scores for breast cancer patients were, in general, 0.5 to 1 SD below these norms. In unadjusted analysis, comparison of patients to healthy controls revealed, in general, that patients scored lower in the majority of cognitive subdomain but only the difference in verbal memory reached statistical significance. Specifically, patients' mean verbal memory was 96.1 ± 17.0 compared with 107.5 ± 18.2 in controls ($p = 0.041$). There was also trend towards a difference for reaction time (patients, 95.6 ± 10.7 vs. controls, 101.9 ± 15.8, $p = 0.108$).

After adjustment for age, exercise behavior, and $\dot{V}O_{2peak}$, the difference in verbal memory was no longer significant ($p = 0.615$).

Relationship between neurocognitive function, fitness, and exercise behavior

The relationship between exercise (total exercise behavior), $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$), and cognitive function subdomains for breast cancer patients only is presented in Table 3. In general, weak correlations were indicated between exercise, $\dot{V}O_{2peak}$, and the majority of cognitive subdomains; however, only the correlation between exercise behavior and visual memory was significant ($r = 0.47$, $p = 0.004$). There was a trend towards a relationship between exercise behavior and composite memory ($r = 0.31$, $p = 0.067$). No other correlations approached significance.

Discussion

Compared with women without a history of breast cancer, in unadjusted analyses, early breast cancer patients exposed to anthracycline-containing chemotherapy, as well as other cytotoxic adjuvant therapies, scored significantly lower in the cognitive domain of verbal memory. In general, patients also performed more poorly on several additional cognitive subdomains but these differences did not approach statistical significance. These find-ings are consistent with several prior reports examining the long-term effects of breast cancer adjuvant therapy on cognitive function. In a recent study of 196 early breast cancer patients treated over 20 years previously with nonanthracycline-containing chemotherapy (i.e., cyclophosphamide, methotrexate, fluorouracil), Koppelmans et al. (2012) found that patients performed significantly worse in several cognitive domains (cognitive function was evaluated using an interview-based, abbreviated neuropsychological examination), including immediate and delayed verbal memory, executive functioning, and psychomotor speed, compared with 1509 women from the general population. These cognitive functions were evaluated using an interview-based, abbreviated neuropsychological examination. Significant deficits in verbal aspects of cognitive function appear to be a consistent finding in studies examining patients shortly following treatment completion as well as those conducted several years after therapy cessation (Schagen et al. 2001; Wefel et al. 2004). Indeed, in a recent meta-analysis of 17 studies involving 807 women previously treated with conventional chemotherapy regimens for early breast cancer, Jim et al. (2012) found that patients' cognitive deficits were mainly in verbal ability as well as visuospatial ability. We conducted adjusted analysis to control for differences in age, exercise behavior, and $\dot{V}O_{2peak}$ between patients and controls. These results indicated no differences in any cognitive subdomain, suggesting that breast cancer patients may have lower cognitive function because of low exercise behavior and $\dot{V}O_{2peak}$, as opposed to the fact they have had a history of breast cancer and breast cancer treatment. Further work is required to clarify the relationship between breast cancer, anticancer therapy, exercise behavior, and CRF.

Despite evidence of consistent deficits in specific domains of cognitive function in breast cancer patients following the completion of therapy, the magnitude of these impairments appears relatively small (Jim et al. 2012). This is in contrast to rather robust cognitive impairments in patients during primary therapy (Brezden et al. 2000). This may suggest that cognitive impairments induced during therapy may be reversible over the long term; nevertheless, few data are available from prospective longitudinal studies that have evaluated patients from diagnosis, through active treatment, and into the post-treatment period. Such studies are critical to understand the time-course, magnitude, and potential reversibility of cognitive impairment as well as identify those patients at greatest risk of therapy-induced impairments. Another critical methodological issue plaguing the current field is the use of a wide range of instruments used to assess cognitive function in cancer patients (Jim et al. 2012). Consequently, the definition of cognitive impairment varies between studies, hindering the ability to conduct cross-study comparisons. Full neuropsychological performance tests performed by licensed clinical neuropsychologists are desirable but such testing requires specialized personnel, more financial resources, and a longer test administration period (~2 h). As such, there has been significant interest in the development and testing of alternative, feasible approaches that retain acceptable specificity and sensitivity (van den Bent et al. 2011). Here, we utilized a computerized test battery to evaluate cognitive function in women with breast cancer. However, investigation of the method as it relates to performance on full neuropsychological tests, in conjunction with functional imaging studies, will be required to fully characterize the specificity and sensitivity of this tool; this question is the focus of several ongoing studies.

The consensus regarding the degree and severity of impairments in cognitive function following the completion of adjuvant therapy in early breast cancer has, not surprisingly, resulted in increased attention on the development and testing of effective strategies that may attenuate or prevent this toxicity. With a view towards future studies, and in light of the promising evidence in persons without a cancer diagnosis, here we explored the potential role of exercise and CRF to modulate cognitive function in breast cancer patients. Overall, both exercise behavior and CRF were weakly associated with cognition outcomes, with only notable correlations indicated between exercise behavior and visual memory and composite memory. There were no significant relationships for CRF and any cognitive function subdomains. The small sample size and limited variability in exercise behavior and CRF measures likely contributed to the lack of statistically significant findings.

Given that this is the first study to examine the relationship between exercise, CRF, and cognitive function in patients with cancer, comparisons with prior work are not possible at present. Nevertheless, the significant, positive correlation between exercise and better performance in select memory-related aspects of cognition observed here are consistent with meta-analytic studies in humans showing a positive relationship between exercise and memory in various adult populations (Hayes et al. 2013; Roig et al. 2013). Similarly, a recent systematic review of the extant literature found a consistent positive correlation between CRF and gray matter volume in several cortical regions (Hayes et al. 2013). Several biological mechanisms are postulated to mediate the positive effects of exercise and CRF on cognitive function in adults with or at risk of cognitive deficits. Specifically, findings of animal studies consistently show that exercise increases adult hippocampal neurogenesis via modulation of various growth and inflammatory mediators such as insulin-like growth factor-1, vascular endothelial growth factor, and brain-derived neurotrophic growth factor (Dishman et al. 2006; Wong-Goodrich et al. 2010). On the basis of the present findings, it is likely premature to launch clinical intervention studies investigating the efficacy of exercise training interventions on cognitive function in women with early breast cancer either during or following the completion of primary adjuvant therapy. To determine whether exercise intervention studies are warranted in this clinical setting, larger cross-sectional and prospective, longitudinal studies are required among relatively homogenous patient cohorts adopting validated measures of cognitive function, exercise behavior, and CRF. Such studies will not only provide critical information on the magnitude of the relationship between exercise and cognition but will also identify the patient subgroups most likely to benefit from an exercise intervention and the dose of exercise required to positively alter cognitive function.

The strengths and limitations of this study deserve mention. The strengths of this study include the reliable and validated measures of cognitive function, exercise behavior, as well as gold standard assessment of CRF ($\dot{V}O_{2peak}$), and our patient study cohort that were uniform in terms of cancer diagnosis (breast cancer), stage of disease (early), histological subtype (ER^+, HER-2 negative), and prior therapy (anthracycline-containing chemotherapy). However, there were also important limitations. The most important limitations are the small sample size and transparent nature of the study purpose. Thus, patients interested in exercise and health, with better physical functioning, and experiencing less treatment-related late effects were more likely to participate. Additionally, cognitive function was only assessed using computer-based methods. Studies that also include other measures of cognitive function such as neuropsychological testing and functional imaging will be required to fully understand the relationship between exercise measures and cognition in the oncology setting.

In summary, breast cancer patients following the completion of primary adjuvant chemotherapy exhibit, in general, worse cognitive performance than healthy women from the general population, and such performance may be related to their level of exercise behavior. Results of this exploratory study highlight the need for future studies to further investigate the role of exercise behavior and possibly CRF in the etiology and prevention and (or) treatment of cognitive impairments in women with early breast cancer.

Acknowledgments

This research was supported in part by funds from George and Susan Beischer awarded to L.W.J.

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Table 1

Participant characteristics.

Variable	**Patients (*n* = 37)**	**Controls (*n* = 14)**	***p***
Age, y	52±12	58±5	0.090
Weight, kg	77±20	68±9	0.131
BMI, $kg \cdot m^{-2}$	27±5	25±4	0.211
Cancer type			
Ductal	28 (76)	–	–
Invasive	2 (5)	–	–
Lobular	7 (19)	–	–
Cancer stage		–	–
IA	2 (5)	–	–
II/IIA/IIB	20 (54)	–	–
IIIA/IIIC	15 (41)	–	–
Surgery			
Lumpectomy	9 (24)	–	–
Mastectomy/partial mastectomy	28 (76)	–	–
Time since primary diagnosis, mo.; median (IQR)	21.7 (9.4, 43.0)	–	–
Time since chemotherapy, mo.; median (IQR)	16.3 (5.8, 32.3)	–	–
Additional therapy		–	–
Cytotoxic therapy*	31 (84)	–	–
Radiation	28 (76)	–	–
Endocrine therapy	26 (70)	–	–
Cardiac risk factors			
Hypertension	10 (27)	1 (7)	0.251
Hyperlipidemia	5 (14)	0 (0)	0.305
Diabetes	1 (3)	0 (0)	>0.999
Current and (or) history of smoking	3 (8)	0 (0)	0.552
Exercise behavior			
Total exercise, $min \cdot wk^{-1}$†	184±141	442±315	<0.001
Moderate plus vigorous-intensity exercise, $min \cdot wk^{-1}$†	108±109	359±302	<0.001
CDC/ACSM guidelines	12 (32)	8 (57)	0.014
Cardiorespiratory fitness			
$\dot{V}O_{2peak}$, $mL \cdot kg^{-1} \cdot min^{-1}$	23.5±6.3	30.6±7.0	0.001
$\dot{V}O_{2peak}$, $L \cdot min^{-1}$	1.7±0.4	2.1±0.4	0.015

Note: Data are presented as means ± SD for continuous data and *n* (%) for categorical data, except as noted. BMI, body mass index; IQR, interquartile range; CDC/ACSM, Centers of Disease Control/American College of Sports Medicine; $\dot{V}O_{2peak}$, peak oxygen consumption.

*Cytotoxic therapy includes taxol, xeloda, abraxane.

†Data available on 35 breast cancer patients and 10 controls.

Table 2

Differences in cognitive function.

Variable	Patients (*n* = 37)	Controls (*n* = 14)	Unadjusted *p*	Adjusted *p*†
Psychomotor speed	91.6±17.9	96.2±15.6	0.397	0.444
Reaction time	95.7±10.7	101.9±15.8	0.108	0.184
Complex attention	88.1±27.6	96.2±22.5	0.330	0.331
Cognitive flexibility	86.7±22.4	89.1±23.4	0.737	0.250
Processing speed	100.9±14.1	100.5±20.2	0.934	0.609
Executive functioning	86.8±22.1	89.0±23.3	0.760	0.272
Composite memory	98.5±15.7	103.4±16.7	0.332	0.705
Verbal memory	96.1±17.0	107.5±18.2	0.041	0.615
Visual memory	101.2±15.0	98.6±15.3	0.585	0.916

Note: Data are presented as means ± SD age-adjusted standardized scores for each test domain (mean = 100; SD = 15). $\dot{V}O_{2peak}$, peak oxygen consumption.

†Adjusted for age, $\dot{V}O_{2peak}$ (mL·kg^{-1}.min^{-1}) and total exercise behavior (min·wk^{-1}).

Table 3

Correlation between exercise behavior, cardiorespiratory fitness, and cognitive function.

	Total exercise behavior, min·wk^{-1}		$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	
Variable	***r***	***p***	***r***	***p***
Psychomotor speed	0.13	0.467	0.17	0.327
Reaction time	0.13	0.455	<0.01	0.977
Complex attention	0.18	0.311	−0.15	0.372
Cognitive flexibility	0.11	0.539	−0.15	0.391
Processing speed	−0.04	0.799	−0.03	0.882
Executive functioning	0.12	0.500	−0.16	0.342
Composite memory	0.31	0.067	0.18	0.287
Verbal memory	0.06	0.720	0.11	0.531
Visual memory	0.47	0.004	0.20	0.244

Note: Age-adjusted standardized scores for each test domain (mean = 100; SD = 15) were obtained from CNS Vital Signs (CNS Vital Signs, LLC, Morrisville, N.C., USA). $\dot{V}O_{2peak}$, peak oxygen consumption.