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Patient-Reported and Objectively Measured Physical Function in Older Breast Cancer Survivors and Cancer-Free Controls

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Abstract

Objectives—Older breast cancer survivors (BCS) consistently report more functional limitations than women without cancer, but whether or not these differences remain when using objective measures of physical functioning and the correlates of these measures is unknown.

Methods—Cross-sectional study comparing older (≥60 years old) BCS (n=84) to similarly aged women without cancer (n=40). Patient-reported physical function was assessed by the SF-36 physical function (SF-36PF) subscale and the Late Life Function & Disability Instrument (LLFDI). Objective measures included the short Physical Performance Battery (sPPB), usual walk speed (m/s), chair stand time (sec) and, grip strength (kg). Potential predictors included age, comorbidities, symptom severity, fatigue and skeletal muscle index (SMI; kg/m^2).

Results—Patient-reported physical function was significantly lower in BCS than controls using SF-36PF (47.3±0.1 vs. 52.9±4.0, p<0.001) and LLFDI (68.2±10.5 vs. 75.0±8.9, p = 0.001). BCS had significantly lower sPPB scores (10.7±0.1 vs. 11.7±0.5, p<0.001), longer chair stand times (12.6±3.7 vs. 10.1±1.4 sec, p<0.001), and lower handgrip strength (22.3±5.0 vs. 24.3±4.4 kg, p = 0.03) than controls, but similar walk speed (1.1± 0.2 vs. 1.1 ± 0.1 m/s, p=0.75). Within BCS, age, comorbidities, SMI, symptom severity and fatigue explained 17.3%−33.1% of the variance across physical function measures. Fatigue was the variable most consistently associated with patient-reported physical functioning and age and comorbidities were the variables most consistently associated with objectively measured physical functioning.

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Author Contributions

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Conclusion—Older BCS should be screened for functional limitations using simple standardized objective tests and interventions that focus on improving strength and reducing fatigue should be tested.

Keywords

Physical functioning; aging; comorbidities; body composition; symptoms; breast cancer; survivorship

INTRODUCTION

Breast cancer is a survivable disease, with 5- and 10-year survival rates for invasive breast cancer at 90% and 83%, respectively, and a 5-year survival rate of 99% for non-invasive disease[1]. Breast cancer survivors are often treated with multiple aggressive therapies that prolong the treatment-related symptom burden of this disease, including fatigue[2, 3], pain[4], and weakness[5]. Together these symptoms and others likely contribute to observational findings that breast cancer survivors report more limitations with daily functioning compared to their cancer-free counterparts. An early report from the Iowa Women's Health Study showed that older female cancer survivors (median age 72 years), including women with breast cancer, were 30–50% more likely to self-report an inability to do activities requiring mobility and strength than women in the same cohort without cancer[6]. Subsequently, others have confirmed that breast cancer survivors self-report lower levels of physical functioning compared to other women without cancer[7, 8].

Functional declines are a particular concern for breast cancer survivors because of the combined effects of chemotherapy, radiation therapy and adjuvant hormone therapy on body composition, neuromuscular function and physical activity levels [9], all of which are known to contribute to functional declines in older adults. Since the majority of breast cancer survivors are older when diagnosed[1], women are already susceptible to age-related declines in physical functioning prior to treatment. Aggressive treatments, in particular chemotherapy, may have the most detrimental impact on physical functioning since the molecular changes that result from chemotherapy are similar to those that occur with aging, including DNA methylation and telomerase shortening[10–12]. We have previously shown that older breast cancer survivors treated with chemotherapy and/or radiation therapy have higher rates of physical frailty than published rates in similarly aged cohorts and that within survivors, women with lower physical activity levels and higher BMI were more likely to be frail than active, leaner women[5]. Frailty is predictive of functional limitations and disability and is traditionally thought of as a geriatric syndrome; thus, an earlier onset and greater prevalence of frailty among breast cancer survivors suggests that treatment may be accelerating the aging process; however, we did not compare our findings to similar measurements in an aged-matched sample of women without cancer.

We have previously proposed a conceptual model of physical function in cancer survivors to guide research that assesses physical function after cancer diagnosis and that tests interventions to preserve functioning during and after treatment [13]. This conceptual framework recognizes that the determinants of physical function in cancer survivors are multi - factorial and also argues for the use of objective measures of physical function in addition to or in place of patient-report. Performance tests are able to identify functional decrements before problems are reported by an individual, are often more sensitive indicators of functional abilities, and are less subject to bias. To date, our conceptual model of physical functioning in breast cancer survivors has not been tested using objective measures of physical function nor in comparison to women without cancer. Objectively measured physical function may better estimate the true prevalence of functional limitations in breast cancer survivors and by identifying predictors of patient-reported and objectively measured physical function, such as age, comorbidities and symptoms, breast cancer survivors at higher risk for future disability onset can be better identified and appropriate interventions considered.

We conducted a cross-sectional, case-control study to: 1) Compare patient-report and objective measures of physical function between older breast cancer survivors and cancer-free controls and 2) Identify variables associated with physical functioning among older breast cancer survivors.

METHODS

Study Design and Sample.

This study used a case-control approach to compare physical functioning between breast cancer survivors and women with no history of cancer. Baseline data from women who completed treatment for early stage breast cancer and who were enrolled in one of two exercise RCTs in breast cancer survivors (NCT00665080, NCT00591747) were used for analyses. Eligibility for the original trials included diagnosis of stage 0-IIIc breast cancer, postmenopausal status, no regular exercise participation, >1 year past chemotherapy and/or radiation therapy, and physician clearance to participate in moderate-intensity exercise. To better examine the combined effects of aging and cancer treatment, we restricted the sample for analysis to include only older women (≥60 years old) treated with chemotherapy. A control group of women who were over the age of 60 and never had a cancer diagnoses (exception of the removal of a basal cell carcinoma) were recruited and tested on the same outcomes as the breast cancer sample. We chose 60 years of age as the lower age limit to define older women in this study, rather than a traditional cutoff of 65 years, because of evidence suggesting that chemotherapy may accelerate aging and hasten early onset frailty in breast cancer survivors [10–12]. Thus, slightly lowering the age range of the sample to 60 years captures cancer survivors who may be vulnerable to geriatric syndromes due to treatment and allows us to identify opportunities for early prevention of functional decline. The study was approved by the Oregon Health & Science University Institutional Review Board and all participants provided written consent prior to data collection.

Power and Sample Size.

An a-priori sample size calculation indicated that a sample of n=33 per group was needed to detect a 5-point difference in self-report physical functioning with a power of 0.8 and alpha = 0.05. For aim 2, a post hoc power calculation was conducted in order to determine the power relative to the variance explained in each model.

Measures

Patient-Reported Outcomes

Demographics and Health History.—An in-house questionnaire was used to collect demographic information on age, income, marital status, race, education and employment and health history, with additional questions to gather cancer history and related clinical variables in breast cancer survivors.

Comorbidities.—The Charlson Comorbidity Index is a valid instrument to classify and provide a weighted index of 19 comorbidities with scores representing low (1–2), medium (3–4), and high (5 or more) comorbid burden[14].

Symptom Severity was measured using a 16-item checklist to assess the presence and severity (1–5 scale, with 1=not at all severe and 5=extremely severe) of common symptoms (fatigue, numbness/tingling in hands/feet, swollen hands/feet, trouble sleeping, trouble concentrating, trouble remembering, hot flashes, night sweats, pain, nausea, urine leakage, shortness of breath, cough, or balance problems) associated with breast cancer and its treatment[15]. Symptom severity was determined by the average ratings across the symptoms which were present. *Fatigue* was specifically measured by the Schwartz Cancer Fatigue scale, a reliable and valid 6-item scale that assesses the level of subjective fatigue a person currently is experiencing[16]. The summed score ranges from 6–30, with higher scores indicating more fatigue. Since we were determining whether symptoms related to cancer treatment predicted physical functioning in breast cancer survivors only, we did not assess symptoms in controls.

Perceived physical functioning was assessed by the SF-36 physical function subscale which assesses limitations in 10 activities related to mobility and physical movements[17]. Norm-based scores range from 0–100, with 50 indicating the population average and high scores indicating better function. We also assessed perceived physical functioning using the *Late Life Function Instrument (LLFDI)* which provides a more granular view of physical functioning by assessing three domains of basic lower extremity function, advanced lower extremity function, and upper extremity function to provide an overall physical function score. Scores range from 0 −100 (low to high function) and the instrument has both high reliability and validity[18].

Objectively Measured Outcomes

Physical function measures: The Short Physical Performance Battery (sPPB) was used to assess lower extremity functioning. The sPPB objectively quantifies balance, gait, and lower-extremity strength, using timed stance, usual walk speed, and timed chair stand tests, respectively. Each test is scored from 0 to 4, then scores are summed, with higher scores indicating greater physical function. The sPPB has acceptable internal consistency[19] and is responsive to clinically meaningful change[20]. We also disaggregated the sPPB to consider the continuous scores on timed chair stand (s) and usual walk speed (m/s) tests as discrete measures of the mobility and strength components of physical function and because they are independent predictors of poor outcomes in older adults[21]. *Upper extremity muscle* *function* was assessed with handgrip dynamometry to measure maximal voluntary isometric muscle force (kg). Grip strength has been used as a measure of upper body physical function in breast cancer survivors [22], is a predictor of disability onset in older adults[23] and is recommended as a screening measure for sarcopenia in clinical geriatric practice [24].

Body composition was measured both with BMI and with whole body densitometry. For *BMI*, height and weight were measured by using a wall-mounted stadiometer and a beam balance scale, respectively. Body mass index (BMI) was calculated as weight in kg adjusted by the square of height in meters^2. *Soft tissue composition* was assessed by dual-energy x-ray absorptiometry (Hologic Inc., Apex software version 4.0) to assess total percent body fat, lean mass (kg) and fat mass (kg). To assess for sarcopenia, a skeletal muscle index (SMI) was calculated as the sum of lean mass of both arms and legs (kg) adjusted by the square of height (m^2) [25].

Statistical Analyses.—All analyses were conducted using IBM SPSS version 24.0 (IBM Corporation, Chicago, USA). Following tests to assess normality, independent samples t-tests or Mann-Whitney U for non-parametric data, were used to compare objective and patient-reported physical function and body composition between cases and controls. Multiple linear regression was used to assess the relative contribution of the following independent variables: age, comorbidity index, SMI, symptom severity, and fatigue to variability in any physical function outcome(s) that were found to be significantly different between breast cancer survivors and controls. Selection of predictors was based on our conceptual model [26] and the published literature that identified these as predictors of patient-reported physical functioning in cancer survivors [27–29]. An observed statistical power ranging from 0.89–0.99 was found from a post-hoc statistical power analysis for multiple regression. All assumptions were assessed and met prior to proceeding with regression analyses.

RESULTS

Study Sample Characteristics (Table 1)

Breast cancer survivors had significantly higher comorbidity scores and significantly greater BMI than controls with mean values placing survivors near to the obese category. Age, race, marital status, education and employment status were similar between groups. The median age of breast cancer survivors and controls was 67.5 years (range: 60–79 years old) and 67.7 years (range: 60–82 years old), respectively, with 83% of both samples comprised of women over 65 years of age. The majority (59%) of breast cancer survivors were diagnosed with stage II disease and the average time since treatment was 7 years. In addition to receiving chemotherapy and surgery, 79% and 76% of women also underwent radiation and anti-hormone therapy, respectively. On average, survivors reported moderately severe symptoms, but low levels of cancer-related fatigue.

Comparisons between Breast Cancer Survivors and Controls (Table 2)

Patient-reported physical function was significantly lower in breast cancer survivors than controls using either the SF-36 physical function scale (cancer = 47.3±0.1, control =

52.9±4.0, p<0.001) or the LLFDI overall physical function score (cancer = 68.2±10.5, control = 75.0±8.9, p = 0.001). On objective measures, breast cancer survivors had significantly lower sPPB scores (cancer = 10.7±0.1 control = 11.7±0.5, p<0.001), longer chair stand times (cancer = 12.6±3.7 s, control = 10.1±1.4 sec, p<0.001), and lower handgrip strength (cancer = 22.3±5.0 kg, control = 24.3±4.4 kg, p = 0.03) than controls. Usual walk speed was not significantly different between groups. Breast cancer survivors had significantly greater lean mass (cancer = 30.7±6.6 kg, control = 27.3±9.8 kg, p = 0.02) and higher SMI than controls (cancer = 6.89 ±0.9 kg/m^2, control = 6.38 ±0.8 kg/m^2, p=0.01). There were no significant differences in % body fat or fat mass between groups. Significant differences remain between groups when restricting the sample to women 65 years of age and older. Similarly, group differences remain when applying a Bonferroni correction to the alpha level (p<0.015) to control for multiple statistical tests, with the exception of handgrip strength and lean mass.

Predictors of Patient-Reported and Objectively Measured Physical Function (Table 3)

Together, age, comorbidities, SMI, symptom severity and fatigue explained 17.3%−33.1% of the variance in the physical function outcomes that differed between survivors and controls (all measures except usual walk speed). Age and comorbidities were consistently associated with objective measures of physical functioning, explaining 20% to 30% of the variance in scores on these tests. Symptom severity and SMI explained additional variance in grip strength, but not chair time or the sPPB. Fatigue was consistently associated with measures of patient-reported physical functioning, with additional variance in LLFDI scores explained by comorbidities and additional variance in SF-36 PF scores explained by SMI.

DISCUSSION

Our case control study comparing older breast cancer survivors treated with chemotherapy to women without cancer confirmed previous findings that breast cancer survivors self-report poorer physical functioning than their cancer-free peers[6, 7]. Our study is the first, however, to show that physical functioning is lower in older breast cancer survivors than in other women when using standard objective physical performance tests that are shown to be more sensitive, specific and unbiased measures of physical functioning. In studies on non-cancer populations, performance measures have predicted future onset disability, nursing home admission and death [21] and recently, lower pre-diagnosis levels of objectively-measured physical function have been linked to faster progression to disability and increased mortality among persons later diagnosed with cancer[30]. Within our breast cancer sample, age, comorbidities, skeletal muscle index, symptom severity and fatigue together explained up to one-third of the variance in physical functioning scores. Age plus comorbidities and fatigue were consistently associated with objectively measured and patient-reported physical functioning, respectively.

Our observation that older breast cancer survivors perform worse than peers without cancer on standard objective functional tests substantiates the reports by survivors that they have more difficulty with daily activities than other women. In our sample, patient-reported physical function in breast cancer survivors was 10% lower than levels reported by controls, while scores on objective measures of function ranged from 10%−25% lower in survivors. Since most patient-report measures of physical functioning cannot easily quantify and distinguish the various physical components that contribute to daily function, including balance, mobility and strength, it is nearly impossible to evaluate which components of functioning may be most affected by cancer and subsequently which components are targets for intervention. In our study we used the chair stand test and grip strength tests to measure lower body and upper body muscle function, respectively, and the walk speed test to measure mobility and dynamic balance. Walk speed did not differ significantly between our cancer and control groups and times for both groups were faster than the walk speeds (<1.0 m/s) associated with an increased risk of future disability[31]. However, both muscle function tests were significantly lower in breast cancer survivors than in controls, suggesting that chemotherapy may have a persistent impact on the musculoskeletal system or possibly that women with breast cancer are predisposed to poorer musculoskeletal health at diagnosis. The times on the chair stand test in breast cancer survivors were 25% slower than in the controls and slower than the >10 second threshold that indicates increased fall risk[32]. Interestingly, however, we did not find muscle mass to be lower in breast cancer survivors, but rather muscle mass was greater when expressed as absolute lean mass or relative to body size. Thus, it may be that cancer treatments affect both muscle quality and neuromuscular contributions to strength development more so than muscle quantity. The impact of chemotherapy on lean mass in postmenopausal breast cancer survivors is unclear and studies have reported decreases, increases or no change across treatment[33]. Further, while sarcopenia is related to muscle weakness and contributes to poor functioning in older adults, the relationship between muscle strength and mass is not linear[34]. Neuromuscular contributions (e.g., large alpha motor neuron innervation and/or muscle fiber recruitment patterns) explain up to 50% of variation in muscle strength in older adults. Several studies assessing neuromuscular fatigue have suggested that central deficits (proximal to the neuromuscular junction) may contribute to the decreased exercise capacity/function in cancer survivors[35, 36]. Within this study, self-reported fatigue was significantly associated with self-reported physical function, and thus may contribute to low physical function despite breast cancer survivors having greater lean mass. Further characterizing the specific functional impairments, particularly as they occur across treatment and into recovery, in older breast cancer survivors is worth continued study so that targeted interventions for older survivors can be appropriately designed.

Our regression analyses limited to breast cancer survivors revealed that both older age and more comorbid conditions were consistently associated with worse physical function across multiple objective tests, while more fatigue consistently associated with worse function across both self-report instruments. While no other study has explicitly evaluated variables associated with objectively measured physical function in older breast cancer survivors, both age and comorbidities are linked to lower scores on these standardized performance tests in larger cohorts of otherwise healthy older adults [37, 38]. In a longitudinal study of breast cancer survivors followed for one year past diagnosis, women over the age of 70 reported functional declines while women aged 60–70 years of age reported no change, suggesting an intersection between aging and cancer that puts much older women at greater risk of developing functional limitations after cancer[39]. Cancer treatment, and specifically chemotherapy, increases the risk for other comorbid conditions such as heart failure[40], and is also associated with significant weight gain that can contribute to or worsen obesity-related diseases such as diabetes, CVD and other cancers[41]. However, it is also possible that women in our sample had more comorbid conditions at the time of their breast cancer diagnosis. Since comorbidities predicted poorer performance across all objective measures, but only one of the two self-report instruments, health status may be an early indicator of impending limitations in daily functioning and thus a signal for early intervention. Women with higher levels of fatigue reported more problems with physical functioning than women with less fatigue, which is consistent with other reports [28, 29]. Interestingly though, fatigue was not significantly associated with any objective measure of function. Thus, it is possible that fatigue influences a woman's perception of her functional abilities, but not necessarily her actual physical ability to perform functional tasks. In breast cancer survivors, fatigue may be influenced by psychological factors such as depression, low self-efficacy and poor body image[42, 43]. Though we did not measure psychosocial variables in our study, the dissociation between fatigue and objectively, but not subjectively, assessed physical functioning among our cohort suggests that fatigued survivors may benefit from cognitively-based interventions in addition to physical interventions aimed at improving overall function.

While our study has several strengths, it also has limitations. Our study was cross -sectional and thus we cannot establish a cause and effect relationship between the independent variables in our regression models and measures of physical function. Reverse causation is possible, where functional limitations could contribute to inactivity, weight gain, and fatigue. However, prospective studies have shown that age, comorbidities, and breast cancer treatment results in unfavorable health behaviors and considerable and persistent fatigue. Our sample could be biased because it is likely that we recruited a sample of women who were motivated and functional enough to be eligible and to consent to participate in supervised, facility-based exercise trials, but who were not active enough to be excluded from the trials. Thus, it remains possible that we may be under-reporting the functional limitations had we assessed a broader population of older women with breast cancer. Further, our sample was mostly Caucasian, had a broad range of time since diagnosis, and was on the younger end of the older adult age range thus our findings may not generalize to women who do not fit these characteristics.

Findings from our study indicate that older breast cancer survivors feel that they have more difficulties with daily functioning than their peers without cancer and when objective assessments of function are applied the discrepancies between survivors and controls may be even greater. Age and comorbidities were the variables mostly strongly associated with physical functioning, suggesting that intervening when women are younger and healthier could prevent future functional decline. Our findings also suggest that interventions should be offered to much older women regardless of their level of comorbidities because they could stand to benefit the most. Objective tests that are easy to administer, like the timed chair stand test could be used to further screen women for weakness well before they start experiencing limitations in their daily function that would be picked up on using patient-reported measures. However, in the busy oncology setting where this additional screening may not be feasible, a patient's age, comorbidities and self-reported function could identify women at highest need for intervention. Interventions could include those that reduce demand during activities, such as decreasing the frequency of activities, using assistive devices, or getting daily help, but these add health care costs and do little to interrupt the trajectory toward disability. Rather, interventions to increase physical capacity such as symptom control or physical activity may utilize less resources and even reverse the course of decline. The objective measures used in our study seem to indicate that weakness, more than limited mobility, may underlie these functional limitations and that interventions to build muscle strength may most effectively improve physical functioning. Despite the consistent findings of worse functional status in older breast cancer survivors and the consistent application of exercise as a countermeasure to functional declines in otherwise healthy older adults, the number of exercise trials aimed to improve functioning in older breast cancer survivors is staggeringly low[44]. In the single report of exercise benefits on physical functioning specific to older cancer survivors, the RENEW trial reported that a home-based program of physical activity, including resistance exercise, and dietary modification improved self-reported physical functioning in older breast, prostate and colon cancer survivors[45]. Other studies in middle age adult cancer survivors suggest that structured training programs including resistance exercise can increase muscle strength and physical functioning[44]. Our findings suggest that an exercise trial in older breast cancer survivors that targets the underlying determinants of functional limitations, e.g., muscle weakness, and that considers additional behavioral strategies to improve a woman's perceptions of her functional abilities is warranted.

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Table 1.

Characteristics of Breast Cancer Survivors and Cancer-Free Controls. Data are presented as mean (SD) for continuous data or % for categorical data*.

General Characteristics	Breast Cancer Survivors (n=84)	Cancer-Free Control (n=40)	p-value**
Age (years)	67.9 (4.4)	69.0 (5.3)	0.20
BMI (kg/m^2)	29.0 (5.8)	26.4 (4.8)	0.01
Comorbidity Index	1.8 (1.7)	0.8 (0.9)	<0.001
Race			0.37
Caucasian (%)	95	100	
Marital Status			0.88
Married/Partnered	56	55	
Divorced/Separated	23	20	
Widowed	14	15	
Single	6	10	
Education			0.10
High school graduate/GED	32	20	
Associate/Technical Degree	13	7	
Bachelor's Degree	30	33	
Advanced Degree	19	40	
Other	5	0	
Employment			0.37
Retired	69	75	
Currently Employed	19	25	
Homemaker	5	0	
Unemployed	6	0	
Cancer Specific Characteristics	**Cancer (n=84)**		
Time Since Diagnosis (mos.)	84.3 (45.4)		
Cancer Stage			
I	24		
II	60		
III	13		
Treatment History			
Surgery	100		
Radiation	79		
Chemotherapy	100		
Anti-hormone therapy	76		
Average Symptom Severity	2.7 (2.9)		
Fatigue	9.9 (4.0)		

*Categorical data may not sum to 100% due to missing data.

**Comparisons used t-tests for continuous data and chi-square test for categorical data.

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Table 2.

Comparison of Patient-Reported Physical Function, Objective Physical Function and Body Composition Between Breast Cancer Survivors and Cancer-Free Controls.

Variable	Breast Cancer Survivors (n=84)	Cancer-Free Control (n=40)	p-value
Patient-Reported Physical Function			
LLFDI Overall Physical Function	68.2 (10.5)	75.0 (8.9)	0.001
SF-36 Physical Function	47.3 (9.1)	52.9 (4.0)	<0.001
Objective Physical Function			
Chair Time (s)	12.6 (3.7)	10.1 (1.4)	<0.001
Hand Grip Strength (kg)	22.3 (5.0)	24.3 (4.4)	0.034
Usual Walk Speed (m/s)	1.1 (0.2)	1.1 (0.1)	0.747
Physical Performance Battery	10.7 (0.1)	11.7 (0.5)	<0.001
Body Composition			
Body Fat (%)	40.5 (6.2)	39.3 (6.5)	0.308
Lean Mass (kg)	43.5 (6.6)	40.6 (6.3)	0.019
Fat Mass (kg)	30.7 (9.8)	27.3 (9.8)	0.077
Skeletal Muscle Index (kg/m^2)	6.8 (0.95)	6.3 (0.8)	0.013
Body Mass Index (kg/m^2)	29.0 (5.8)	26.4 (4.8)	0.009

LLFDI: Late Life Function and Disability Instrument

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Table 3.

Standardized Beta-Coefficients, 95% Confidence Intervals, and Unadjusted R^2 from Linear Regression Model in Breast Cancer Survivors. Significant beta-coefficients in **bold**.

	Physical Performance Battery	Hand Grip Strength (kg)	Chair Time (s)	LLFDI Overall Physical Function	SF-36 Physical Function
Age (years)	**−0.29**	−0.32	**0.22**	−0.07	−0.18
	(−0.17, −0.02)	(−0.59, −0.13)	(0.01, 0.38)	(−1.04, 0.49)	(−0.83, 0.10)
Comorbidity	**−0.23**	**−0.21**	**0.29**	**−0.29**	−0.12
Index	(−0.40, −0.01)	(−1.24, −0.03)	(0.20, 1.20)	(−4.95, −0.84)	(−1.89, 0.54)
Skeletal Muscle	−0.05	**0.42**	0.2	−0.01	**−0.24**
Index (kg/m^2)	(−0.41, 0.26)	(1.09, 3.12)	(−0.03, 1.64)	(−3.70, 3.37)	(−4.32, −0.20)
Symptom	−0.15	**−0.3**	0.14	−0.08	−0.06
Severity	(−1.06, 0.25)	(−4.73, −0.74)	(−0.67, 2.62)	(−9.15, 4.27)	(−4.99, 3.01)
Fatigue	−0.09	−0.02	0.19	**−0.46**	**−0.26**
	(−0.12, 0.06)	(−0.30, 0.25)	(−0.04, 0.22)	(−2.81, −0.97)	(−1.14, −0.04)
R^2	0.17	0.33	0.27	0.33	0.20