A PROSPECTIVE EXAMINATION OF CHANGE IN EXECUTIVE FUNCTION AND PHYSICAL ACTIVITY IN OLDER BREAST CANCER SURVIVORS

by

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For the people with cancer who received treatment on phase one pharmaceutical clinical trials at Huntsman Cancer Hospital. Thank you for talking with me about your experiences. You inspired me to seek graduate training in psycho-oncology and research in cancer symptom management.

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ABSTRACT

Only one third of older breast cancer survivors (BCS) meet national physical activity (PA) guidelines. Theories of self-regulation and research with older adults suggest that executive function (EF) plays an important role in PA, yet the impact of lower EF on older survivors' PA is unknown. My project addressed this gap using secondary data from the Thinking and Living with Cancer (TLC) cohort study, which examined cognitive function among older BCS pre-treatment, followed every 12 months, and contemporaneously assessed matched controls. My first aim was to test two hypotheses regarding EF change and PA and determine if these relationships differ between BCS and controls. My hypotheses were: 1) EF decline from baseline to 12 months will predict lower PA at 24 months, and 2) lower PA at 12 months will predict EF decline from 12 to 24 months. My second aim was to explore whether the effects of EF change on PA in BCS differed based on risk factors for accelerated cognitive decline (i.e., older age, more advanced cancer stage, comorbidity, and *APOE* ε4 genotype). The TLC study measured EF with neuropsychological tests and PA with the International Physical Activity Questionnaire-Short Form. For aims 1 and 2, I used multiple regression with multiple imputation. Primary results showed no significant effect of EF change from baseline to 12 months on PA at 24 months (β=-0.01, p=0.88) and no significant group (BCS vs. controls) by EF interaction (β=-0.05, p=0.33). Separate models in BCS and controls showed similar findings. In the entire sample, PA at 12 months significantly predicted EF change from 12 to 24 months (β=0.17, p=0.01), but there was no significant group by PA interaction (β=-0.06, p=0.54). Separate analyses by group found a significant effect of PA for controls (β=0.07, p=0.02), but not for BCS (β=0.05, p=0.27). Regarding the second aim, there were no significant interactions between EF change and the proposed risk factors on PA. Findings were largely inconsistent with theory and prior research. Continued research in this area will inform future exercise interventions to improve physical and cognitive health for the growing population of older cancer survivors.

CHAPTER 1. INTRODUCTION

In the United States, female breast cancer survivors (BCS) aged 65 and older are among the largest groups of older cancer survivors, comprising an estimated 2.5 million women (American Cancer Society, 2019). Due to advances in cancer treatment, 90% of BCS are living 5 or more years after diagnosis (Howlader et al., 2019). Although BCS' increased longevity is encouraging, older cancer survivors are faced with increased risk of secondary malignancies, obesity, cardiovascular disease, diabetes, and accelerated functional decline (Bradshaw et al., 2016; Cespedes Feliciano et al., 2017; Deimling, Arendt, Kypriotakis, & Bowman, 2009). Furthermore, many BCS' quality of life and daily activities are substantially affected by persistent symptoms such as fatigue, pain, distress, and cognitive symptoms (Debess, Riis, Engebjerg, & Ewertz, 2010; Extermann et al., 2017; Janelsins et al., 2016).

Longitudinal descriptive studies and intervention research have linked physical activity to reduced risk of secondary cancers, cardiovascular disease, and other chronic diseases as well as improved functional status in cancer survivors (Blair et al., 2014; Brown, Winters-Stone, Lee, & Schmitz, 2012; de Boer, Worner, Verlaan, & van Leeuwen, 2017; Jones et al., 2016). Additionally, randomized clinical trials have shown that physical activity can improve symptoms, mental health, and cognitive function in cancer survivors (Cormie, Nowak, Chambers, Galvao, & Newton, 2015; Daum, Cochrane, Fitzgerald, Johnson, & Buford, 2016; Schmitz et al., 2010; Sedjo et al., 2016). Proposed physiological mechanisms for the effect of physical activity on survivors' cognitive function include reduced systemic inflammation and greater neurogenesis facilitated by increased expression of neurotrophic and neuroprotective proteins (e.g., brain-derived neurotrophic factor, vascular endothelial growth factor, and insulin like growth factor) (Zimmer et al., 2016). Despite the significant cognitive and health benefits of physical activity, only 33% of older cancer survivors meet national guidelines of 150 minutes of moderate or 75 minutes of vigorous intensity physical activity per week (Tarasenko, Chen, & Schoenberg, 2017), and 44% are sedentary (i.e., report no leisure time physical activity) (National Cancer Institute, 2019). Although older cancer survivors and older adults in general show comparable levels of non-adherence to physical activity guidelines (National Cancer Institute, 2019; Tarasenko et al., 2017), older cancer survivors are understudied in physical

activity research; thus, predictors of their physical activity initiation and maintenance are largely unknown.

Background

Low adherence to physical activity among older cancer survivors might be explained in part by difficulties with the executive domain of cognitive functioning. Whereas physical activity shows promise for improving cognitive functioning in cancer survivors (Furmaniak, Menig, & Markes, 2016; Mustian, Sprod, Janelsins, Peppone, & Mohile, 2012), the effect of executive functioning on subsequent physical activity has not been examined in older cancer survivors. However, in the general population of older adults, executive function and physical activity appear to have a bidirectional relationship (Best, Nagamatsu, & Liu-Ambrose, 2014; Daly, McMinn, & Allan, 2015). In fact, one study of older adults found that over a six-year period, executive function predicted physical activity with 55% greater magnitude than the effect of physical activity on subsequent executive function (Daly et al., 2015). Comparable or stronger relationships between executive function and subsequent physical activity may be expected in older BCS due to proposed accelerated aging effects of cancer and its treatment (Demark-Wahnefried, Morey, Sloane, Snyder, & Cohen, 2009; Mandelblatt et al., 2014).

A detrimental effect of lower executive functioning on older BCS' physical activity is consistent with Self-Regulation Theories (Bandura, 2004, 2005; Hall & Fong, 2007, 2015). These theories posit that executive functioning is an important contributor to self-regulatory appraisals (e.g., self-efficacy, intentions) and behaviors (e.g., goal setting, planning) that facilitate health behaviors such as physical activity (Bandura, 2004; Hall & Fong, 2015). Indeed, reduced executive functioning and global cognitive functioning have been associated with lower levels of physical activity, poor self-efficacy for physical activity, and functional decline among community-dwelling older adults (Best, Davis, & Liu-Ambrose, 2015; Gothe et al., 2014; Kim, 2016; McAuley et al., 2011; McHugh & Lawlor, 2015; Rajan, Hebert, Scherr, Mendes de Leon, & Evans, 2015). In older cancer survivors, self-regulation-based constructs (e.g., self-efficacy, intentions, planning) also appear to be associated with physical activity (Courneya et al., 2009; Craike, Gaskin, Mohebbi, Courneya, & Livingston, 2018; Karvinen et al., 2009; Morey et al., 2015; Ottenbacher et al., 2011; Trinh, Plotnikoff, Rhodes, North, & Courneya, 2012; Ungar, Sieverding, Ulrich, & Wiskemann, 2015); however, research with older cancer survivors has not

yet examined relationships between executive function, self-regulatory appraisals and behaviors, and physical activity.

The impact of executive functioning on physical activity among older BCS may be similar to what has been found in the general population of older adults, or it may differ due to BCS' unique challenges. Cancer and its treatment appear to affect several cognitive domains, including executive function (Janelsins, Kesler, Ahles, & Morrow, 2014; Krolak, Collins, Weiss, Harris, & Van der Jagt, 2017), and lead to changes in the structure and function of frontal brain regions (i.e., areas associated with executive function) (Amidi et al., 2017; Chen et al., 2017; Deprez, Billiet, Sunaert, & Leemans, 2013; Kesler, Watson, & Blayney, 2015; McDonald & Saykin, 2013). Additionally, cancer survivors are often faced with symptoms, side effects, and distress that have been associated with lower physical activity (Blair et al., 2014; Brown et al., 2014; Courneya et al., 2009; Dunberger et al., 2013; Giacalone et al., 2013; Grov, Fossa, & Dahl, 2011; Mosher et al., 2009; Sprod et al., 2012). Theory suggests that executive function is needed for flexible thinking and problem solving to address such barriers to physical activity (Hofmann, Schmeichel, & Baddeley, 2012). Therefore, older BCS may have an even greater need for executive functioning skills in order to overcome barriers to physical activity associated with cancer and its treatment.

The impact of executive functioning on physical activity may be particularly relevant for older cancer survivors, as older age is associated with lower global cognitive functioning among survivors (Janelsins et al., 2018; Jansen, Cooper, Dodd, & Miaskowski, 2011; Ono et al., 2015). Additionally, several biological factors may place certain older BCS at greater risk for cancer-related cognitive impairment and lead to a greater impact of executive functioning on physical activity. Having a more advanced cancer stage and greater than two comorbid medical conditions have been related to lower cognitive performance even prior to systemic cancer treatment (Ahles et al., 2008; Mandelblatt et al., 2014). Additionally, emerging longitudinal evidence also suggests that BCS with one or more Apolipoprotein E (*APOE*) ε4 alleles (i.e., a genotype related to neurodegeneration) (Jagust, 2013) are more likely to show lowered cognitive performance after chemotherapy than BCS without an *APOE* ε4 allele (Ahles et al., 2003; Koleck et al., 2014; Mandelblatt et al., 2018).

These risk factors for accelerated cognitive decline may also be related to physical activity. Indeed, older age and comorbidity are independently associated with lower physical

activity among cancer survivors (Lynch et al., 2016; Mora & Valencia, 2018). These risk factors and advanced cancer stage may also relate to greater barriers to physical activity and fewer facilitators. For example, social support is an important facilitator of physical activity among older adults (Lindsay Smith, Banting, Eime, O'Sullivan, & van Uffelen, 2017; Thornton et al., 2017), and the risk for social isolation increases with older age (Iliffe et al., 2007). Additionally, more advanced stage disease and greater medical comorbidity contribute to more severe somatic and psychological symptoms (e.g., fatigue, depression) (Hallet et al., 2019; Lie et al., 2015), which are barriers to physical activity among older cancer survivors (Hardcastle et al., 2018; Ottenbacher et al., 2011). Although rates of sedentary lifestyles are similar among older adults regardless of *APOE* genotype (Fenesi et al., 2017; Tan et al., 2017), carrying at least one *APOE* ε4 allele appears to increase risk for cognitive decline (Ahles et al., 2003; Koleck et al., 2014; Mandelblatt et al., 2018). Compensating for reduced facilitators and increased barriers to physical activity would theoretically require greater executive functioning skills (Hofmann et al., 2012), and these skills could be lacking in those with risk factors for cognitive decline. Therefore, age, cancer stage, comorbidity, and *APOE* genotype should be explored as potential moderators of the relationship between executive function and physical activity among older BCS.

The Present Study

The present study uses data from the Thinking and Living with Cancer (TLC) cohort study (R01CA129769, PI: Jeanne Mandelblatt), which is a prospective, multi-site study of older (i.e., aged 60 years and older) BCS and controls who are frequency matched for age, education, race, and geographic locale. The TLC study is the only large prospective examination of objective cognitive function in older BCS assessed before systemic cancer therapy (pre-treatment baseline) and 12 and 24 months later as well as contemporaneously assessed controls. To address gaps in the current understanding of the relationship between executive function and physical activity in older BCS, the present study addresses two specific aims:

Aim 1: To test two hypotheses regarding the association between executive function change and physical activity and determine if these relationships differ between BCS and controls.

Hypothesis 1: Executive function decline from baseline to 12 months will predict lower physical activity at 24 months.

This hypothesis is illustrated in Figure 1 and is based on Self-Regulation Theory (Bandura, 1991, 2004; Hall & Fong, 2007, 2015) and evidence from studies of older adults showing that better executive function predicts greater physical activity with moderate effect sizes (Best et al., 2014; Hall, Zehr, Paulitzki, & Rhodes, 2014; McAuley et al., 2011; Olson et al., 2017).

Hypothesis 2: Lower physical activity at 12 months will predict executive function decline from 12 to 24 months.

This hypothesis is also illustrated in Figure 1 and is based on strong evidence that physical activity can improve executive function in older adults (Albinet, Abou-Dest, Andre, & Audiffren, 2016; Anderson-Hanley, Arciero, Westen, Nimon, & Zimmerman, 2012; Baker et al., 2010; Merom et al., 2016) and emerging evidence of this relationship in cancer survivors (Chan, McCarthy, Devenish, Sullivan, & Chan, 2015; Cormie et al., 2015; Furmaniak et al., 2016; Mustian et al., 2012). Testing this hypothesis in older BCS builds the evidence base for the potential utility of physical activity to address executive difficulties associated with cancer and aging.

Aim 2: To explore whether the effects of executive function change on physical activity in BCS differ based on selected risk factors for accelerated cognitive decline (i.e., older age, more advanced cancer stage, comorbidity, and *APOE* ε4 genotype).

This exploratory aim is based on evidence that these risk factors may affect cancer survivors' cognitive function. These risk factors are: older age, more advanced cancer stage (i.e., invasive disease), at least two comorbid medical conditions, and at least one *APOE* ε4 allele (Ahles et al., 2008; Ahles et al., 2003; Janelsins et al., 2018; Jansen et al., 2011; Koleck et al., 2014; Mandelblatt et al., 2014; Ono et al., 2015). Not only may these risk factors affect executive function, but they may be associated with increased barriers to physical activity, resulting in greater need for executive function in order to problem solve. This may result in a stronger effect of executive function on physical activity among BCS with these risk factors. Conversely, executive function and physical activity may have greater range restriction among BCS with these risk factors. This range restriction could decrease the strength of the relationship between executive function and physical activity. Because the TLC study is the largest

prospective study of older BCS' objective cognitive function to also examine these risk factors for accelerated cognitive decline, it presents a unique opportunity to explore their impact on the relationship between executive function and physical activity. If exploratory tests show that older BCS with proposed risk factors experience stronger effects of executive function on physical activity, then findings would inform future targeted physical activity interventions.

CHAPTER 2. METHOD

This project examined data from the TLC study, a multi-site prospective longitudinal study of BCS aged 60 and older and matched healthy controls (R01CA129769). Although recruitment and follow-up are ongoing for the TLC study, the current project used baseline and 12- and 24-month post-baseline follow-up data from participants recruited between August 2010 and December 2015. Accrual sites included four academic and nine community practices in four regions of the U.S.: Los Angeles (City of Hope National Medical Center), New York area (Memorial Sloan-Kettering Cancer Center and community affiliates in New Jersey and Long Island), Tampa (Moffitt Cancer Center), and Washington, D.C. (Georgetown Lombardi Comprehensive Cancer Center and community sites in D.C., Maryland, Virginia, and New Jersey). Indianapolis (Indiana University) was added as an accrual site after December 2015. The study protocol was approved by all institutional review boards and met HIPAA standards.

Participants

Eligible BCS were female, aged 60 years and older, English speaking, and within 4-10 weeks post-diagnosis of primary non-metastatic breast cancer (American Joint Committee on Cancer stages 0-III). BCS were ineligible if they had ever had a stroke, moderate or severe traumatic brain injury, major psychiatric or neurodegenerative disorder, or within the last five years had another cancer diagnosis or systemic cancer treatment. BCS were excluded at follow-up if they experienced breast cancer recurrence or developed a new cancer or condition that rendered them ineligible (e.g., stroke). Non-cancer controls were eligible if they met the same criteria as the BCS with the exception of a breast cancer diagnosis, and they were ineligible at follow-up for the same reasons as the BCS. Controls were matched to BCS on age (within five years), race/ethnicity, education (<high school, high school to <college, college+), and geographic locale. All participants received a $50 gift card per assessment.

Procedure

The procedures for the TLC study have been published (Mandelblatt et al., 2018). Recruitment, informed consent, screening, and data collection are described briefly.

BCS were recruited from medical oncology clinics at participating sites and enrolled after diagnosis and prior to systemic hormonal therapy or chemotherapy. Controls consisted of friends of the BCS and community-recruited older adults. Community recruitment involved outreach to senior centers and retirement communities, newsprint, and other media. Of controls, 24% were friends and 76% were community-recruited, and these groups showed comparable demographics. Among the eligible BCS and controls, 36.2% of survivors and 97.6% of controls consented to participate (Figure 2). Consent rates for BCS were 17.2% to 72.7% across study sites (median 62.5%), and the lowest consent rate occurred at a large urban cancer center with many competing research projects.

Participants provided written informed consent for each study component and were asked to provide a research proxy consent. Those who declined to provide a research proxy consent were still able to participate. After informed consent, participants were screened in-person or over the telephone using the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Wide Range Achievement Test, 4th edition (WRAT-4), a measure of word reading and a proxy for literacy and cognitive reserve (Manly, Schupf, Tang, & Stern, 2005). Those who scored ≤24 on the MMSE or <3rd grade level on the WRAT-4 were excluded, as this indicated that they may not have the ability to complete the study. Participants were also ineligible if their performance on baseline cognitive tests were >3 standard deviations below normative values.

Baseline assessments for BCS were completed before systemic cancer therapy and after surgery, with the exception of seven BCS treated with neoadjuvant therapy who completed baseline prior to surgery and systemic cancer therapy. Neuropsychological testing (approximately 55 minutes, completed in-person) and self-report measures (approximately 30-40 minutes, completed either in-person, over the telephone, or via mail) were administered at baseline and yearly follow-up assessments. Assessments were performed by trained research staff who completed certification for neuropsychological test administration every two years. Medical records were reviewed for BCS' clinical data (e.g., diagnosis date, chemotherapy, hormonal therapy) at baseline and annually to determine eligibility for follow-up assessments (e.g., recurrence). Blood specimens were collected from participants at baseline and processed and stored at -120°C. Biospecimens were batch tested for Apolipoprotein E (*APOE*) genotype using TaqMan assays (rs429358 assay identifier: C_3084793-20; rs7412 assay identifier:

C_906973_10; Life Technologies, Carlsbad, CA) on a 7900HT Fast Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA). TaqMan Genotyper Software version 1.3 (Thermo Fisher Scientific) was used to complete group-blinded analyses. Routine standards at the study biobank provided quality assurance for genetic testing.

Measures

Executive function

The executive function domain was measured by computing the mean of six tests of cognitive abilities associated with executive function. 1) The Neuropsychological Assessment Battery (NAB) Digits Forward and 2) Digits Backward tested auditory attention and working memory (Stern & White, 2003). Each of these tests included seven items, with two trials per item, in which the examinee repeated a series of digits forward or in reverse order with spans of 3 to 9 digits. 3) The Trail Making Test Part A (TMT-A) and 4) Part B (TMT-B) from the Halstead-Reitan Neuropsychological Battery measured psychomotor speed, visual attention, and task switching (Reitan & Wolfson, 1985). The examinee quickly connected numbers in order for TMT-A and alternated between numbers and letters in order for TMT-B. 5) The Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Test-III measured psychomotor speed, visual attention, and incidental learning and was also sensitive to general impairment (Lezak, Howieson, & Loring, 2004; Wechsler, 1997). The examinee quickly associated symbols to numbers based on the corresponding number to symbol code. 6) The Controlled Oral Word Association Test (COWA) measured semantic knowledge, verbal fluency, and cognitive flexibility (Ruff, Light, Parker, & Levin, 1996). This test included three, one-minute trials in which the examinee quickly generated words for each of the three letter cues.

The study team performed a factor analysis to confirm that the factor structure of this cognitive domain at baseline demonstrated substantial agreement (domain Cronbach's α=.74) (Clapp et al., 2018). Neuropsychological tests used to assess executive function in this study have established reliability and validity in diverse older adult populations and have been recommended by the International Cognition and Cancer Task Force (Wefel, Vardy, Ahles, & Schagen, 2011) or the National Alzheimer's Coordinating Center's Unified Data Set (Weintraub

et al., 2009). Practice effects with multiple assessments were minimized by using alternate forms of the NAB (Stern & White, 2003).

Physical activity

Physical activity volume was measured with the 6-item International Physical Activity Questionnaire-Short Form (IPAQ-SF) that assessed vigorous and moderate activities and walking (i.e., light activity) during leisure and work over the past week (e.g., "During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?" and "How much time did you usually spend doing vigorous physical activities on one of those days?"). Days were multiplied by time (in minutes) and activities were weighted by Metabolic Equivalent of Tasks (MET) (vigorous=8, moderate=4, walking=3.3) to estimate the number of MET minutes per week (Craig et al., 2003). MET minutes may be examined in three ways: (1) continuously, (2) grouped into high, moderate, and low volume categories, and (3) dichotomized as below or above the weekly guideline of 600 MET minutes per week (Craig et al., 2003). IPAQ data have been found to moderately correlate with measures of physical fitness independent of Body Mass Index, which suggests that the IPAQ captures physiologically relevant activity (Minder et al., 2014). Baseline physical activity was not included in primary analyses, as the majority of BCS had recently undergone surgery (mean time from surgery to baseline assessment=54.5 days, SD=51.3 days), and their reported physical activity would not accurately represent their normal activity.

Age

Collected during the baseline interview, age was considered a continuous moderator in aim 2.

Cancer stage

Collected during medical record review, cancer stage was dichotomized (i.e., stage 0 to I disease and stage II to III disease) at a cut point found to be clinically significant in published baseline TLC study findings (Mandelblatt et al., 2014) and considered a moderator in aim 2.

Comorbidity

Medical comorbidities were assessed via participant self-report with a checklist of 25 medical conditions (Mandelblatt et al., 2014). Self-reported medical comorbidities have been found to be reliable and valid when compared to older adults' medical records (Colditz et al., 1986; Haapanen, Miilunpalo, Pasanen, Oja, & Vuori, 1997; Mandelblatt et al., 2001; Mandelblatt et al., 2010; Silliman & Lash, 1999). The number of medical comorbidities was dichotomized (i.e., 0 or 1 and 2+) at a cut point found to be clinically significant in prior research with cancer samples (Deimling, Sterns, Bowman, & Kahana, 2007; Hewitt, Rowland, & Yancik, 2003; Mandelblatt et al., 2014) and considered a moderator in aim 2.

APOE genotype

Participants with any *APOE* ε4 allele were considered positive for the *APOE* ε4 genotype, and this variable was considered a dichotomous (i.e., positive or negative) moderator in aim 2.

Covariates

Clinical (i.e., receipt of chemotherapy, number of days between surgery and the baseline assessment), demographic (i.e., age, education), and psychological factors (i.e., fatigue, depressive symptoms, anxiety) and baseline physical function were considered covariates. Covariates were determined a priori based on prior research indicating that these variables are associated with cognitive function and/or physical activity in older adults with and without breast cancer (Ahles et al., 2008; Blair et al., 2014; Demark-Wahnefried et al., 2009; Mandelblatt et al., 2014; Ono et al., 2015). Information regarding breast cancer and its treatment (e.g., diagnosis date, cancer stage, history of chemotherapy, hormonal therapy, radiation therapy, and dates of cancer treatments) was collected from medical records after enrollment by trained research staff at each study site. Demographic information was collected during the baseline interview. Baseline physical function was measured with the physical component score of the 12-item Short-Form Health survey (SF-12) (Ware Jr, Kosinski, & Keller, 1996). Psychological factors were assessed at baseline and during each follow-up. Fatigue was measured with the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (Cella, 1998), depressive symptoms

with the 20-item Center for Epidemiologic Studies-Depression Scale (Radloff, 1977), and anxiety with the 20-item State-Trait Anxiety Inventory (Spielberger, 1983). Each of these measures has demonstrated validity and reliability in cancer samples (Cella, Lai, Chang, Peterman, & Slavin, 2002; Hann, Winter, & Jacobsen, 1999; Schreier & Williams, 2004; Treanor & Donnelly, 2015).

Data Analysis

Frequencies, means, and standard deviations were computed in SPSS (IBM SPSS Statistics for Windows, Version 25.0; Armonk, NY, USA) to characterize all study variables. Prior to the main analyses, all continuous variables were examined for normality (i.e., skewness <3.0 and/or kurtosis <8.0) and outliers (Kline, 2011). The Log_e transformation was employed for continuous MET minutes due to excessive skewness. Preliminary data analyses also included paired-samples *t*-tests to compare BCS and healthy controls on demographics (i.e., age, education) and other covariates (i.e., depressive symptoms, anxiety, fatigue, physical function) in order to characterize the sample.

Missing data

Outcome data were coded for missingness (1=yes, 0=no) at 12- and 24-month follow-ups. Demographic and medical variables were used to predict missingness using logistic regression analysis. Data were assumed to be missing at random (MAR), defined as systematic variance in missingness that is explained by observed data patterns. Multiple imputation was employed prior to analytic models for aims 1 and 2 because this approach retains sample size by generating several plausible values for missing data based on a specified imputation model (Jakobsen, Gluud, Wetterslev, & Winkel, 2017; Rubin, 1996). Therefore, the analyses with the whole sample, BCS, and controls were completed in two steps: 1) regression was used in the imputation models to create several imputed datasets, and 2) analytic models were then employed on each imputed dataset and parameter estimates were pooled. Separate analytic models can be completed using data generated from an imputation model if all predictors in the analytic models are included in the imputation model along with auxiliary variables (Rubin, 1996). Demographic and medical variables significantly associated with missingness were

included in imputation models as auxiliary variables. Participants with missing data at all three time points for either executive function or physical activity were excluded, as imputation models would not include prior levels of these variables as predictors.

Separate imputation models were employed for the whole sample, BCS, and controls to include all predictors in analytic models for aims 1 and 2 (i.e., age, education, fatigue, depression, anxiety, physical function, physical activity, and executive function) along with identified auxiliary variables. The imputation model for the whole sample also included the group variable (BCS or control) and interactions of group with executive function and physical activity at 12 months. The imputation model for controls included the same predictors with the exception of group and interactions including group. The imputation model for BCS also included covariates specific to BCS and additional predictors in the aim 2 analytic models: the receipt of chemotherapy, days between surgery and the baseline assessment, cancer stage (0=stage 0-1, 1=stage 2-3), baseline comorbidity (0=0-1 comorbid conditions, 1=≥2 comorbid conditions), *APOE* genotype (0=ε4 negative, 1=ε4 positive), and interactions of executive function at 12 months with age, cancer stage, comorbidity, and *APOE* genotype. Arbitrary missing patterns and categorical variables were present in the whole sample, BCS, and controls; therefore, fully conditional specification imputation methods were employed in all imputation models with regression for continuous variables and logistic regression for binary and ordinal variables (van Buuren, 2007).

Variable computation

Executive function domain scores were the mean raw scores for the neuropsychological tests, and then z-scores were calculated based on the control mean and standard deviation at baseline. Residualized change scores were calculated on executive function domain z-scores to represent change in executive function, as this method accounts for variance predicted by prior executive function (Cronbach & Furby, 1970). Computation of residualized change scores was done by regressing executive function at 12 or 24 months on executive function at the prior time point (i.e., baseline or 12 months respectively) and then subtracting the predicted value from the observed value.

Physical activity volume was examined continuously by the Log_e of MET minutes per week in primary analyses, and sensitivity analyses included dichotomous (i.e., below or above

the guideline of 600 MET minutes per week) and categorical (i.e., high, moderate, and low intensity) self-reported physical activity. Categorical physical activity is determined according to the IPAQ scoring algorithm (International Physical Activity Questionnaire, 2005). Low activity volume is either no reported activity, or some activity that does not meet requirements for moderate or high intensity activity. Moderate activity volume is either 1) three or more days of vigorous activity of at least 20 minutes per day, 2) five or more days of moderate intensity activity and/or walking at least 30 minutes per day, or 3) five or more days of any combination of walking, moderate, or vigorous intensity activities meeting a minimum of 600 MET minutes per week. High activity volume is either 1) at least three days of vigorous intensity activity achieving at least 1500 MET minutes per week, or 2) seven of any combination of walking, moderate, or vigorous intensity activities achieving at least 3000 MET minutes per week.

To improve interpretation of intercept estimates, continuous variables without a meaningful zero point (i.e., all continuous variables except the residualized change in executive function) were mean-centered. Effect coding was used for the dichotomous group variable (BCS=1, control=-1) to reduce multicollinearity between the group predictor variable and the interaction between group and executive function/physical activity.

Aim 1

My primary aim was to test two hypotheses regarding the association between executive function change and physical activity and determine if these relationships differ between BCS and controls. Hypothesis 1 is that executive function decline from baseline to 12 months will predict lower physical activity at 24 months. Hypothesis 2 is that lower physical activity at 12 months will predict executive function decline from 12 to 24 months. These hypotheses were examined with two moderated multiple regression models with multiple imputation using SAS version 9.4 software (SAS Institute Inc., Cary NC). Models included covariates (i.e., age, education, fatigue, depression, anxiety, physical function). Group (i.e., BCS or control) was the moderator variable in both models to determine if the relationships differed between older BCS and non-cancer controls. The main effect of group was also assessed in both models. The final analytic sample size for the primary analyses using multiple imputation included 320 BCS and 323 controls. A sensitivity power analysis in G*Power showed that with a two-tailed α=0.01 and N=643, there was 80% power to detect small main effects (f^2=0.03) and moderate interaction

effects (f^2=0.17) using multiple regression (Cohen, 1988). Prior research with older adults has shown moderate effect sizes (βs=0.34 to 0.42) for the positive relationship between cognitive function and physical activity (Atkinson et al., 2010; Best et al., 2015; Daly et al., 2015).

Each hypothesis was also tested in BCS and controls separately with multiple regression using multiple imputation in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Covariates for controls were the same as those included in the moderated models. Covariates for BCS also included receipt of chemotherapy (0=hormone therapy only, 1=received chemotherapy and hormone therapy) and time between surgery and the baseline assessment in days. Continuous physical activity was used for these models, and exploratory models included dichotomous and categorical physical activity. Logistic regression was employed for analytic models predicting dichotomous physical activity, and proportional odds cumulative logit was employed to predict categorical physical activity.

Structural Equation Modeling (SEM) was also used as an omnibus test of the relationships between physical activity and executive function over time in grouped auto-regressive cross-lagged (ARCL) models using full-information maximum likelihood estimation to account for missing data. BCS or control was the grouping variable. This approach deviates from the primary hypotheses, as it includes baseline physical activity. Including baseline physical activity in the ARCL models allows for estimation of the covariance between baseline executive function and physical activity. Without estimating and controlling for this covariance, the remaining parameter estimates may be inflated (Selig & Little, 2012). Model fit was assessed holistically by a combination of the χ^2 test, root mean square error of approximation (RMSEA $\leq$ 0.05 is good fit, $\leq$ 0.10 is adequate fit), comparative fit index (CFI $\geq$ 0.95 is acceptable fit), and Tucker Lewis index (TLI $\geq$ 0.95 is acceptable fit) (Byrne, 2012; Kline, 2011). Modification indices were considered when model fit was less than adequate. When models were modified, the χ^2 difference test (χ^2(unmodified model) - χ^2(modified model), *df*(unmodified model) - *df*(modified model)) was used to determine if the modified model fit was significantly improved relative to the unmodified model fit. Then the standardized parameter estimates were examined to identify any statistically significant relationships between executive function and physical activity at baseline and 12- and 24-month follow-up. ARCL models were examined with and without covariates (i.e., age, education, and baseline fatigue, depression, anxiety, and physical function).

Aim 2

My secondary aim was to explore whether the effects of executive function change on physical activity in BCS differed based on selected risk factors for accelerated cognitive decline (i.e., older age, more advanced cancer stage, comorbidity, *APOE* ε4). Each risk factor (i.e., age, cancer stage, comorbidity, and *APOE* genotype) was examined as a moderator in BCS using separate moderated multiple regressions. Physical activity was measured continuously by the Log_e of MET minutes per week. Multiple imputation was employed to address missing data and covariates were included in regression models. The Benjamini-Hochberg procedure was planned to reduce type I error due to the number of comparisons (B-H critical value=(i/m)Q=(rank of p-value/4)0.05) (Benjamini & Hochberg, 1995). There was not sufficient power to conduct definitive tests of moderation by risk factors among BCS; however, results can be used to plan for sufficient power in subsequent research.

CHAPTER 3. RESULTS

Preliminary Analyses

Demographics

On average, participants were 68 years old, college educated, and had high average estimated cognitive reserve (Table 1). Most were White non-Hispanic and did not have an *APOE* ε4 allele. Chi-square and t-tests showed no significant differences between BCS and controls on age, years of education, cognitive reserve, race, ethnicity, or *APOE* genotype. Regarding clinical characteristics of BCS (Table 2), most had early stage disease (i.e., DCIS, Stage 1), received hormone therapy without chemotherapy, and had a mastectomy. On average, BCS completed the baseline assessment approximately 2 months after surgery.

Normality and outliers

Descriptive statistics for main variables (i.e., executive function, physical activity, and covariates) were computed for BCS and controls (Table 3). Continuous variables were examined for normality and outliers. For BCS, days from surgery to baseline, depressive symptoms at 12 months, and physical activity at 24 months (i.e., MET minutes per week) showed excessive kurtosis (i.e., >8.0). Physical activity at 24 months also showed excessive skewness (i.e., >3.0) for BCS. For controls, physical activity at 12 and 24 months showed excessive kurtosis. All other variables showed adequate normality for BCS and controls. One participant, a BCS, had extreme negative executive function scores at each time point (i.e., z<-3.5). After excluding this participant, descriptive statistics and group comparisons on demographic information did not markedly change.

Group comparisons

Main study variables were compared between BCS and controls using t-tests and chi-square tests. T-tests showed that compared to controls, BCS had poorer executive function scores ($t(613.90)=2.36$, $p<0.05$, M(D)=0.13, SE(D)=0.05) and reported less physical activity in $Log_{(e)}$MET minutes per week at baseline ($t(590)=4.44$, $p<0.001$, M(D)=0.41, SE(D)=0.09).

However, there were no significant differences in executive function scores or physical activity at 12 or 24 months (p>0.05). Similarly, when examining categories of physical activity, BCS were more likely to report lower levels of activity at baseline (MET categorical score: $\chi^2(2)=22.23$, p<0.001; MET dichotomous score: $\chi^2(1)=19.67$, p<0.001), but this difference was no longer significant at 12 or 24 months (p>0.05). BCS also reported greater baseline depressive symptoms ($t(526.98)=-4.39$, p<0.001, M(D)=-2.43, SE(M)=0.55) and anxiety ($t(533.37)=-4.63$, p<0.001, M(D)=-2.68, SE(D)=0.58), but these differences were no longer significant at 12 or 24 months (p>0.05). Additionally, BCS reported greater fatigue than controls at baseline ($t(538.80)=5.30$, p<0.001, M(D)=3.12, SE(D)=0.59) and 12 months ($t(424.38)=3.34$, p<0.001, M(D)=2.07, SE(D)=0.62), but this difference was no longer significant at 24 months (p>0.05). There were no significant differences between BCS and controls in physical function at any time point (p>0.05). BCS and controls were not significantly different with respect to comorbidities at baseline, 12 months, or 24 months (p>0.05). These comparisons did not markedly change after excluding the BCS outlier.

Missingness

Participants who at least partially completed 12- and 24-month follow-up assessments (i.e., completers) were compared to those who refused or were lost to follow-up (i.e., non-completers). In controls, t-tests showed that 12-month non-completers had fewer years of education ($t(318)=-2.99$, p<0.01, M(D)=-1.27, SE(D)=0.42) and lower cognitive reserve ($t(318)=-2.14$, p<0.05, M(D)=-6.53, SE(D)=3.04) than completers, and 24-month non-completers had fewer years of education than completers ($t(100.61)=-2.280$, p<0.05). The remaining t-tests for BCS and controls showed no significant differences between completers and non-completers on other demographics, main study variables, or covariates (p>0.05). Chi-square tests showed that for BCS and controls, 12- and 24-month completers and non-completers did not differ on race, ethnicity, *APOE* genotype, baseline medical comorbidities, or physical activity (i.e., dichotomous: <600 or ≥600 MET-minutes per week; categorical: low, moderate, high) at baseline or 12 months (p>0.05). For BCS, there were no significant differences in cancer stage or treatment between 12- and 24-month completers and non-completers. For controls, 24-month non-completers were more likely to report at least 2 comorbidities at 12

months than completers ($\chi^2(1)=4.03$, $p<0.05$). These comparisons did not markedly change after excluding the BCS outlier.

The amount of missing data relative to the number of BCS and controls who completed each time point was computed (Table 3). The greatest amount of missing data for BCS was found for physical activity at 24 months (14.2% missing). For controls, the greatest amount of missing data was found for physical function at 24 months (8.8% missing). Logistic regressions showed that missing executive function at 12 months was not significantly associated with covariates or baseline physical activity or executive function for controls. BCS with more days between surgery and baseline were more likely to have missing data for 12 month executive function (OR=1.01, $p<0.05$) and physical activity (OR=1.01, $p<0.05$). Controls with greater $Log_{(e)}$ transformed physical activity at baseline were less likely to have missing physical activity data at 12 months (OR=0.60, $p<0.05$). BCS with higher baseline anxiety were less likely to have missing executive function data at 24 months (OR=0.87, $p<0.05$). Missing physical activity data at 24 months were more likely for BCS with fewer years of education (OR=0.79, $p<0.05$), less than two medical comorbidities at baseline (OR=0.20, $p<0.01$), and at least two medical comorbidities at 12 months (OR=6.63, $p<0.01$). Controls identifying as White Hispanic or non-Hispanic were more likely to have missing 24-month executive function (OR=2.85, $p<0.05$) and physical activity data (OR=2.73, $p<0.05$). Ethnicity and *APOE* genotype were not significant predictors of executive function or physical activity missingness for BCS or controls. Cancer stage and treatment type were not significant predictors of executive function or physical activity missingness for BCS. These findings did not markedly change after excluding the BCS outlier.

Several variables were added to imputation models as auxiliary variables due to significant associations with missingness. In the imputation models for the whole sample and for BCS, comorbidity at 12 months was added as an auxiliary variable. For controls, cognitive reserve, race, and comorbidity at 12 months were added as auxiliary variables. Due to the substantial amount of missing data (53.7% of the sample had incomplete data when considering all variables in planned analyses), and the recommendation to use a greater number of imputations than the proportion of the sample with incomplete data (White, Royston, & Wood, 2011), 100 imputed datasets were generated by each of the three imputation models.

Primary Analyses

Aim 1

The relationship between executive function change from baseline to 12 months and physical activity at 24 months was examined with multiple regression, including baseline covariates, and using multiple imputation to address missing data. Model 1 tested this relationship in the entire sample of BCS and controls and included main effects of Group (BCS or control) and executive function change and the interaction between these variables. The main and interaction effects were not significant (Table 4). Baseline physical function was the only significant covariate (β=0.17, p<0.01), such that better physical function at baseline was associated with greater physical activity at 24 months. Results of separate regressions for BCS (Model 2) and controls (Model 3) showed similar findings, with a significant effect for baseline physical function in BCS only (β=0.22, p<0.01). Intercepts were significant (p<0.01), which indicates that physical activity at 24 months was significantly different from zero when there was no residualized change in executive function and covariates were at their average level.

The relationship between physical activity at 12 months and executive function change from 12 to 24 months was also examined with multiple regression, including baseline covariates, and using multiple imputation to address missing data. Model 4 tested this relationship in the entire sample and included main effects of Group (BCS or control) and physical activity and the interaction between these variables. Whereas the Group effect and Group x physical activity interaction were not significant (Table 5), there was a significant positive effect for physical activity (β=0.17, p=0.01), such that greater physical activity at 12 months was associated with increased executive function from 12 to 24 months. Significant covariates were age (β=-0.15, p<0.01), education (β=0.11, p=0.02), and physical function (β=-0.11, p=0.03) such that younger age, higher education, and lower baseline physical function were associated with increased executive function at 24 months. Results of separate regressions showed no significant effects of covariates or physical activity on executive function change for BCS. However, there was a trend for a significant effect of age (β=-0.07, p=0.08). For controls, there was a significant positive effect of physical activity on executive function change (β=0.07, p=0.02), and significant covariates were age (β=-0.07, p=0.01) and physical function (β=-0.07, p=0.04). There was also a trend for a significant effect of education (β=0.05, p=0.09).

Aim 2

Moderated multiple regression was used to explore potential moderators (i.e., age, cancer stage, comorbidity, *APOE* genotype) of the relationship between executive function change from baseline to 12 months and physical activity at 24 months. Models included covariates and used multiple imputation to address missing data. Results of these models are reported in Table 6. In each model, effects of executive function, the potential moderator, and the interaction between these variables were not significant. Baseline physical function was the only significant covariate in each of the models (Model 7: β=0.22, p<0.01; Model 8: β=0.22, p<0.01; Model 9: β=0.18, p=0.02; Model 10: β=0.21, p<0.01), such that better baseline physical function was associated with greater physical activity at 24 months. Intercepts for each of the models were also significant ($p\leq$0.01), indicating that at average levels of age, education, fatigue, depression, anxiety, physical function, and time since surgery, and for BCS who did not receive chemotherapy, physical activity significantly differed from zero when there was no change in executive function. The Benjamini-Hochberg procedure was not necessary given the lack of significant moderation effects.

Secondary Analyses

Dichotomous physical activity

Logistic regression with multiple imputation was used to examine the effect of executive function change from baseline to 12 months on dichotomous physical activity at 24 months (0=less than 600 MET minutes per week, 1=greater than 600 MET minutes per week). Model 11 tested this relationship in the entire sample and included main effects of Group (BCS or control) and executive function change and the interaction between these variables. None of these effects were statistically significant (Table 7). Physical function was a significant covariate (β=0.32, OR=1.05, p=0.01), such that better physical function at baseline was associated with a 5% greater odds of meeting guidelines for volume of physical activity at 24 months. There was a non-significant trend for an effect of age (β=-0.19, p=0.09). Results of separate logistic regressions showed no significant effects of executive function on dichotomous physical activity for BCS (Model 12) or controls (Model 13), and there were no significant covariates for controls. For BCS, physical function was a significant covariate (β=0.47, OR=1.07, p=0.01). Significant

intercepts for all three models (p<0.01) indicate that physical activity was significantly greater than zero when there was no residualized change in executive function and other covariates were at their average level.

The relationship between dichotomous physical activity at 12 months and executive function change from 12 to 24 months was examined with multiple regression using multiple imputation. Model 14 tested this relationship in the entire sample of BCS and controls and included main effects of Group (BCS or control) and physical activity and the interaction between these variables. None of these effects were statistically significant (Table 8). Significant covariates were age (β=-0.15, p<0.01) and education (β=0.10, p=0.03), such that younger age and higher education were associated with increased executive function at 24 months. There was a non-significant trend for worse baseline physical function to be associated with increased executive function (β=-0.09, p=0.07).

These relationships were also tested in separate models for BCS and controls. There were no significant effects of main variables or covariates for BCS (Model 15), although there was a non-significant trend for age (β=-0.07, p=0.07). Among controls (Model 16), age was a significant covariate (β=-0.07, p=0.02), and there were non-significant trends for fatigue (β=0.06, p=0.09), physical function (β=-0.06, p=0.06), and meeting physical activity guidelines (β=0.13, p=0.07).

Categorical physical activity

Proportional odds cumulative logit regressions with multiple imputation were used to examine the effect of executive function change from baseline to 12 months on categorical physical activity (i.e., low, moderate, and high) at 24 months. Model 17 tested this relationship in the entire sample of BCS and controls and included main effects of Group (BCS or control) and executive function change and the interaction between these variables. None of these effects were significant (Table 9). Physical function was a significant covariate (β=0.31, OR=1.04, p<0.01), such that better physical function at baseline was associated with a 4% greater cumulative odds of high or moderate physical activity at 24 months. Non-significant trends were found for age (β=-0.18, OR=0.97, p=0.08) and baseline fatigue (β=0.24, OR=1.03, p=0.06).

Results of separate cumulative logit regressions showed no significant effects of executive function change on categorical physical activity for BCS (Model 18) or controls

(Model 19). For BCS, physical function was a significant covariate (β=0.48, OR=1.07, p=0.01). For controls, age was a significant covariate (β=-0.30, OR=0.96, p=0.03), and there was a non-significant trend for baseline depression (β=-0.29, OR=0.95, p=0.09). In all three models, the intercepts were significant for high compared to low physical activity (Model 17: β=-0.87, OR=0.42 p<0.01; Model 18: β=-1.10, OR=0.33, p<0.01; Model 19: β=-0.68, OR=0.51, p<0.01) and for moderate compared to low activity (Model 17: β=1.19, OR=3.29, p<0.01; Model 18: β=1.15, OR=3.16, p<0.01; Model 19: β=1.31, OR=3.71, p<0.01). This indicates that when all covariates were equal to their average, no change in executive function from baseline to 12 months was associated with a greater probability of low than high physical activity at 24 months, and a greater probability of moderate than low physical activity at 24 months. However, because there were not significant effects of executive function, these probabilities remained constant regardless of change in executive function.

The relationship between categorical physical activity at 12 months and executive function change from 12 to 24 months was examined with multiple regression using multiple imputation. Model 20 tested this relationship in the entire sample and included main effects of Group (BCS or control) and physical activity and the interaction between these variables. The Group effect and its interaction with physical activity were not significant (Table 10); however, high physical activity was associated with increased executive function at 24 months compared to low physical activity (β=0.28, p=0.04). Significant covariates were age (β=-0.15, p<0.01) and education (β=0.10, p=0.03), such that younger age and higher education were associated with increased executive function at 24 months. There was a non-significant trend for worse baseline physical function to be associated with increased executive function (β=-0.10, p=0.06). The intercept also showed a non-significant trend for low physical activity to be associated with decline in executive function when all other covariates were equal to their average (β=-0.17, p=0.07).

These relationships were also tested in separate models for BCS and controls. There were no significant effects of physical activity or covariates for BCS (Model 21). There was a non-significant trend for age (β=-0.07, p=0.08). In controls (Model 22), there was a significant effect for high compared to low physical activity (β=0.18, p=0.02), and age was a significant covariate (β=-0.07, p=0.03). There were also non-significant trends for physical function (β=-0.06, p=0.06) and moderate compared to low physical activity (β=0.13, p=0.09). The intercept also

showed a non-significant trend for low physical activity to be associated with lower executive function when all other covariates were equal to their average (β=-0.12, p=0.05).

Structural equation modeling

Grouped auto-regressive cross-lagged (ARCL) structural equation models tested the relationship between executive function and physical activity over time from baseline to 24-month follow-up. The first ARCL model tested the relationship between executive function and Log_e transformed MET minutes of physical activity per week at baseline and 12 and 24 months. This model did not include covariates and was grouped into BCS or controls. The model showed poor fit ($\chi^2(8)$=126.68, p<0.01, RMSEA=0.22, CFI=0.92, TLI=0.71). The covariance between baseline and 24-month executive function was added to the model because modification indices (MI) indicated increased model fit by adding this parameter (BCS: MI=66.38, Controls: MI=28.28). The modified model showed fair fit ($\chi^2(6)$=21.98, p<0.01, RMSEA=0.09, CFI=0.92, TLI=0.71), and the additional covariance in this model significantly improved the fit from the prior model ($\chi^2(2)$difference=104.70, p<0.01). For both BCS and controls, the auto-regressive pathways were significant (see Table 11 and Figure 3), indicating that values of executive function were correlated over time as well as reports of physical activity. For BCS, there were no statistically significant cross-lagged relationships between executive function and physical activity. However, there were non-significant trends for relationships between lower baseline physical activity and higher 12-month executive function (β=-0.08, p<0.10) and between lower 24-month physical activity and higher 24-month executive function (β=-0.09, p<0.10). For controls, the only significant cross-lagged relationship was a positive association between 12-month physical activity and 24-month executive function (β=0.09, p<0.05), consistent with hypothesis 2. There was also a non-significant trend for baseline physical activity to be positively correlated with executive function (β=0.09, p<0.10).

Two additional ARCL models were examined. The first removed the covariance between baseline and 24-month executive function and added covariates (i.e., age, education, and baseline fatigue, depression, anxiety, and physical function). This model showed poor fit ($\chi^2(8)$=115.76, p<0.01, RMSEA=0.21, CFI=0.93, TLI=0.16). The covariance between baseline and 24-month executive function was added to the model because MI indicated increased model fit by adding this parameter (BCS: MI=64.26, Controls: MI=28.02). This model showed adequate fit

($\chi^2(6)=13.36$, $p=0.04$, RMSEA=0.06, CFI=0.99, TLI=0.92), and the additional covariance in this model significantly improved the fit from the prior model ($\chi^2(2)$ difference=102.40, $p<0.01$). For both BCS and controls, the auto-regressive pathways were significant (see Table 12 and Figure 4), indicating that values of executive function were correlated over time as well as reports of physical activity. For BCS, the only significant cross-lagged relationship was an association between lower baseline physical activity and higher 12-month executive function ($\beta=-0.12$, $p<0.01$). For controls, the only significant cross-lagged relationship was an association between greater 12-month physical activity and higher 24-month executive function ($\beta=0.08$, $p<0.05$).

Exploring physical function covariate

Because physical function appeared to be a consistently significant covariate in models predicting physical activity in BCS and executive function in controls, further exploratory analyses were indicated. First, baseline physical function was dichotomized at the median score in BCS (median score: 54.81) and controls (median score: 55.08). Second, separate t-tests in BCS and controls were conducted to explore differences in Log_e transformed physical activity and executive function domain z-score at each time point between those with higher and lower baseline physical function. Third, scatterplots with regression lines were used to explore physical activity and executive function over time by dichotomized baseline physical function. Physical activity appeared to increase over time in BCS and remain stable over time in controls (Figure 5). Among BCS, those with lower baseline physical function reported significantly lower physical activity at baseline than those with higher baseline physical function ($t(249.22)=-4.15$, mean difference=-0.55, $p<0.001$); this difference was a non-significant trend with respect to physical activity at 12 months ($t(192)=-1.71$, mean difference=-0.28, $p=0.09$) and 24 months ($t(164)=-1.74$, mean difference=-0.33, $p=0.08$). Among controls, those with lower baseline physical function reported significantly lower physical activity at each time point than those with higher baseline physical function (baseline: $t(321)=-3.58$, mean difference=-0.44, $p<0.001$; 12 months: $t(285)=-3.21$, mean difference=-0.37, $p<0.01$; 24 months: $t(228)=-3.01$, mean difference=-0.42, $p<0.01$) .

Executive function appeared to increase over time in BCS and controls (Figure 6). Among BCS, those with lower baseline physical function had significantly lower executive function at baseline than those with higher baseline physical function ($t(302)=-3.30$, mean

difference=-0.28, $p<0.01$); this difference was a non-significant trend with respect to executive function at 12 months ($t(184.14)=-1.82$, mean difference=-0.18, $p=0.07$) and 24 months ($t(194)=-1.89$, mean difference=-0.20, $p=0.06$). Among controls, those with lower baseline physical function had significantly lower executive function at baseline than those with higher baseline physical function ($t(311)=-2.43$, mean difference=-0.17, $p<0.05$) and 12 months ($t(281)=-2.08$, mean difference=-0.15, $p<0.05$). This difference at 24 months was not significant ($t(230)=-0.46$, mean difference=-0.04, $p=0.65$).

CHAPTER 4. DISCUSSION

The current project is a secondary data analysis of the TLC study, which is the largest cohort of older breast cancer survivors and matched healthy controls with objective measures of cognitive function prior to systemic cancer treatment and at yearly follow-up. Older BCS are understudied in general, and little is known about their cognitive function and physical activity. The TLC study provided a unique opportunity to examine the prospective relationship between executive function and physical activity among older BCS and matched healthy controls. Prior research has shown that physical activity may improve executive function in older adults (Albinet et al., 2016; Anderson-Hanley et al., 2012; Baker et al., 2010; McAuley et al., 2011; Olson et al., 2017) and cancer survivors (Furmaniak et al., 2016; Mustian et al., 2012); however, this research has not specifically focused on older cancer survivors. In older adults without cancer, previous research has found a bidirectional relationship between executive function and physical activity (Buckley, Cohen, Kramer, McAuley, & Mullen, 2014; Daly et al., 2015). In contrast to prior research, executive function did not predict physical activity in the current sample of older BCS or controls; however, physical activity was associated with executive function in controls. These findings were consistent across analyses, although significance was attenuated when physical activity was dichotomous.

The lack of evidence for an effect of executive function on physical activity is inconsistent with prior literature and theory. Self-regulation theory and prior research in older adults suggest that lower executive function could have a negative impact on physical activity (Bandura, 2005; Buckley et al., 2014; Hall & Fong, 2007, 2015; McAuley et al., 2011; Olson et al., 2017). According to self-regulation theories, executive difficulties may affect cognitive and emotional appraisals (e.g., by lowering self-efficacy) and interfere with self-regulatory behaviors (e.g., goal setting, planning) that facilitate physical activity behavior (Bandura, 1991, 2004, 2005; Buckley et al., 2014; Hall & Fong, 2007, 2015). The inconsistency of the present findings with theory might be due to reduced sensitivity of neuropsychological tests to subtle deficits in executive function. The specificity of objective performance-based executive function tests is also questionable because they require additional cognitive abilities (e.g., attention, processing speed, incidental learning, semantic knowledge, verbal fluency) (Bryan & Luszcz, 2000). Some have argued that a combination of self and informant behavior rating scales have better

ecological validity for executive function than performance-based measures (Isquith, Roth, & Gioia, 2013; McAlister & Schmitter-Edgecombe, 2016; Roth, Isquith, & Gioia, 2014). However, neuropsychological measures in this study are similar to those used in prior research that found effects of executive function on physical activity in older adults over similar periods of time (i.e., 1-2 years) (Daly et al., 2015; McAuley et al., 2011; Olson et al., 2017).

Results may indicate that executive function did not affect physical activity for the current sample. Participants in the TLC study were highly educated and appeared to have intact cognitive and physical function (Mandelblatt et al., 2018). Furthermore, executive function showed only a small change over the study period in BCS and controls. Additionally, adherence to national guidelines for physical activity was greater in the current sample (56.6% in BCS and 76.8% in controls at baseline) than in prior research with older adults and older cancer survivors (National Cancer Institute, 2019; Tarasenko et al., 2017). Results also showed demographic and medical differences between completers and non-completers of follow-ups and significant predictors of missing data. Controls who completed follow-ups had more education, greater cognitive reserve, and were less likely to have two or more comorbidities than controls who did not complete follow-ups. For BCS, missing data for executive function or physical activity were related to more time between surgery and baseline, lower baseline anxiety, less education, and greater comorbidities. For controls, missing data for executive function or physical activity were more likely for participants identifying as White, and missing physical activity data were related to lower physical activity at a prior time point. Although the statistical approach controlled for these factors to an extent, the sample's characteristics may have contributed to null findings.

Alternatively, the relationship between executive function abilities and reported physical activity may be complex. One study of older adults found that lower executive function was significantly associated with both objective and subjective daily functional ability; however, the correlation between executive function and objective functional ability was significantly greater than the correlation between executive function and self-reported functional ability (Mitchell & Miller, 2008). This may have been an effect of measurement method, or it may indicate low accuracy of self-reported functional ability (i.e., reduced insight). Future research may determine if those with worse executive function and low insight overreport their physical activity to a greater degree than those with intact insight.

Regarding the second hypothesis, findings indicate that physical activity at 12 months was related to executive function at 24 months among older adults without cancer, but not older BCS. Analyses with categorized physical activity showed that for controls, a high level of physical activity predicted increased executive functioning when compared to a low level physical activity. This positive, small relationship between physical activity and executive function is consistent with that found in observational studies of older adults (Bixby et al., 2007; Blumenthal et al., 2017; Daly et al., 2015). Although physical activity did not significantly predict executive function in BCS, the effect sizes in models with continuous physical activity are similar between BCS and controls. This discrepancy may be due in part to a difference in statistical power, given the two additional covariates for BCS. Of note, few studies with older adults or cancer survivors have prospectively examined the relationship between physical activity and cognitive function over a similar period of time (i.e., 6-24 months) without testing an intervention (Daly et al., 2015; Phillips, Lloyd, Awick, & McAuley, 2017). Interventions have found small to moderate effects of physical activity on executive function in older adults (Ludyga, Gerber, Brand, Holsboer-Trachsler, & Puhse, 2016; Sanders, Hortobagyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019) and cancer survivors (Myers, Erickson, Sereika, & Bender, 2018). The clinical significance of the small effect of physical activity on executive function is currently unclear. However, physical activity may be mitigating subtle cognitive decline due to aging and cancer treatments, and cancer survivors report that even subtle cognitive symptoms have a negative impact on their quality of life and functioning (Klemp et al., 2018; Reid-Arndt, Hsieh, & Perry, 2010).

In secondary analyses, lower baseline physical activity in BCS predicted higher executive function at 12 months. This result should be interpreted with caution as baseline physical activity was measured after surgery, and these secondary models did not control for cancer treatment type and time since surgery because they were grouped by BCS or control. Furthermore, BCS reported significantly less physical activity and lower executive function at baseline than controls. Significant group differences in physical activity and executive function at baseline but not at follow-up suggest that BCS might have experienced improvement to match controls by follow-up; however, attrition was greater for BCS than controls, which may have affected the findings. The baseline differences may have been due to a combination of the biological effects of cancer, surgery, and symptoms and the psychological impact of a cancer

diagnosis—all of which could have dissipated over time. Indeed, BCS showed greater symptoms of depression, anxiety, and fatigue compared to controls at baseline, and, with the exception of fatigue at 12 months, these differences were non-significant at follow-ups.

Regarding the second aim, the null effect of executive function change on physical activity in BCS was consistent across age, cancer stage, comorbidity, and *APOE* ε4 genotype. Theoretically, the largely intact executive function in our sample could have been used to ameliorate effects of risk factors on barriers and facilitators for physical activity. Additionally, the relatively small change in executive function from baseline to 12 months could have contributed to its null relationship with physical activity across subgroups of BCS. Also of note, only 17% of BCS had the *APOE* ε4 genotype, which further limited statistical power.

Physical activity in BCS was not related to age, cancer stage, comorbidity, or *APOE* ε4 genotype. Findings do not converge with prior research indicating that lower physical activity is associated with older age and greater comorbidity among older adults and cancer survivors (Lynch et al., 2016; Mora & Valencia, 2018), but converge with research indicating no difference in activity level between cancer survivors as a function of disease stage (Shin et al., 2017) and between older adults with or without an *APOE* ε4 allele (Fenesi et al., 2017; Tan et al., 2017). The inconsistency of our findings with prior research may be due to greater than typical activity in the current sample of BCS. The range of ages in the present study was also restricted, as this study targeted BCS over 60 years of age. This sample may also have been better equipped to manage health-related barriers to physical activity due to protective factors. Indeed, BCS in the TLC study were highly educated and recruited from academic cancer centers, which may indicate greater access to resources (Mandelblatt et al., 2018). Furthermore, BCS missing physical activity data at 24 months had fewer years of education, less than two comorbidities at baseline, and at least two medical comorbidities at 12 months. Therefore, sample characteristics and attrition may have led to an underestimation of the degree to which risk factors affect physical activity in the population of older BCS.

Baseline physical function was a consistently significant covariate in models testing the relationship between executive function change from baseline to 12 months on physical activity at 24 months in the whole sample and in BCS; however, it was not a significant covariate in these models for controls. Exploratory t-tests and graphs showed a stable higher level of physical activity over time for controls with higher as compared to lower baseline physical

function, whereas BCS with lower baseline physical function appeared to increase their physical activity over time to a greater degree than BCS with higher baseline physical function. The moderate positive relationship between physical function and physical activity is well established for older adults and older cancer survivors (Daum et al., 2016; Gine-Garriga, Roque-Figuls, Coll-Planas, Sitja-Rabert, & Salva, 2014; Layne et al., 2017; Morey et al., 2015; Portegijs, Keskinen, Tsai, Rantanen, & Rantakokko, 2017). Not only does physical activity appear to improve physical function (Daum et al., 2016; Gine-Garriga et al., 2014; Layne et al., 2017), but those with higher physical function are more likely to engage in physical activity (Morey et al., 2015; Portegijs et al., 2017). Additionally, physical function as reported by the SF-12 includes difficulties engaging in physical activities (e.g., accomplishing less in work or activities, limitations in climbing stairs), which could have substantial overlap with participants' amount of physical activity. The effects of similar measurement also may be relevant, as both constructs were self-reported. The lack of a significant relationship between physical function and physical activity for controls is unclear and inconsistent with prior research in older adults (Gine-Garriga et al., 2014; Layne et al., 2017; Portegijs et al., 2017). Controls had greater range and less missing data for baseline physical function compared to BCS, so it is less likely that range restriction and missing data for physical function affected this result. In fact, covariates were largely unrelated to physical activity at 24 months in controls. Because the sample reported greater activity than is typically found among older adults and older cancer survivors (National Cancer Institute, 2019; Tarasenko et al., 2017), standard predictors of physical activity may be less relevant for this sample. Predictors of degrees of physical activity among active older adults requires further study.

Baseline physical function was also a significant or trending covariate in models testing the relationship between physical activity at 12 months and executive function change from 12 to 24 months in the whole sample and in controls; however, it was not a significant covariate in these models for BCS. Whereas prior research with older adults found a positive bidirectional relationship between physical activity and executive function (Gale, Allerhand, Sayer, Cooper, & Deary, 2014), in the current study, better baseline physical function predicted lower executive function change from 12 to 24 months. Prior findings from the TLC study showed that executive function improved over time for BCS and controls (Mandelblatt et al., 2018). Furthermore, exploratory t-tests and graphs showed that controls with better baseline physical function had

stable executive function, whereas controls with worse baseline physical function appeared to have greater room for improvement in executive function over time.

Strengths of the current project warrant mention. The TLC study is the largest prospective, controlled study of cognitive performance in older BCS starting before systemic cancer treatment. Recruiting BCS aged 60 years and older was also a strength because this large, understudied group may be at risk for cognitive symptoms due to potential accelerated aging from cancer and its treatment (Ahles, Root, & Ryan, 2012). The sample was recruited from diverse regions of the U.S. and its racial and ethnic diversity is representative of American breast cancer survivors. In addition, measures included objective cognitive performance and validated self-report questionnaires.

Along with these strengths, several limitations should be noted. First, there were measurement limitations. Performance-based measures of executive function may not be sufficiently sensitive to detect subtle cognitive symptoms reported by cancer survivors and may not represent executive difficulties in daily life (Isquith et al., 2013; McAlister & Schmitter-Edgecombe, 2016; Roth et al., 2014). Additionally, self-reported physical activity is susceptible to over-estimation from social desirability and poor recall (Adams et al., 2005; Sallis & Saelens, 2000). Second, the study sample was generally well-educated, high functioning, and cognitively intact at baseline and primarily recruited from academic medical centers. Also, the response rate among BCS (36% of eligible BCS consented to participate) was low compared to prior longitudinal research on cancer-related cognitive impairment (Jansen et al., 2011; Krolak et al., 2017; Underwood et al., 2019). Therefore, results may underestimate the prevalence and severity of cognitive difficulties and overestimate physical activity in the general population of older BCS. Third, study attrition and missing data may have affected the results. There were differences between those who did and did not complete follow-ups (e.g., lower education and cognitive reserve among non-completers), and there were significant predictors of missing data (e.g., lower baseline executive function and physical activity for BCS, lower baseline physical activity for controls). Although the statistical approach controlled for these factors, a relationship between the values of the missing data and the prior values cannot be ruled out. Such a relationship would indicate that the data are missing not at random (MNAR), although this cannot be verified. Fourth, despite the large sample, there was insufficient power to detect

significant interaction effects. Finally, the current project consisted of post-hoc analyses, as the TLC study was not designed to address the aims of the current project.

There are a number of important directions for future research on the relationship between executive function and physical activity among older cancer survivors. First, multiple measures could be utilized, such as self and informant reported behavior rating scales (e.g., Behavior Rating Inventory of Executive Function, Dysexecutive Questionnaire, Frontal Systems Behavior Scale) in addition to performance-based measures of executive function and actigraphy. Multiple methods of measurement are recommended to address the limitations of specific measures and provide a better estimate of latent constructs (Cole & Maxwell, 2003; Kline, 2011; Miyake et al., 2000). Examining consistency between self and informant reported behavior rating scales and performance-based measures of executive function may also be a way to estimate insight into executive abilities. Then researchers could determine whether executive function insight predicts greater consistency between actigraphy and self-reported physical activity. Second, recruitment from multiple community-based sites may provide a more diverse and representative sample of older cancer survivors, especially with respect to socioeconomic status. Third, a theoretical model may be examined by including measures of cognitive and emotional appraisals and behavioral self-regulation that may mediate an effect of executive function on physical activity. This study could also identify protective factors that may buffer the effect of executive function decline on physical activity (e.g., high social support for physical activity, low symptoms, enjoyment of exercise, access to safe walking paths or gyms). Finally, future research may examine whether executive function correlates with physical activity when older cancer survivors are attempting to change their activity, such as during an exercise intervention.

In conclusion, the current project aimed to test whether change in executive function predicted physical activity, and whether physical activity predicted change in executive function in older cancer survivors and matched healthy controls. The primary aim of this project was based on theory and research with older adults suggesting a bidirectional effect between executive function and physical activity (Bandura, 1991, 2004, 2005; Best et al., 2014; Daly et al., 2015; Hall & Fong, 2007, 2015). In contrast to this research, current findings indicate that change in executive function from baseline to 12 months did not predict physical activity at 24 months in BCS and controls. However, physical activity at 12 months significantly predicted

increased executive function at 24 months, but only for controls. In addition, the null effect of executive function change on physical activity in BCS did not differ based on selected risk factors for accelerated cognitive decline. Although the study had several strengths, results should be interpreted with caution, given limitations in measurement, sampling biases, and attrition. There are many potential directions for future research. For example, multiple methods of measurement and community-based recruitment would address several limitations of the current project. Further research is needed to determine whether the relationship between executive function and physical activity is bidirectional in older BCS and survivors of other cancers. Examining this relationship and elucidating its mechanisms will inform the development of future exercise interventions to improve the physical and mental health and cognitive function of the large population of older cancer survivors.

APPENDIX A. TABLES

Table 1

Participant Characteristics

Characteristic	BCS (*N*=320) *n* (%)[a]	Controls (*N*=323) *n* (%)[a]	*t* or χ^2(df)	*p*
Age				
Mean (SD)	68.09 (6.07)	67.41 (6.73)	-1.33(641)	0.18
Range	60 - 98	60 - 91		
Missing	0	0		
Years of Education				
Mean (SD)	15.23 (2.17)	15.52 (2.21)	1.73(641)	0.09
Range	9 - 18	6 - 18		
Missing	0	0		
WRAT[b] standard score				
Mean (SD)	111.34 (15.38)	111.64 (15.79)	0.24(641)	0.81
Range	80-145	74-145		
Missing	0	0		
Race				
Black or African American	26 (8.1)	28 (8.7)	4.08(4)	0.40
White	265 (82.8)	271 (83.9)		
American Indian or Alaska Native	1 (0.3)	4 (1.2)		
Asian	16 (5.0)	9 (2.8)		
Multiracial or other	12 (3.8)	10 (3.1)		
Missing	0	1 (0.3)		
Ethnicity				
Hispanic	23 (7.2)	26 (8.0)	0.17(1)	0.68
Non-Hispanic	297 (92.8)	297 (92.0)		
Missing	0	0		
APOE genotype				
ε4+	53 (16.6)	79 (24.5)	3.31(1)	0.07
ε4-	225 (70.3)	233 (72.1)		
Missing	42 (13.1)	11 (3.4)		

Note. BCS = Breast cancer survivors; WRAT = Wide Range Achievement Test, 4th edition, word reading subtest; *APOE* = apolipoprotein E.

[a]Unless otherwise specified.

[b]Mean and standard deviation of standard score are 100 and 15, respectively.

Table 2

Clinical Characteristics of Breast Cancer Survivors (N=320)

Characteristic	*n* (%)
AJCC stage	
0 (DCIS)	34 (10.6)
Stage 1	181 (56.6)
Stage 2	87 (27.2)
Stage 3	17 (5.3)
Unknown	1 (0.3)
Missing	0 (0.0)
Systemic treatment	
Hormone and Chemotherapy	91 (28.4)
Hormone only	229 (71.6)
Missing	0 (0.0)
Local treatment	
Lumpectomy with radiation	138 (43.1)
Lumpectomy only	41 (12.8)
Mastectomy	139 (43.4)
None	2 (0.6)
Missing	0 (0.0)
Days from surgery to baseline	
Mean (SD)	48.53 (52.21)
Range	[a]-160 – 421[b]
Missing (%)	2 (0.01)

Note. AJCC = American Joint Commission on Cancer; DCIS = Ductal Carcinoma In Situ.
[a]There were seven cases that completed baseline before surgery because they were scheduled for neoadjuvant systemic therapy.
[b]Six cases completed baseline more than six months post-surgery.

Table 3

Descriptive Statistics for Main Variables at Each Time Point

Variable	Baseline		12 months		24 months	
	BCS (*n*=320)	Controls (*n*=323)	BCS (*n*=243)	Controls (*n*=291)	BCS (*n*=211)	Controls (*n*=239)
Executive function z-score						
Mean (SD)	-0.18 (0.75)*	-0.05 (0.61)	-0.01 (0.74)	0.01 (0.62)	-0.01 (0.78)	0.11 (0.66)
Range	-3.57-1.81	-1.78-1.39	-3.65-1.95	-1.70-1.58	-3.78-1.82	-1.71-1.89
Missing (%)	0 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)	3 (0.1)	1 (0.0)
MET minutes/week						
Mean	1450.64	2167.38	1930.68	2066.15	1985.25	2069.78
(SD)	(1337.07)*	(2142.77)	(1919.37)	(1935.22)	(2203.97)	(2039.71)
Range	33-8253	33-15066	33-10479	33-13146	33-15863	50-16212
Missing (%)	37 (11.6)	14 (4.3)	31 (12.8)	14 (4.8)	30 (14.2)	17 (7.1)
MET categorical						
Low, *n* (%)	98 (30.6)*	61 (18.9)	58 (23.9)	54 (18.6)	47 (22.3)	48 (20.1)
Moderate, *n* (%)	126 (39.4)*	141 (43.7)	88 (36.2)	129 (44.3)	85 (40.3)	96 (40.2)
High, *n* (%)	59 (18.4)*	107 (33.1)	66 (27.2)	94 (32.3)	49 (23.2)	78 (32.6)
Missing (%)	37 (11.6)	14 (4.3)	31 (12.8)	14 (4.8)	30 (14.2)	17 (7.1)
MET dichotomous						
<600, *n* (%)	102 (31.9)*	61 (18.9)	57 (23.5)	57 (19.6)	48 (22.7)	52 (21.8)
≥600, *n* (%)	181 (56.6)*	248 (76.8)	155 (63.8)	220 (75.6)	133 (63.0)	170 (71.1)
Missing (%)	37 (11.6)	14 (4.3)	31 (12.8)	14 (4.8)	30 (14.2)	17 (7.1)
SF-12 PCS						
Mean (SD)	52.14 (6.89)	51.96 (7.24)	49.99 (7.53)	51.03 (7.89)	49.06 (8.21)	50.35 (8.72)
Range	21-60	14-63	17-65	13-61	20-60	15-61
Missing (%)	27 (8.4)	10 (3.1)	29 (11.9)	8 (2.7)	19 (9.0)	21 (8.8)
CES-D						
Mean (SD)	7.15 (7.96)*	4.73 (5.48)	5.69 (6.13)	4.95 (5.34)	5.30 (6.34)	5.17 (6.21)
Range	0-43	0-32	0-37	0-31	0-42	0-35
Missing (%)	20 (6.3)	6 (1.9)	19 (7.8)	10 (3.4)	14 (6.6)	16 (6.7)

Table 3 continued

STAI						
Mean (SD)	29.41 (8.41)*	26.74 (5.68)	27.81 (7.99)	27.01 (6.38)	26.75 (5.98)	27.20 (6.67)
Range	22-74	20-62	20-66	22-62	20-50	20-64
Missing (%)	14 (4.4)	9 (2.8)	16 (6.6)	7 (2.4)	12 (5.7)	12 (5.0)
FACIT-F						
Mean (SD)	43.18 (8.55)*	46.30 (5.85)	44.13 (7.62)*	46.15 (6.01)	44.63 (7.44)	45.90 (7.38)
Range	6-52	16-52	17-52	18-52	20-52	7-52
Missing (%)	13 (4.1)	4 (1.2)	16 (6.6)	7 (2.4)	13 (6.2)	13 (5.4)
Comorbidities						
0-1, *n* (%)	111 (34.7)	115 (35.6)	73 (30.0)	87 (29.9)	61 (28.9)	64 (26.8)
>2, *n* (%)	197 (61.6)	203 (62.8)	155 (63.8)	197 (67.7)	138 (65.4)	164 (68.6)
Missing (%)	12 (3.8)	5 (1.5)	15 (6.2)	7 (2.4)	12 (5.7)	11 (4.6)

Note. BCS = Breast cancer survivors; MET = Metabolic Equivalent of Task; SF-12 PCS = Short Form Health Survey-12 Physical Component Score; CES-D = Center for Epidemiologic Studies-Depression Scale; STAI = State Trait Anxiety Inventory; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue.

*Significantly different from controls at the same time point ($p<0.05$).

Table 4

Regression Parameter Estimates for Aim 1, Hypothesis 1

	df	B	SE	β	*t*	*p*
Model 1[a]						
Intercept	786.09	7.07	0.06	0.00	128.01	<0.01*
BCS[b]	976.14	-0.04	0.06	-0.03	-0.73	0.47
Age	562.19	-0.01	0.01	-0.08	-1.58	0.11
Education	549.73	0.01	0.03	0.03	0.52	0.60
Fatigue	536.79	0.02	0.01	0.12	1.80	0.07†
Depression	375.39	-0.01	0.01	-0.05	-0.62	0.53
Anxiety	416.32	0.02	0.01	0.11	1.53	0.13
Physical function	416.73	0.03	0.01	0.17	3.06	<0.01*
Executive function	638.33	-0.02	0.15	-0.01	-0.16	0.88
Executive function by BCS[b]	1076.50	-0.14	0.14	-0.05	-0.98	0.33
Model 2[c]						
Intercept	582.94	7.00	0.11	0.00	66.53	<0.01*
Age	568.73	-0.02	0.02	-0.12	-1.58	0.11
Education	328.57	0.03	0.05	0.05	0.60	0.55
Fatigue	364.50	0.02	0.01	0.17	1.66	0.10
Depression	329.69	0.01	0.02	0.07	0.55	0.59
Anxiety	245.73	0.02	0.02	0.12	1.00	0.32
Physical function	643.88	0.04	0.01	0.22	3.11	<0.01*
Received chemotherapy	529.27	-0.01	0.21	-0.01	-0.04	0.97
Time since surgery	241.38	0.00	0.00	0.01	0.13	0.90
Executive function	376.02	-0.28	0.23	-0.22	-1.22	0.22
Model 3[d]						
Intercept	1060.00	7.13	0.07	0.00	97.07	<0.01*
Age	871.25	-0.01	0.01	-0.06	-0.89	0.37
Education	621.06	0.01	0.04	0.01	0.20	0.84
Fatigue	847.07	0.01	0.02	0.08	0.91	0.37
Depression	569.75	-0.03	0.02	-0.13	-1.38	0.17
Anxiety	818.55	0.00	0.02	0.02	0.27	0.79
Physical function	551.76	0.02	0.01	0.10	1.25	0.21
Executive function	880.66	0.25	0.22	0.22	1.10	0.27

Note. BCS = Breast cancer survivor; SE = standard error.

[a]Model 1: Hypothesis 1 tested in the whole sample – effect of executive function residualized change from baseline to 12 months on physical activity (Log_e of Metabolic Equivalent of Task (MET) minutes per week) at 24 months.

[b]Breast cancer survivor compared to control group.

[c]Model 2: Hypothesis 1 tested in breast cancer survivors (BCS) – effect of executive function residualized change from baseline to 12 months on physical activity (Log_e of MET minutes per week) at 24 months.

[d]Model 3: Hypothesis 1 tested in controls – effect of executive function residualized change from baseline to 12 months on physical activity (Log_e of MET minutes per week) at 24 months.

†p<0.10.

*p<0.05.

Table 5

Regression Parameter Estimates for Aim 1, Hypothesis 2

	df	B	SE	*β*	*t*	*p*
Model 4[a]						
Intercept	1900000	0.00	0.02	0.00	-0.08	0.94
BCS[b]	1007.30	-0.01	0.02	-0.04	-0.44	0.66
Age	1260.90	-0.01	0.00	-0.15	-3.37	<0.01*
Education	917.95	0.02	0.01	0.11	2.27	0.02*
Fatigue	887.45	0.00	0.00	0.07	1.16	0.25
Depression	949.27	0.00	0.00	0.04	0.58	0.56
Anxiety	994.86	-0.01	0.00	-0.08	-1.30	0.20
Physical function	973.99	-0.01	0.00	-0.11	-2.14	0.03*
Physical activity	446.84	0.06	0.02	0.17	2.46	0.01*
Physical activity by BCS[b]	502.17	-0.01	0.02	-0.06	-0.61	0.54
Model 5[c]						
Intercept	3688.20	0.04	0.04	0.03	0.86	0.39
Age	900.33	-0.01	0.01	-0.07	-1.78	0.08†
Education	578.32	0.02	0.02	0.04	1.10	0.27
Fatigue	419.71	0.00	0.01	0.03	0.59	0.56
Depression	579.44	0.01	0.01	0.04	0.72	0.47
Anxiety	1011.80	-0.01	0.01	-0.08	-1.60	0.11
Physical function	761.83	-0.01	0.01	-0.05	-1.19	0.23
Received chemotherapy	685.89	-0.11	0.09	-0.11	-1.30	0.19
Time since surgery	311.53	0.00	0.00	-0.07	-1.60	0.11
Physical activity	328.94	0.04	0.04	0.05	1.11	0.27
Model 6[d]						
Intercept	2550000	0.00	0.02	0.00	0.00	1.00
Age	734.31	-0.01	0.00	-0.07	-2.44	0.01*
Education	716.96	0.02	0.01	0.05	1.68	0.09†
Fatigue	1932.80	0.01	0.01	0.05	1.42	0.16
Depression	888.83	0.00	0.01	0.01	0.27	0.79
Anxiety	1277.50	0.00	0.01	0.00	0.12	0.90
Physical function	663.39	-0.01	0.00	-0.07	-2.04	0.04*
Physical activity	803.49	0.07	0.03	0.07	2.28	0.02*

Note. BCS = Breast cancer survivor; SE = standard error.

[a]Model 4: Hypothesis 2 tested in the whole sample – effect of physical activity (Log_e of Metabolic Equivalent of Task (MET) minutes per week) at 12 months on executive function residualized change from 12 to 24 months.

[b]Breast cancer survivor compared to control group.

[c]Model 5: Hypothesis 2 tested in BCS – effect of physical activity (Log_e of MET minutes per week) at 12 months on executive function residualized change from 12 to 24 months.

[d]Model 6: Hypothesis 2 tested in controls – effect of physical activity (Log_e of MET minutes per week) at 12 months on executive function residualized change from 12 to 24 months.

†$p<0.10$.

*$p<0.05$.

Table 6

Regression Parameter Estimates for Aim 2 in Breast Cancer Survivors

	df	B	SE	*β*	*t*	*p*
Model 7[a]						
Intercept	602.12	7.01	0.11	0.00	66.14	0.01*
Age	738.76	-0.02	0.02	-0.11	-1.54	0.12
Education	330.25	0.03	0.05	0.05	0.61	0.54
Fatigue	372.76	0.02	0.01	0.17	1.68	0.09†
Depression	337.77	0.01	0.02	0.07	0.56	0.58
Anxiety	248.21	0.02	0.02	0.12	0.99	0.32
Physical function	667.18	0.04	0.01	0.22	3.10	<0.01*
Received chemotherapy	526.07	-0.01	0.21	-0.01	-0.05	0.96
Time since surgery	242.45	0.00	0.00	0.01	0.13	0.89
Executive function	357.58	-0.29	0.24	-0.23	-1.21	0.23
Executive function by Age	863.00	0.00	0.03	0.02	0.16	0.87
Model 8[b]						
Intercept	460.46	7.00	0.13	0.00	55.32	0.01*
Stage	507.94	-0.01	0.10	-0.01	-0.08	0.94
Age	576.29	-0.02	0.02	-0.12	-1.59	0.11
Education	333.32	0.03	0.05	0.05	0.60	0.55
Fatigue	363.52	0.02	0.01	0.17	1.67	0.10
Depression	331.68	0.01	0.02	0.07	0.55	0.58
Anxiety	248.94	0.02	0.02	0.12	1.01	0.31
Physical function	655.04	0.04	0.01	0.22	3.10	<0.01*
Received chemotherapy	462.19	0.00	0.23	0.00	-0.02	0.98
Time since surgery	243.93	0.00	0.00	0.01	0.12	0.91
Executive function	407.88	-0.27	0.23	-0.22	-1.18	0.24
Executive function by Stage	1122.20	0.05	0.19	0.04	0.26	0.79
Model 9[c]						
Intercept	618.06	7.06	0.11	0.05	64.93	<0.01*
Comorbidity	498.96	-0.18	0.10	-0.15	-1.82	0.07†
Age	573.45	-0.02	0.02	-0.09	-1.25	0.21
Education	325.64	0.03	0.05	0.05	0.57	0.57
Fatigue	349.08	0.02	0.01	0.15	1.51	0.13
Depression	318.23	0.01	0.02	0.07	0.55	0.58
Anxiety	239.93	0.02	0.02	0.12	1.02	0.31
Physical function	597.24	0.03	0.01	0.18	2.43	0.02*
Received chemotherapy	524.35	-0.04	0.21	-0.03	-0.20	0.84
Time since surgery	235.06	0.00	0.00	0.01	0.09	0.93
Executive function	372.72	-0.26	0.24	-0.21	-1.12	0.26
Executive function by Comorbidity	699.06	-0.06	0.21	-0.05	-0.28	0.78

Table 6 continued

Model 10[d]						
Intercept	455.04	7.09	0.13	0.07	54.89	0.01*
APOE ε4	346.28	0.16	0.13	0.13	1.24	0.22
Age	541.14	-0.03	0.02	-0.12	-1.64	0.10
Education	318.57	0.04	0.05	0.06	0.78	0.43
Fatigue	365.64	0.02	0.01	0.15	1.50	0.13
Depression	332.15	0.01	0.02	0.05	0.37	0.71
Anxiety	243.72	0.02	0.02	0.13	1.10	0.27
Physical function	631.39	0.04	0.01	0.21	2.87	<0.01*
Received chemotherapy	527.44	0.02	0.21	0.01	0.08	0.94
Time since surgery	245.51	0.00	0.00	0.02	0.22	0.83
Executive function	301.62	-0.33	0.32	-0.26	-1.03	0.30
Executive function by *APOE* ε4	379.17	-0.10	0.30	-0.08	-0.35	0.73

Note. SE = standard error; *APOE* = apolipoprotein E.

[a]Model 7: Testing aim 2: To explore whether the effect of executive function residualized change from baseline to 12 months on physical activity (Log_e of Metabolic Equivalent of Task (MET) minutes per week) at 24 months differs in breast cancer survivors based on proposed moderators. Moderator is age (i.e., interaction between executive function and age).

[b]Model 8: Aim 2 – Moderator is stage of disease (i.e., 0-1 vs. 2-3).

[c]Model 9: Aim 2 – Moderator is comorbidity (i.e., 0-1 vs. ≥2 comorbid medical conditions).

[d]Model 10: Aim 2 – Moderator is *APOE* genotype (i.e., no *APOE* ε4 allele vs. at least one *APOE* ε4 allele).

†$p<0.10$.

*$p<0.05$.

Table 7

Regression Parameter Estimates for Aim 1, Hypothesis 1 with Dichotomous Physical Activity

	df	B	SE	Exp(B)	β	*t*	*p*
Model 11[a]							
Intercept	878.51	-1.06	0.11	0.35	1.06	9.22	<0.01*
BCS[b]	1210.70	-0.05	0.11	0.95	-0.05	-0.47	0.64
Age	779.08	-0.03	0.02	0.97	-0.19	-1.72	0.09†
Education	562.42	0.02	0.06	1.02	0.04	0.37	0.71
Fatigue	723.83	0.02	0.02	1.02	0.17	1.20	0.23
Depression	497.29	-0.01	0.03	0.99	-0.08	-0.43	0.67
Anxiety	549.53	0.02	0.02	1.02	0.16	0.96	0.34
Physical function	607.19	0.05	0.02	1.05	0.32	2.75	0.01*
Executive function	771.13	-0.13	0.31	0.88	-0.05	-0.44	0.66
Executive function by BCS[b]	1257.30	-0.03	0.28	0.97	-0.01	-0.09	0.92
Model 12[c]							
Intercept	504.15	0.99	0.22	2.69	0.99	4.54	<0.01*
Age	709.69	-0.05	0.03	0.95	-0.28	-1.63	0.10
Education	500.52	0.05	0.08	1.05	0.10	0.57	0.57
Fatigue	493.20	0.04	0.03	1.04	0.37	1.60	0.11
Depression	527.49	0.03	0.04	1.03	0.22	0.74	0.46
Anxiety	316.53	0.03	0.04	1.03	0.24	0.81	0.42
Physical function	775.20	0.07	0.02	1.07	0.47	2.73	0.01*
Received chemotherapy	609.67	-0.01	0.41	0.99	-0.01	-0.01	0.99
Time since surgery	385.24	0.00	0.00	1.00	0.15	0.74	0.46
Executive function	569.72	-0.39	0.41	0.68	-0.39	-0.94	0.35

Table 7 continued

Model 13[d]							
Intercept	1698.30	1.13	0.15	3.10	1.13	7.39	<0.01*
Age	1056.50	-0.02	0.02	0.98	-0.15	-1.00	0.32
Education	868.77	0.02	0.07	1.02	0.05	0.28	0.78
Fatigue	1094.10	0.00	0.03	1.00	0.01	0.04	0.97
Depression	818.80	-0.05	0.04	0.95	-0.26	-1.31	0.19
Anxiety	1277.60	0.00	0.03	1.00	-0.02	-0.08	0.93
Physical function	693.57	0.03	0.02	1.03	0.19	1.13	0.26
Executive function	979.78	0.12	0.47	1.13	0.12	0.25	0.80

Note. BCS = Breast cancer survivor; SE = standard error.

[a]Model 11: Hypothesis 1 tested in the whole sample – effect of executive function residualized change from baseline to 12 months on dichotomous physical activity at 24 months (likelihood of meeting physical activity guidelines of at least 600 Metabolic Equivalent of Task (MET) minutes per week compared to not meeting them).

[b]Breast cancer survivor compared to control group.

[c]Model 12: Hypothesis 1 tested in BCS – effect of executive function residualized change from baseline to 12 months on dichotomous physical activity at 24 months.

[d]Model 13: Hypothesis 1 tested in controls – effect of executive function residualized change from baseline to 12 months on dichotomous physical activity at 24 months.

†$p<0.10$.

*$p<0.05$.

Table 8

Regression Parameter Estimates for Aim 1, Hypothesis 2 with Dichotomous Physical Activity

	df	B	SE	*β*	*t*	*p*
Model 14[a]						
Intercept	4507.20	-0.02	0.02	-0.05	-1.04	0.30
BCS[b]	916.75	0.00	0.03	0.00	-0.02	0.98
Age	1298.50	-0.01	0.00	-0.15	-3.34	<0.01*
Education	938.51	0.02	0.01	0.10	2.18	0.03*
Fatigue	909.52	0.01	0.00	0.08	1.36	0.17
Depression	929.37	0.00	0.00	0.04	0.53	0.60
Anxiety	946.32	0.00	0.00	-0.07	-1.19	0.23
Physical function	1021.80	-0.01	0.00	-0.09	-1.85	0.07†
Meeting PA guidelines[c]	565.54	0.04	0.03	0.09	1.57	0.12
Meeting PA guidelines[c] by BCS[b]	587.16	-0.02	0.03	-0.05	-0.79	0.43
Model 15[d]						
Intercept	666.39	-0.01	0.07	-0.01	-0.14	0.89
Age	923.46	-0.01	0.01	-0.07	-1.81	0.07†
Education	583.23	0.02	0.02	0.04	1.05	0.29
Fatigue	431.19	0.00	0.01	0.03	0.63	0.53
Depression	578.16	0.01	0.01	0.04	0.68	0.50
Anxiety	1017.30	-0.01	0.01	-0.07	-1.51	0.13
Physical function	845.95	-0.01	0.01	-0.04	-1.06	0.29
Received chemotherapy	689.59	-0.11	0.09	-0.11	-1.25	0.21
Time since surgery	308.12	0.00	0.00	-0.07	-1.55	0.12
Meeting PA guidelines[c]	437.46	0.06	0.09	0.06	0.63	0.53

Table 8 continued

Model 16[e]						
Intercept	1131.60	-0.10	0.06	-0.10	-1.66	0.10
Age	769.98	-0.01	0.00	-0.07	-2.37	0.02*
Education	732.88	0.02	0.01	0.05	1.62	0.11
Fatigue	2170.60	0.01	0.01	0.06	1.68	0.09†
Depression	898.46	0.00	0.01	0.01	0.20	0.84
Anxiety	1317.80	0.00	0.01	0.01	0.20	0.84
Physical function	708.19	-0.01	0.00	-0.06	-1.91	0.06†
Meeting PA guidelines	818.22	0.13	0.07	0.13	1.80	0.07†

Note. BCS = Breast cancer survivor; SE = standard error; PA = physical activity.

[a]Model 14: Hypothesis 2 tested in the whole sample – effect of dichotomous physical activity at 12 months on executive function residualized change from 12 to 24 months (likelihood of meeting physical activity guidelines of at least 600 Metabolic Equivalent of Task (MET) minutes per week compared to not meeting them).

[b]Breast cancer survivor compared to control group.

[c]At least 600 MET-minutes per week compared to less than 600 MET-minutes per week.

[d]Model 15: Hypothesis 2 tested in BCS – effect of dichotomous physical activity at 12 months on executive function residualized change from 12 to 24 months.

[e]Model 16: Hypothesis 2 tested in controls – effect of dichotomous physical activity at 12 months on executive function residualized change from 12 to 24 months.

†$p<0.10$.

*$p<0.05$.

Table 9

Regression Parameter Estimates for Aim 1, Hypothesis 1 with Categorical Physical Activity

	df	B	SE	Exp(B)	*β*	*t*	*p*
Model 17[a]							
Intercept, High activity	878.60	-0.87	0.11	0.42	-0.87	-8.02	<0.01*
Intercept, Moderate activity	827.59	1.19	0.12	3.29	1.19	10.12	<0.01*
BCS[b]	949.60	-0.12	0.09	0.89	-0.12	-1.31	0.19
Age	604.60	-0.03	0.02	0.97	-0.18	-1.76	0.08†
Education	490.03	0.03	0.05	1.03	0.06	0.59	0.56
Fatigue	659.95	0.03	0.02	1.03	0.24	1.91	0.06†
Depression	595.12	0.00	0.02	1.00	-0.02	-0.13	0.90
Anxiety	470.22	0.03	0.02	1.03	0.19	1.41	0.16
Physical function	660.44	0.04	0.01	1.04	0.31	3.02	<0.01*
Executive function	1151.20	-0.11	0.24	0.90	-0.04	-0.44	0.66
Executive function by BCS[b]	2084.70	-0.23	0.22	0.79	-0.09	-1.04	0.30
Model 18[c]							
Intercept, High activity	582.48	-1.10	0.20	0.33	-1.10	-5.56	<0.01*
Intercept, Moderate activity	610.98	1.15	0.20	3.16	1.15	5.77	<0.01*
Age	681.03	-0.01	0.02	0.99	-0.08	-0.57	0.57
Education	461.10	0.10	0.07	1.11	0.22	1.49	0.14
Fatigue	362.40	0.03	0.02	1.03	0.27	1.29	0.20
Depression	421.52	0.02	0.03	1.02	0.18	0.73	0.47
Anxiety	330.41	0.04	0.03	1.04	0.34	1.51	0.13
Physical function	388.99	0.07	0.03	1.07	0.48	2.72	0.01*
Received chemotherapy	384.14	-0.17	0.36	0.84	-0.17	-0.46	0.64
Time since surgery	282.68	0.00	0.00	1.00	0.21	1.15	0.25
Executive function	915.39	-0.48	0.32	0.62	-0.48	-1.50	0.13

Table 9 continued

Model 19[d]							
Intercept, High activity	1230.50	-0.68	0.14	0.51	-0.68	-4.75	<0.01*
Intercept, Moderate activity	1543.40	1.31	0.16	3.71	1.31	8.12	<0.01*
Age	712.38	-0.04	0.02	0.96	-0.30	-2.17	0.03*
Education	622.89	-0.03	0.06	0.97	-0.07	-0.53	0.60
Fatigue	886.43	0.04	0.03	1.04	0.23	1.34	0.18
Depression	966.54	-0.05	0.03	0.95	-0.29	-1.72	0.09†
Anxiety	1198.50	0.02	0.03	1.02	0.11	0.71	0.48
Physical function	836.59	0.02	0.02	1.02	0.18	1.23	0.22
Executive function	1967.00	0.18	0.36	1.20	0.18	0.51	0.61

Note. BCS = Breast cancer survivor; SE = standard error.

[a]Model 17: Hypothesis 1 tested in the whole sample – effect of executive function residualized change from baseline to 12 months on categorical (low, moderate, high) physical activity at 24 months.

[b]Breast cancer survivor compared to control group.

[c]Model 18: Hypothesis 1 tested in BCS – effect of executive function residualized change from baseline to 12 months on categorical (low, moderate, high) physical activity at 24 months.

[d]Model 19: Hypothesis 1 tested in controls – effect of executive function residualized change from baseline to 12 months on categorical (low, moderate, high) physical activity at 24 months.

†$p<0.10$.

*$p<0.05$.

Table 10

Regression Parameter Estimates for Aim 1, Hypothesis 2 with Categorical Physical Activity

	df	B	SE	*β*	*t*	*p*
Model 20[a]						
Intercept	1849.80	-0.08	0.04	-0.17	-1.83	0.07†
BCS[b]	1006.60	0.01	0.05	0.03	0.30	0.77
Age	1244.00	-0.01	0.00	-0.15	-3.21	<0.01*
Education	919.10	0.02	0.01	0.10	2.17	0.03*
Fatigue	983.87	0.01	0.00	0.08	1.31	0.19
Depression	931.87	0.00	0.00	0.04	0.55	0.58
Anxiety	954.12	0.00	0.00	-0.07	-1.17	0.24
Physical function	883.81	-0.01	0.00	-0.10	-1.91	0.06†
Moderate physical activity	1449.10	0.08	0.06	0.18	1.51	0.13
High physical activity	866.26	0.13	0.06	0.28	2.10	0.04*
Moderate physical activity by BCS[b]	951.77	-0.03	0.06	-0.05	-0.45	0.65
High physical activity by BCS[b]	888.77	-0.04	0.06	-0.09	-0.70	0.48
Model 21[c]						
Intercept	885.03	-0.02	0.07	-0.02	-0.21	0.83
Age	993.06	-0.01	0.01	-0.07	-1.78	0.08†
Education	595.60	0.02	0.02	0.04	1.02	0.31
Fatigue	432.61	0.00	0.01	0.03	0.65	0.52
Depression	567.80	0.01	0.01	0.04	0.66	0.51
Anxiety	1001.00	-0.01	0.01	-0.07	-1.50	0.13
Physical function	964.23	-0.01	0.01	-0.04	-1.14	0.26
Received chemotherapy	711.44	-0.11	0.09	-0.11	-1.24	0.22
Time since surgery	303.12	0.00	0.00	-0.07	-1.50	0.13
Moderate physical activity	772.42	0.05	0.09	0.05	0.51	0.61
High physical activity	501.07	0.09	0.11	0.09	0.83	0.40

Table 10 continued

Model 22[d]						
Intercept	1713.60	-0.12	0.06	-0.12	-1.95	0.05†
Age	775.56	-0.01	0.00	-0.07	-2.22	0.03*
Education	723.22	0.02	0.01	0.05	1.63	0.10
Fatigue	1990.90	0.01	0.01	0.05	1.55	0.12
Depression	828.74	0.00	0.01	0.01	0.29	0.77
Anxiety	1232.60	0.00	0.01	0.01	0.23	0.81
Physical function	710.65	-0.01	0.00	-0.06	-1.91	0.06†
Moderate physical activity	1236.10	0.13	0.07	0.13	1.68	0.09†
High physical activity	1377.70	0.18	0.08	0.18	2.27	0.02*

Note. BCS = Breast cancer survivor; SE = standard error.

[a]Model 20: Hypothesis 2 tested in the whole sample – effect of categorical physical activity (low, moderate, high) at 12 months on executive function residualized change from 12 to 24 months.

[b]Breast cancer survivor compared to control group.

[c]Model 21: Hypothesis 2 tested in BCS – effect of categorical physical activity (low, moderate, high) at 12 months on executive function residualized change from 12 to 24 months.

[d]Model 22: Hypothesis 2 tested in controls – effect of categorical physical activity (low, moderate, high) at 12 months on executive function residualized change from 12 to 24 months.

†$p<0.10$.

*$p<0.05$.

Table 11

Parameter Estimates for Grouped ARCL Model

	Baseline	12 Month		24 Month	
Group	EF	EF	PA	EF	PA
Predictor	*β (SE)*	*β (SE)*	*β (SE)*	*β (SE)*	*β (SE)*
BCS					
Baseline EF	*n/a*	0.84 (0.02)**	0.04 (0.06)	*n/a*	*n/a*
Baseline PA	0.07 (0.05)	-0.08 (0.04)†	0.49 (0.05)**	*n/a*	*n/a*
12 Month EF	*n/a*	*n/a*	*n/a*	0.29 (0.07)**	0.04 (0.07)
12 Month PA	*n/a*	0.06 (0.07)	*n/a*	0.04 (0.04)	0.55 (0.06)**
24 Month EF	0.76 (0.04)**	*n/a*	*n/a*	*n/a*	*n/a*
24 Month PA	*n/a*	*n/a*	*n/a*	-0.09 (0.05)†	*n/a*
Control					
Baseline EF	*n/a*	0.83 (0.02)**	0.02 (0.05)	*n/a*	*n/a*
Baseline PA	0.09 (0.05)†	0.04 (0.03)	0.43 (0.05)**	*n/a*	*n/a*
12 Month EF	*n/a*	*n/a*	*n/a*	0.48 (0.06)**	0.01 (0.05)
12 Month PA	*n/a*	0.00 (0.06)	*n/a*	0.09 (0.04)*	0.63 (0.04)**
24 Month EF	0.56 (0.07)**	*n/a*	*n/a*	*n/a*	*n/a*
24 Month PA	*n/a*	*n/a*	*n/a*	-0.04 (0.06)	*n/a*

Note. ARCL = autoregressive cross-lagged; EF = executive function; PA = physical activity; SE = standard error; BCS = Breast cancer survivor; n/a = not applicable.

†$p < 0.10$.

*$p < 0.05$.

**$p < 0.01$.

Table 12

Parameter Estimates for Grouped ARCL Model with Covariates

	Baseline		12 Month		24 Month	
Group	EF	PA	EF	PA	EF	PA
Predictor	*β (SE)*	*β (SE)*	*β (SE)*	*β (SE)*	*β (SE)*	*β (SE)*
BCS						
Baseline EF	*n/a*	*n/a*	0.79 (0.04)**	0.03 (0.11)	*n/a*	*n/a*
Baseline PA	0.01 (0.03)	*n/a*	-0.08 (0.03)**	0.47 (0.07)**	*n/a*	*n/a*
12 Month EF	*n/a*	*n/a*	*n/a*	*n/a*	0.29 (0.07)**	-0.10 (0.12)
12 Month PA	*n/a*	*n/a*	0.02 (0.03)	*n/a*	0.02 (0.03)	0.52 (0.07)**
24 Month EF	0.28 (0.04)**	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
24 Month PA	*n/a*	*n/a*	*n/a*	*n/a*	-0.06 (0.03)†	*n/a*
Age	-0.04 (0.01)**	-0.02 (0.01)	-0.02 (0.01)**	0.00 (0.01)	-0.04 (0.01)**	-0.02 (0.01)
Education	0.08 (0.02)**	0.00 (0.03)	0.01 (0.01)	-0.01 (0.03)	0.06 (0.02)**	0.03 (0.04)
Fatigue	0.00 (0.01)	0.02 (0.01)†	0.00 (0.01)	0.01 (0.01)	0.00 (0.01)	0.01 (0.01)
Depression	-0.01 (0.01)	-0.02 (0.01)	0.00 (0.01)	0.01 (0.02)	0.00 (0.01)	0.01 (0.02)
Anxiety	0.00 (0.01)	0.02 (0.01)†	0.00 (0.01)	0.00 (0.01)	-0.01 (0.01)†	0.01 (0.02)
Physical function	0.02 (0.01)*	0.04 (0.01)**	0.01 (0.00)**	0.01 (0.01)	0.00 (0.01)	0.02 (0.01)*
Control						
Baseline EF	*n/a*	*n/a*	0.81 (0.04)**	0.08 (0.09)	*n/a*	*n/a*
Baseline PA	0.03 (0.03)	*n/a*	0.01 (0.02)	0.38 (0.05)**	*n/a*	*n/a*
12 Month EF	*n/a*	*n/a*	*n/a*	*n/a*	0.46 (0.07)**	-0.06 (0.10)
12 Month PA	*n/a*	*n/a*	-0.01 (0.02)	*n/a*	0.05 (0.03)*	0.69 (0.06)**
24 Month EF	0.12 (0.02)**	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
24 Month PA	*n/a*	*n/a*	*n/a*	*n/a*	-0.02 (0.02)	*n/a*
Age	-0.03 (0.01)**	-0.02 (0.01)*	-0.01 (0.00)†	0.00 (0.01)	-0.02 (0.01)**	-0.01 (0.01)
Education	0.05 (0.01)**	0.05 (0.03)†	0.00 (0.01)	-0.04 (0.03)	0.04 (0.01)**	0.02 (0.03)
Fatigue	-0.01 (0.01)	0.04 (0.01)*	0.00 (0.00)	0.00 (0.01)	0.01 (0.01)	0.01 (0.01)
Depression	0.00 (0.01)	0.01 (0.01)	-0.01 (0.01)	-0.03 (0.01)*	0.00 (0.01)	-0.01 (0.02)
Anxiety	-0.02 (0.01)	-0.01 (0.01)	0.01 (0.00)	0.02 (0.01)	0.00 (0.01)	0.00 (0.01)
Physical function	0.00 (0.01)	0.02 (0.01)†	0.01 (0.00)†	0.01 (0.01)	-0.01 (0.00)	0.00 (0.01)

Note. ARCL = autoregressive cross-lagged; EF = executive function; PA = physical activity; SE = standard error; BCS = Breast cancer survivor; n/a = not applicable.

†$p < 0.10$.

*$p < 0.05$.

**$p < 0.01$.

APPENDIX B. FIGURES

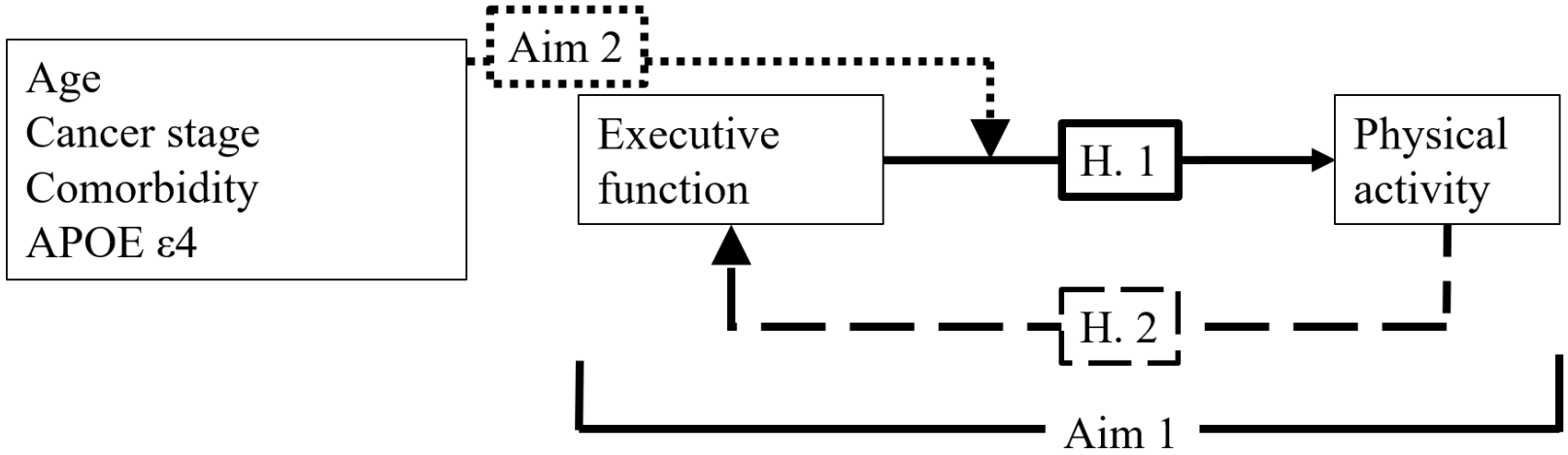

Figure 1. Theoretical framework for the aims of the current project.

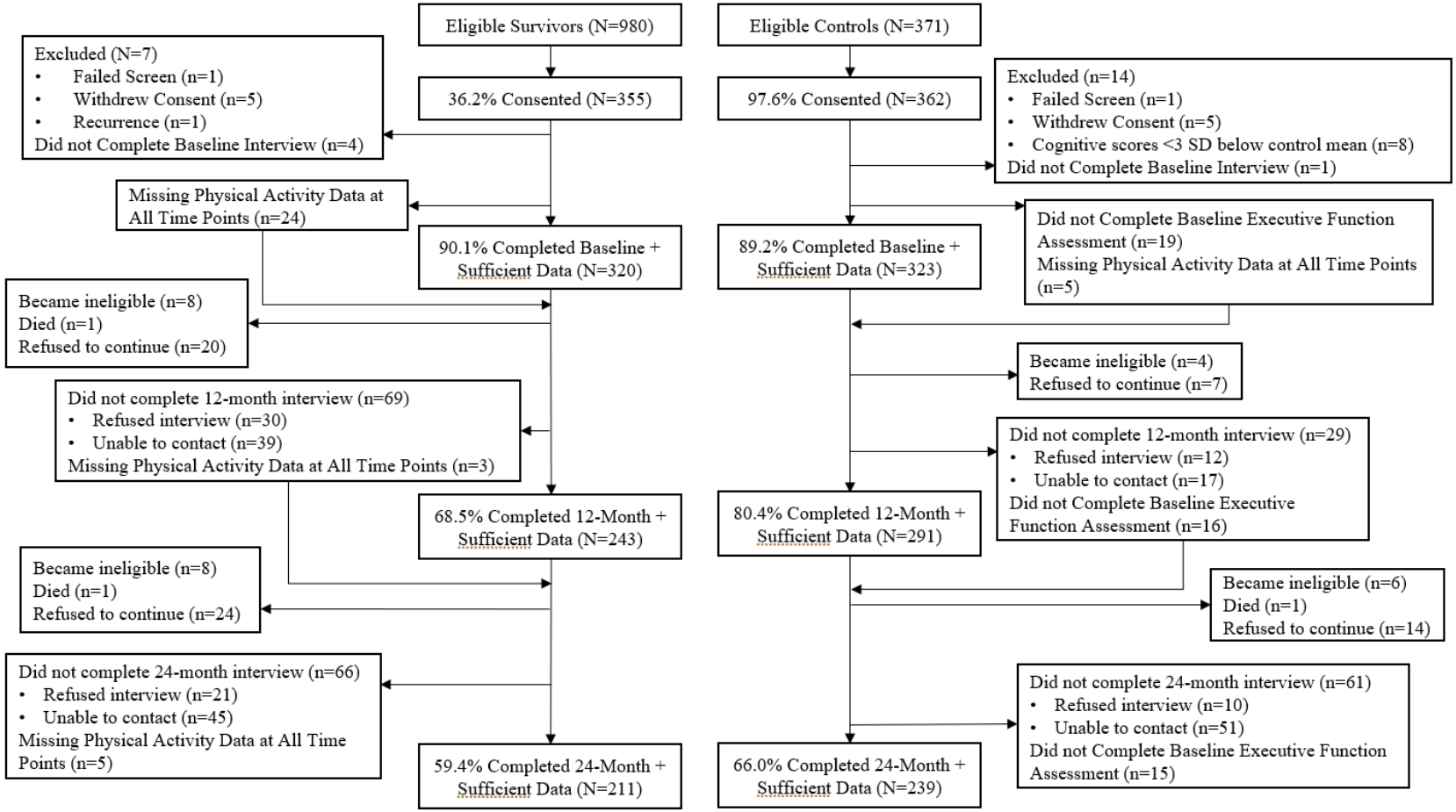

Figure 2. Study flowchart. Unless they refused to continue study participation, participants who did not complete or partially completed an assessment remained eligible to complete the next assessment.

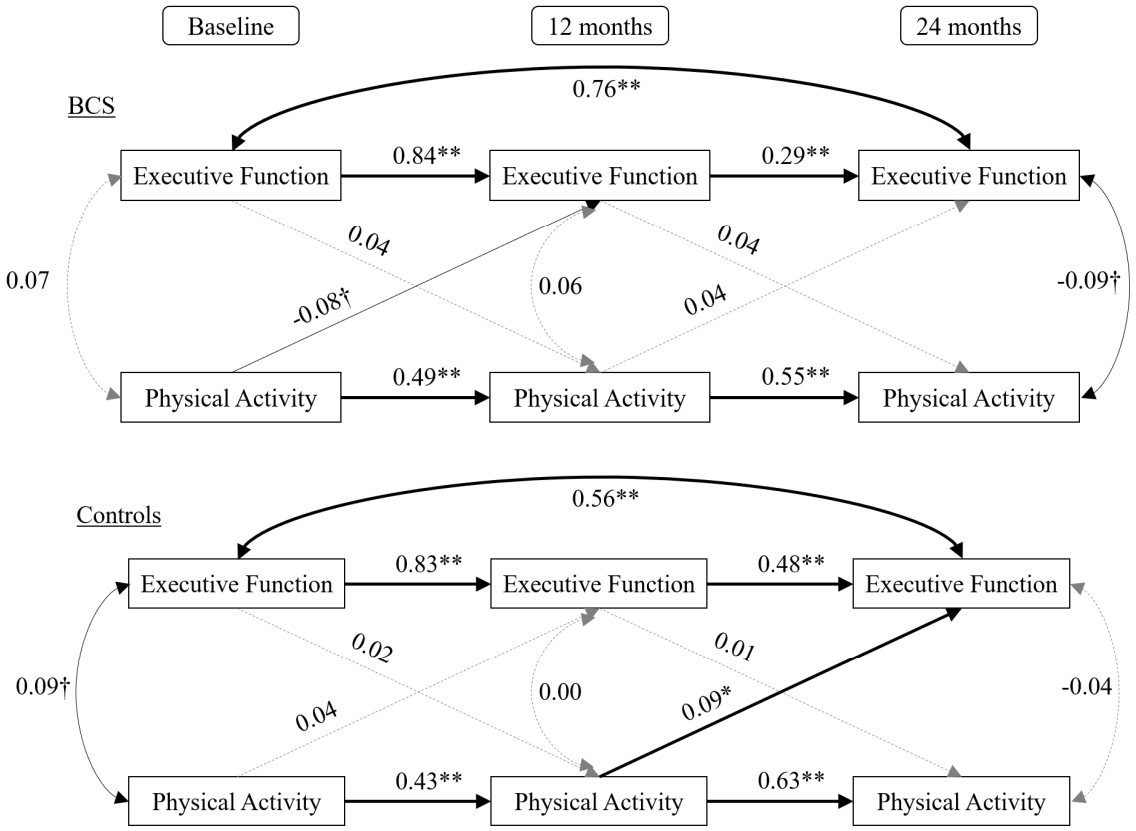

Figure 3. Auto-regressive cross-lagged model, grouped into breast cancer survivors (BCS) and controls. Coefficients are standardized.

†$p < 0.10$.
*$p < 0.05$.
**$p < 0.01$.

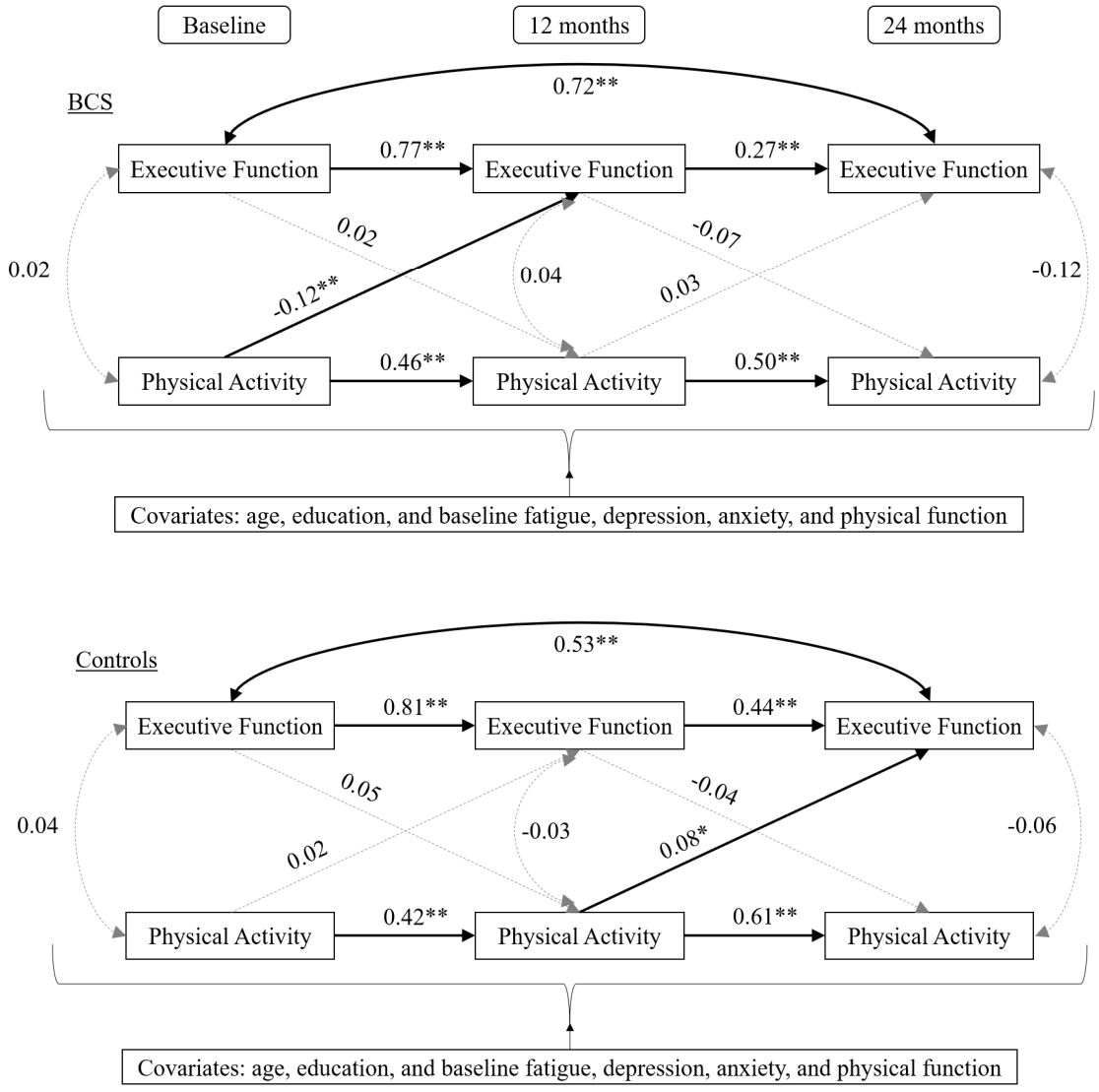

Figure 4. Auto-regressive cross-lagged model, grouped into breast cancer survivors (BCS) and controls. Covariates included. Coefficients are standardized.

†$p < 0.10$.
*$p < 0.05$.
**$p < 0.01$.

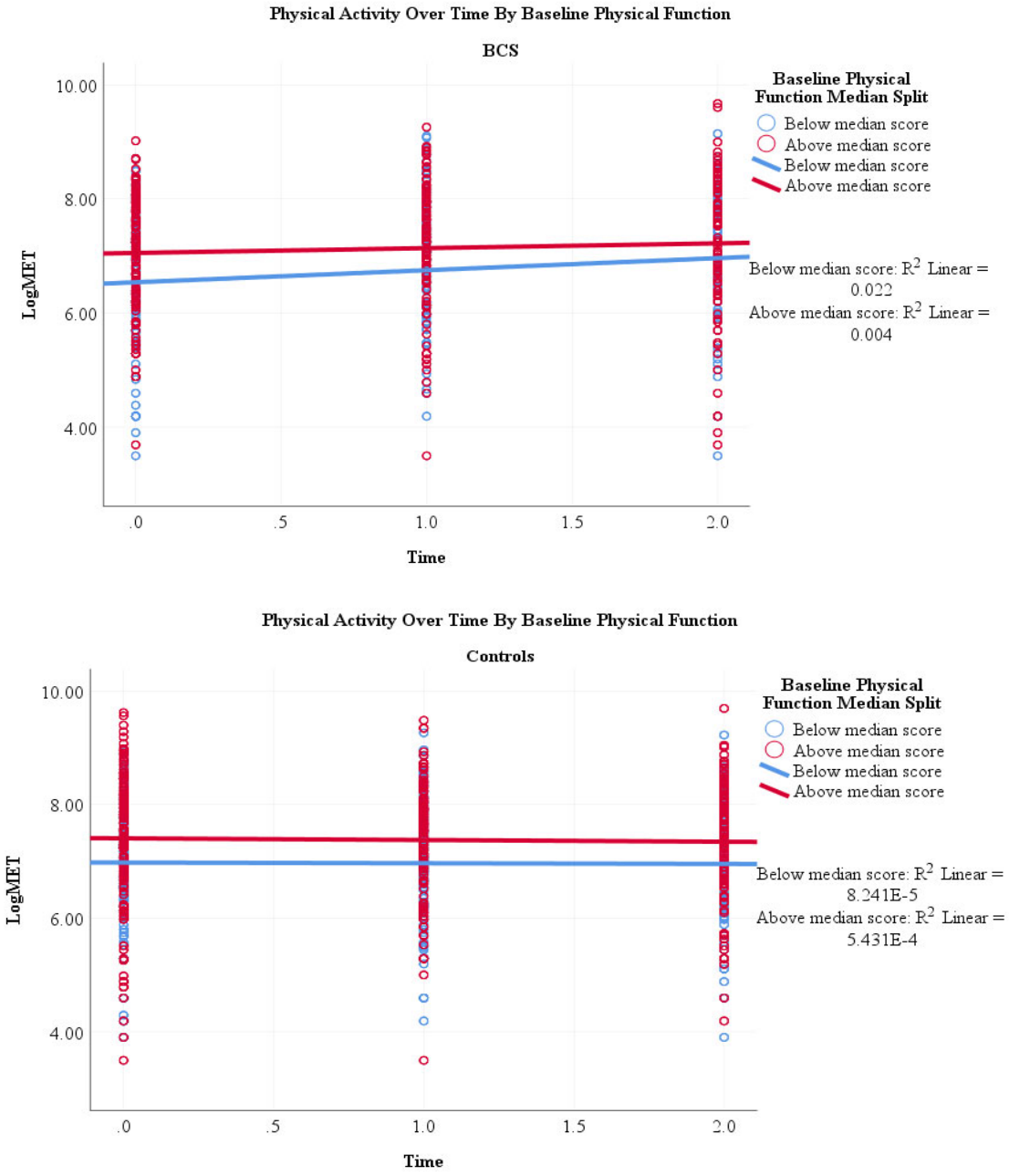

Figure 5. Scatterplots with regression lines for physical activity over time by baseline physical function. Time is in years. BCS = breast cancer survivors. LogMET = Log_e of Metabolic Equivalent of Task (MET) minutes per week.

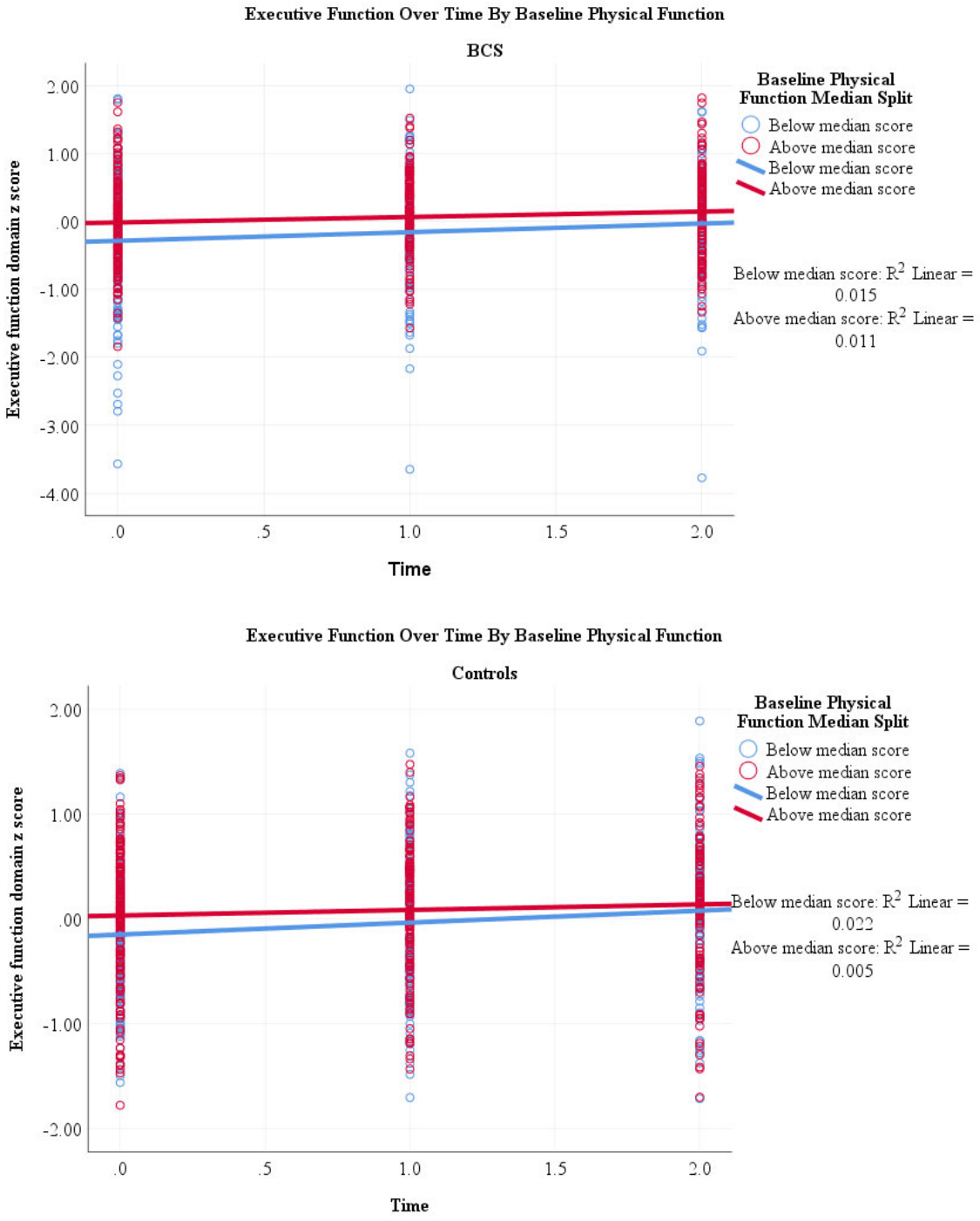

Figure 6. Scatterplots with regression lines for executive function over time by baseline physical function. Time is in years. BCS = breast cancer survivors.

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VITA

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Education

- **Ph.D.**, *Clinical Psychology* (APA Accredited), Track: Clinical Health Psychology, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana
- **M.S.**, *Clinical Psychology,* Indiana University-Purdue University Indianapolis, Indianapolis, Indiana
- **B.S.**, *Psychology*, University of Utah, Salt Lake City, Utah

Research Fellowships

- National Cancer Institute F31 Ruth L. Kirschstein National Service Award. *A prospective examination of change in executive function and physical activity in older breast cancer survivors.* F31CA220964. Danielle Tometich, M.S. (PI). Role: Predoctoral Fellow. Primary sponsor: Catherine Mosher, Ph.D., Co-sponsor: Andrew Saykin, Psy.D. Contributors: Jeanne Mandelblatt, MD, Bryan Schneider, MD, Joanne Daggy, Ph.D.
- National Cancer Institute T32 Award. *Interdisciplinary Training in Behavioral Oncology.* T32CA117865. Victoria L. Champion, Ph.D., RN, FAAN (PI). Role: Predoctoral Fellow. Primary mentor: Andrew Saykin, Psy.D. Secondary mentors: Catherine E. Mosher, Ph.D., Brenna McDonald, Psy.D., and Victoria Champion, Ph.D.
- National Cancer Institute R25 Award. *Training in Research for Behavioral Oncology and Cancer Control.* R25CA117865. Victoria L. Champion, Ph.D., RN, FAAN (PI). Role: Predoctoral Fellow. Primary mentor: Andrew Saykin, Psy.D. Secondary mentors: Catherine E. Mosher, Ph.D., Brenna McDonald, Psy.D., and Victoria Champion, Ph.D.

Honors and Awards

- Clinical Award from the IUPUI Clinical Psychology PhD program
- IUPUI Graduate Office Travel Fellowship Award
- IUPUI Graduate & Professional Education Grant
- IUPUI School of Science Graduate Student Council Travel Award
- Graduate Student Abstract Award for Behavioral and Population Science/Epidemiology Research

- IUPUI Clinical Psychology Program Research Funding Award
- IUPUI Elite 50 Graduate Student award for service to the campus and community
- IUPUI Clinical Psychology Program Research Funding Award
- 1st Place Graduate Student Abstract Award for Outstanding Research in Pain or Palliative Care – Society of Behavioral Medicine Pain SIG
- University of Utah Undergraduate Research Opportunities Program Assistantship
- University of Utah Dean's List, all semesters

Publications

- Carroll, J. E., Small, B. J., **Tometich, D.,** Zhai, W., Zhou, X., Luta, G. … Mandelblatt, J. (in press). Sleep disturbances and neurocognitive outcomes in older breast cancer patients: Interaction with genotype. *Cancer.*
- Secinti, E., **Tometich, D.,** Johns, S. A., & Mosher, C. E. (2019). The relationship between acceptance of cancer and distress: A meta-analytic review. *Clinical Psychology Review, 71*, 27-38. doi: 10.1016/j.cpr.2019.05.001
- **Tometich, D.,** Small, B., Carroll, J., Zhai, W., Luta, G., Zhou, X., . . . Mandelblatt, J. (2019). Pre-treatment psychoneurological symptoms and their association with longitudinal cognitive function and quality of life in older breast cancer survivors. *Journal of Pain and Symptom Management, 57*, 596-606. doi: 10.1016/j.jpainsymman.2018.11.015
- Mandelblatt, J., Small, B., Luta, G., Hurria, A., Jim, H., McDonald, B., . . . **Tometich, D.** (22nd), . . . Ahles, T. (2018). Cancer-related cognitive outcomes among older breast cancer survivors in the Thinking and Living with Cancer (TLC) study. *Journal of Clinical Oncology, 36*, 3211-3222. doi: 10.1200/JCO.18.00140
- **Tometich, D.,** Mosher, C., Hirsh, A., Rand, K., Johns, S., Matthias, M., . . . Miller, K. (2018). Metastatic breast cancer patients' expectations and priorities for symptom improvement. *Supportive Care in Cancer, 26*, 3781-3788. doi: 10.1007/s00520-018-4244-8.
- Mosher, C., Daily, S., **Tometich, D.,** Matthias, M., Hirsh, A., Johns, S., . . . Miller, K. (2018). Factors underlying metastatic breast cancer patients' perceptions of symptom importance: A qualitative analysis. *European Journal of Cancer Care, 27*, 1-6. doi: 10.1111/ecc.12540

- **Tometich, D.,** Mosher, C., Winger, J., Badr, H., Snyder, D., Sloane, R., & Demark-Wahnefried, W. (2017). Effects of diet and exercise on weight-related outcomes for breast cancer survivors and their adult daughters: An analysis of the DAMES trial. *Supportive Care in Cancer, 25,* 2559-2568. doi: 10.1007/s00520-017-3665-0
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- Duff, K., **Tometich, D.,** & Dennett, K. (2015). The modified Telephone Interview for Cognitive Status is more predictive of memory abilities than the Mini-Mental State Examination. *Journal of Geriatric Psychiatry and Neurology*, *28,* 193-197. doi: 10.1177/0891988715573532
- Garrido-Laguna, I., **Tometich, D.,** Hu, N., Ying, J., Geiersbach, K., Whisenant, J., . . . Sharma, S. (2015). N of 1 case reports of exceptional responders accrued from pancreatic cancer patients enrolled in first-in-man studies from 2002 through 2012. *Oncoscience, 2,* 285-293.
- Dennett, K., **Tometich, D.,** & Duff, K. (2013). Demographic corrections for the modified Telephone Interview for Cognitive Status. *The Clinical Neuropsychologist*, *27*, 1121-1130. doi: 10.1080/13854046.2013.809794
- Duff, K., Callister, C., Dennett, K., & **Tometich, D.** (2012). Practice effects: A unique cognitive variable. *The Clinical Neuropsychologist*, *26*, 1117-1127. doi: 10.1080/13854046.2012.722685
- Duff, K., Dennett, K., & **Tometich, D.** (2012). Predicting current memory with the modified Telephone Interview for Cognitive Status. *The American Journal for Alzheimer's Disease and Other Dementias*, *27*, 175-179. doi: 10.1177/1533317512442997

Selected Presentations

- **Tometich, D.,** McDonald, B. C., Saykin, A., West, J., Conroy, S., Moser, L. R., … & Champion, V. (2019, March). Proinflammatory cytokines in breast cancer survivors and controls: Associations with physical activity and cognition. *Annals of Behavioral Medicine, 53* (Supp 1), S7. Poster presentation at the Society of Behavioral Medicine in Washington, D.C.

- Secinti, E., **Tometich, D. B.,** Johns, S. A., Stutz, P. V., & Mosher, C. E. (2019, March). Symptom experiences in advanced stage cancer: Relationships to Acceptance and Commitment Therapy constructs. *Annals of Behavioral Medicine, 53* (Supp 1), S511. Oral presentation at the Society of Behavioral Medicine in Washington, D.C.
- Chinh, K., **Tometich, D. B.,** Johns, S. A., Stutz, P. V., & Mosher, C. E. (2019, March). Symptom experiences in post-treatment cancer survivors: Relationships to mindfulness and acceptance-based constructs. *Annals of Behavioral Medicine, 53* (Supp 1), S512. Oral presentation at the Society of Behavioral Medicine in Washington, D.C.
- **Tometich, D.,** Small, B., Carroll, J. E., Zhai, W., Luta, G., Zhou, X., … Mandelblatt, J. (2018, April). Pre-treatment symptom clusters and their association with longitudinal cognitive function in older breast cancer survivors. Poster presentation at the International Cancer and Cognition Task Force Conference in Sydney, Australia.
- Carroll, J., Small, B., Zhai, W., Zhou, X., Luta, G., **Tometich, D. (presenter)**, … Mandelblatt, J. (2018, April). Sleep disturbances and cognitive decline in older cancer patients: Interaction with *APOE* e4 and *BDNF* genotype. Oral presentation at the International Cancer and Cognition Task Force Conference in Sydney, Australia.
- Small, B., Jim, H., Ahles, T., Luta, G., McDonald, B., Nudelman, K., **Tometich, D.,** & Mandelblatt, J. (2018, April). Leisure activities and cognitive performance among older breast cancer patients and non-cancer controls. *Annals of Behavioral Medicine, 52* (Supp 1), S474. Oral presentation at the Society of Behavioral Medicine in New Orleans, Louisiana.
- **Tometich, D.,** Mosher, C., Rand, K., & Hirsh, A. (2017, April). Symptom clusters in metastatic breast cancer patients. *Annals of Behavioral Medicine, 51* (Supp 1), S2439. Poster presentation at the Society of Behavioral Medicine in San Diego, California.
- **Tometich, D.,** Mosher, C., Rand, K., & Hirsh, A. (2016, April). Symptom importance in metastatic breast cancer patients. *Annals of Behavioral Medicine, 50* (Supp 1), S6. Poster and oral presentation at the Society of Behavioral Medicine in Washington, D.C.
- Reese, Z. L., **Tometich, D.,** Patel, S. B., Sharma, S., & Garrido-Laguna, I. (2015, January). Exceptional responses in patients with upper gastrointestinal malignancies enrolled in first-in-man studies: 2002-2012. *ASCO Meeting Abstracts, 33*, 311. Poster presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco, California.

- Patel, S. B., **Tometich, D.,** Reese, Z. L., Sharma, S., & Garrido-Laguna, I. (2015, January). Exceptional responses in patients with metastatic colorectal cancer enrolled in first-in-man studies from 2002 through 2012. *ASCO Meeting Abstracts, 33*, 687. Poster presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco, California.