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Impact of increasing physical activity on cognitive functioning in breast cancer survivors: Rationale and study design of Memory & Motion

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Abstract

Introduction—Many breast cancer survivors experiences problems with cognitive functioning that can persist years after treatment. Increasing physical activity has been shown to improve cognitive functioning in healthy and cognitively impaired adults, but has not yet been tested in cancer survivors. The primary aim of this randomized controlled trial is to examine the effects of a 3-month physical activity intervention compared to a waitlist control arm on neuropsychological outcomes and subjective cognitive concerns in breast cancer survivors.

Methods—Eighty sedentary breast cancer survivors, self-reporting difficulties with cognition, will be randomized into an Exercise arm or Control arm. The Exercise arm includes an activity tracker (i.e., a Fitbit), phone calls, plus tailored and non-tailored email content. The Control arm will receive emails on women's health topics on the same schedule as the Exercise arm. Assessments conducted at baseline and 3 months include: neuropsychological testing, cognitive concerns and other aspects of quality of life, and 7 days of a hip-worn accelerometer. Participants will also provide fasting blood draws to assess brain-derived neurotrophic factor, Insulin-like growth factor 1, insulin resistance, and C-reactive protein. Primary and secondary outcomes are changes in neuropsychological testing and cognitive concerns. Biomarkers will be examined to further understand the underlying relationship between physical activity and cognition.

Conclusion—The Memory & Motion study is designed to test whether increasing physical activity can improve cognitive functioning in breast cancer survivors. Results from this study

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could be used to guide development of interventions to improve cognitive functioning in breast cancer survivors.

Keywords

breast cancer; cognitive functioning; physical activity; randomized controlled trial

INTRODUCTION

Changes in cognitive functioning are an important issue for breast cancer survivors given that up to 75% experience impairments that can last for many years after the end of treatment.¹⁻⁴ One potential risk factor for impairment is low levels of physical activity: 28 to 43% of women diagnosed with breast cancer lead sedentary lives,^{5,6} and lack of physical activity has been associated with poor cognitive outcomes in many studies of non-cancer populations.⁷⁻¹³ Preliminary research suggests that in cancer patients, higher levels of physical activity are related to better outcomes on neuropsychological tests.¹⁴⁻¹⁷ To our knowledge, there are no published data on randomized clinical trials testing whether increasing physical activity can improve cognitive functioning in cancer survivors.

Many cancer survivors also self-report difficulties with cognitive functioning that are not evident on neuropsychological tests.^{18,19} These self-reported concerns are as important as neuropsychological testing because they reflect difficulties patients perceive in their daily lives.^{4,18,20} Cognitive concerns are often associated with fatigue, anxiety, and depression.¹⁸ Physical activity in cancer patients can decrease fatigue²¹⁻²⁴, anxiety²³, and depression^{21,23,24}; suggesting that physical activity could improve subjective cognitive concerns as well. Determining if a physical activity intervention can improve cognitive concerns is an important step in improving breast cancer survivors' quality of life.

Little is known about the underlying biological mechanisms linking physical activity with cognition in cancer survivors. Animal models and human research indicate several pathways through which physical activity may enhance brain functioning.^{7,25-28} One key pathway is through Brain-derived neurotrophic factor (BDNF), a biomarker of brain health.^{27,29} BDNF is regulated by insulin and cytokines and therefore is likely part of a central mechanism through which physical activity integrates with elements of metabolism to impact cognition. Thus, measures of metabolism and inflammation have potential to be important mechanisms as well.

The current study will examine the effects of a 3-month randomized controlled trial of a physical activity intervention on cognitive functioning in breast cancer survivors. Eighty sedentary breast cancer survivors at baseline and 3 months will wear an accelerometer for 7 days, complete neuropsychological testing and measures of cognitive concerns and quality of life, and provide a fasting blood draw. The primary and secondary aims of this pilot study are to explore the effects of a physical activity intervention on changes in neuropsychological testing and subjective cognitive concerns, in comparison to a control arm. The tertiary aim will explore whether changes in biological measures completely or partially explain the effect of the physical activity intervention on changes in neuropsychological tests and cognitive concerns. It is hypothesized that breast cancer

survivors who receive the physical activity intervention will show improved neuropsychological testing and decreased cognitive concerns compared to women in the control arm. In association with this result, it is expected that the physical activity intervention will increase circulating concentrations of BDNF, decrease inflammatory factors, and improve insulin resistance; and that these markers will mediate the relationship between physical activity and cognitive outcomes. This paper describes the design and rationale of this randomized controlled trial.

METHODS

Overview of Study Design

The Memory & Motion study will examine the effects of a 3-month physical activity intervention on changes in neuropsychological testing and subjective cognitive concerns in breast cancer survivors. Eighty participants will be randomly assigned to receive (1) an individually tailored, theory-based physical activity intervention (Tailored Exercise Intervention), or (2) the comparison group (Waitlist Wellness Contact Control Condition). The UCSD institutional review board approved all study procedures and all participants will provide written informed consent.

Eligibility Criteria—Eligible participants must be female breast cancer survivors, age 21–85, who were diagnosed less than 5 years prior to study enrollment and meet the following inclusion/exclusion criteria.

Inclusion criteria: (1) not scheduled for or currently undergoing chemotherapy or radiotherapy, (2) sedentary, defined as self-reporting that they engaging in less than 60 minutes of moderate to vigorous physical activity each week, (3) accessible geographically, defined as willingness to travel to La Jolla, CA, and by telephone, (4) have access to the internet, and (5) self-report on a one item question that they are experiencing “foggy” or changes in their memory, thinking, or concentration.

Exclusion criteria: (1) history of coronary heart disease, diabetes, stroke, orthopedic conditions that limit mobility, or any other serious medical condition that could make it potentially unsafe to be in an unsupervised physical activity intervention, (2) other primary or recurrent invasive cancer within the last 10 years (other than nonmelanoma skin cancer or carcinoma of the cervix in situ), (3) unable to commit to a 3-month intervention schedule, and (4) any condition that, in the investigators’ judgment, would contraindicate increased physical activity or otherwise interfere with participation in the study.

Recruitment—The primary method of recruitment will be through registry lists of breast cancer survivors who have agreed to be contacted for research studies at the UC San Diego Moores Cancer Center. Women provide consent to be contacted for research through multiple avenues: women seen in the Cancer Center’s mammography clinic, physician referral, and previously screened for other research studies at the Cancer Center. Additional recruitment methods will include referrals from the breast cancer oncologists and nurse practitioners at the UC San Diego Moores Cancer Center and posting of flyers throughout

the Cancer Center. We also plan to use tumor registry lists to mail letters to breast cancer survivors.

Pre-Randomization—Potential participants are first screened over the phone to describe the study and determine eligibility. All interested and eligible women are scheduled for an in-person visit. At this visit, signed informed consent is obtained, a fasting blood draw is taken, height and weight are measured and participants complete a battery of neuropsychological testing, cognitive concerns questionnaires, and other quality of life measures (see measures section for details). At the end of this visit participants are given an accelerometer to wear for 7 days and bring back to the randomization visit.

Randomization—Randomization is stratified by having had chemotherapy or not using a permuted block randomization scheme with random-sized blocks of size 6 or 8. A computerized randomization scheme has been created by the Moores Cancer Centers' Biostatistics Shared Resource. After randomization, participants in both groups review the expectations and requirements of their group assignment (See Treatment Conditions for more detail).

3 Month Measurement visit—Participants are asked to wear an accelerometer during the week prior to the end of study visit. At this visit, participants repeat the same measures that were completed at the baseline measurement visit including neuropsychological testing, blood draw, anthropometric measures, and a battery of psychosocial measures. Participants will receive \$50 and their Fitbit to keep (control arm will receive a Fitbit at this final visit) for completing the 3 month measurement visit.

TREATMENT CONDITIONS

Tailored Exercise Intervention

Parts of this intervention have been used to successfully increase physical activity in a variety of populations including cancer survivors.^{30–34} A new component, not used in the previous studies, is the use of a Fitbit One. The Fitbit is an accelerometer-based activity meter that provides real-time feedback of number of steps taken and minutes of moderate intensity activity. The Fitbit is a tiny (0.5" × 0.5" × 1.5") physical activity tracker that can be clipped to the waistband on pants, center of the bra, or placed in the front pants pocket. The Fitbit device displays the wearer's accumulated daily steps, mileage, and floors climbed. The Fitbit wirelessly uploads data to a website that provides graphical visualizations of daily activity patterns. To promote accountability, participants are informed that study staff will be able to see all the data collected by the Fitbit and that they will receive feedback on the Fitbit data during the scheduled phone calls.

Participants in the exercise arm are first given a Fitbit One and shown how to use the Fitbit and Fitbit.com. Next they are taken on a 10 minute walk around the UC San Diego campus at 65 to 75% of their maximum heart rate to demonstrate the level of exertion needed to be at moderate intensity. Participants are also given a suggested pace per mile they should aim for to be at moderate intensity based on the 10 minute walk. Using motivational interviewing techniques, a starting goal with a specific plan for meeting that goal is set. A

discussion is also had about how to gradually increase the amount of exercise over time so that they can meet the study's goal of engaging in at least 150 minutes of moderate to vigorous physical activity per week.³⁵ Two phone calls are scheduled at the 2 week point and the 6 week point to review progress and revise goals as needed, but all participants are given the option of additional calls if needed.

To further support participants' efforts to increase their activity, they receive an email every three days for 3 months. These emails target components of Social Cognitive Theory³⁶ with content including: 1) tracking physical activity; 2) how to get social support for being active; 3) online resources including how to find places to be active and exercise videos; and 4) tips on how to change outcome expectations and use your own thoughts to help motivate you to exercise. They also receive monthly email prompts to complete online exercise surveys that assess current motivational readiness for physical activity and other Transtheoretical Model (TTM)^{37,38} and Social Cognitive³⁶ constructs (e.g., process of change, self-efficacy). The online surveys consist of 4 questionnaires: 1) Stages of Change for Physical Activity³⁹; 2) Processes of Change for Physical Activity⁴⁰; 3) Decisional Balance for Physical Activity⁴¹; 4) Self-Efficacy for Physical Activity³⁹. The information gathered by these surveys is used by a computerized expert system to generate individually tailored feedback reports.³⁰⁻³⁴ The tailored reports provide feedback on: 1) how the participant compares to profiles of individuals who have successfully adopted and maintained physical activity (normative feedback); and 2) following the month 1 assessment, feedback regarding progress made on specific topic areas and changes in minutes of physical activity participation since the individual's prior assessment (progress feedback). The tailored feedback reports are available immediately after completing the questionnaire.

Adherence to the Intervention—Adherence to the intervention will be assessed by data collected from the Fitbit on minutes of moderate intensity or greater activity. The data are wirelessly uploaded to the user's personal account and can be downloaded by our research team through a database called Fitabase (Small Steps Lab). Through Fitabase we can download minute by minute activity data including metabolic equivalents (METs), intensity category, and steps. From the Fitbit data we will have objective information on level of adherence throughout the 3 month intervention.

Waitlist Wellness Contact Control Condition—Participants in the control arm will receive emails on the same schedule as the intervention group. Emails consist of a variety of women's health topics including healthy eating, stress reduction, and general brain health. Much of the content comes from the U.S. Department of Health and Human Services' Office on Women's Health's book "The Healthy Woman: A complete guide for all ages" (<http://www.womenshealth.gov/publications/our-publications/the-healthy-woman>). At the final visit, participants in the wellness arm are given a Fitbit and provided with the exercise intervention described above.

DESIGN CONSIDERATIONS

Several considerations were made when designing the current study. We chose a waitlist control arm because increasing exercise has many known benefits for breast cancer

survivors and felt it was important to support increasing activity in all participants. In addition, having a waitlist group rather than a standard control group was appealing the clinicians and we expect will have higher appeal for participants than a standard control which will aid in recruitment.

Most of the research on cognitive functioning and breast cancer survivors has been limited to those who received chemotherapy. However, there is evidence that cognitive impairments do not only occur in those who received chemotherapy, with several studies reporting impairments in women with breast cancer prior to treatment.^{2,42,43} Based on the evidence that some women experience impairments not related to treatment, we chose to base our eligibility on self-reported difficulties with cognition, and not base it on cancer treatments. We will conduct exploratory analyses to investigate whether the impacts of a physical activity intervention on cognitive functioning differs between breast cancer survivors who received surgery and radiation treatment compared to women who also received chemotherapy.

Another consideration was how best to track adherence of physical activity across the intervention. We elected to use the Fitbit for several reasons. First, Fitbit has an open application program interface that allows for access to the minute-by-minute data through third-party programs. With access to the minute level data we will be able to use the continuous physical activity data across the 3 months to objectively measure adherence in the intervention arm. Second, we wanted a device that could be used to support increasing activity as well as activity assessment. Through Fitabase we have a way to easily monitor each participant's activity level which will be used to help guide the 2 and 6 week phone calls. Finally, we wanted a user friendly device that would appeal to our sample of breast cancer survivors. The Fitbit One that will be used in the current study has only one button on the device and Fitbit.com displays the activity data in simple charts. Many activity devices have complicated interfaces that provide a high level of detail that we did not feel would be appropriate for an older sedentary group of women. In addition, other trials at the Moores Cancer Center using the Fitbit found that the Fitbit One was well liked even among those who were not technologically savvy.

A fourth design consideration was what neuropsychological tests to administer. We decided to use the NIH Toolbox Cognition Battery. This computerized battery of neuropsychological tests was specifically developed as a research measure that could be used across broad types of research studies and serve as a common currency for comparing findings. It also is a brief measure that assesses 5 major cognitive domains: Executive Function; Attention; Episodic Memory; Language; Working Memory; Processing Speed. We chose the National Institutes of Health (NIH) Toolbox to decrease participant burden while assessing many areas of cognition, which will be easily comparable to other studies.

MEASURES

Cognitive Functioning Measures

Neuropsychological testing—The NIH Toolbox Cognition Domain (nihtoolbox.org) is a computer based that can be administered in about 45 minutes and has been validated and

normed in individuals age 3 to 85. The testing uses multiple forms and Computer Adaptive Testing (CAT) to minimize practice effects. It also has minimal floor and ceiling effects. There are seven tests which yield a total score and the following summary scores: Cognitive Function Composite Score, Fluid Cognition Composite Score and Crystallized Cognition Composite Score.⁴⁴

Subjective Cognitive Concerns—The Patient Reported Outcomes Measurement Information System (PROMIS) Applied Cognition Abilities and General Concerns scale will be used to assess self-reported cognitive problems (nihpromis.org). This measure uses CAT to assess perception that one's cognitive ability has not changed (Abilities) and perceptions of changes/difficulties (General Concerns). The Applied Cognition Abilities and Concerns measures assess patient-perceived functional abilities and problems in the past 7 days with regard to cognitive tasks in the specific areas (e.g. concentration, memory).

Physical Activity Measures

Accelerometer—For seven days prior to each assessment point, all participants will wear the GT3X+ Actigraph (ActiGraph, LLC) which measures movement and intensity of activity and has been validated against heart rate telemetry⁴⁵ and total energy expenditure.^{46,47} The GT3X+ provides second-by-second estimates of activity that can be categorized into minutes spent in sedentary, light, moderate, and vigorous activity using calibration thresholds.⁴⁸ Sufficient wear time across the 7 days will be defined as having 5 days with 600 minutes of wear time; or 3000 minutes (50 hours) across 4 days. Participants with incomplete accelerometer data will be asked to re-wear the device for the number of missing days. Accelerometer data will be used to determine change over time from baseline to 3 months.

Fitbit data—Fitbit data will be used for a more in depth examine in the exercise arm on adherence to being active throughout the intervention (see adherence section above).

Biological Measures

Fasting blood samples—12 ml of fasting blood will be collected in EDTA tubes and stored at the UC San Diego Moores Cancer Center. Plasma from the blood will be isolated immediately by centrifugation at 4°C, then aliquoted and stored at -80°C. Biomarker assays will be conducted after data collection is complete in order to minimize batch-to-batch variation. Plasma component levels will be measured using immune-based assays (e.g. ELISA) or standard biochemical/spectrophotometric assays run at UCSD's NIH-funded Clinical and Translational Research Institute. Planned assays to be measured include: BDNF, Insulin-like growth factor 1 (IGF-1), Homeostatic model assessment – insulin resistance (HOMA-IR) and C-reactive protein (CRP).

Psychosocial Measures

PROMIS measures developed for Cancer survivors using computer adaptive testing will be used to measure depression, anxiety, and fatigue (nihpromis.org). CAT forms are used for each. With CAT, participant responses guide the system's choice of subsequent items from the full item bank PROMIS instruments.

Depression—The PROMIS Depression measure assess self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).

Anxiety—The PROMIS Anxiety measure assesses self-reported fear, worry, dread, hyper-arousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness).

Fatigue—The PROMIS Fatigue measure evaluate a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities.

Other Measures

Anthropometric Measurements—Height and weight will be collected in clinic to calculate Body Mass Index (BMI).

Demographics—Including self-reported age, education, income, race/ethnicity, marital status, and medication inventory.

Clinical—Medical chart review including date of diagnosis, stage at diagnosis, cancer treatments, and hormonal therapy.

DATA ANALYSIS AND SAMPLE SIZE CONSIDERATIONS

Consistent with the three aims, there are three goals of the analyses: (1) to explore the effects of a physical activity intervention vs. wellness control on changes in neuropsychological outcomes over 3 months, (2) to explore the effects of a physical activity intervention vs. wellness control on changes in cognitive concerns over the 3 month study period and, (3) to examine potential biological mechanisms of the effects of the physical activity intervention on changes in neuropsychological outcomes and cognitive concerns.

Based on a sample-size of 80 with 1:1 randomization to treatment or control, this study has 80% power to detect an effect size of 0.32 (Cohen's f), based on a one-way ANOVA with Type I error set to 0.05.⁴⁹ Prior research suggests a medium-large effect size^{28,50,51} such that those randomized to the physical activity intervention will show greater improvements in neuropsychological testing over 3 months compared to those randomized to the wellness control condition. We acknowledge that for this study, we may not have sufficient power to detect more modest effects of the intervention, and hence we will also calculate intervention-associated effect sizes for each of the outcome measures.

As a preliminary step, we will assess potential between-group differences in baseline characteristics (demographics, baseline exercise level, baseline neuropsychological

outcomes and cancer related variables) using graphical methods, non-parametric and parametric tests as appropriate (e.g., Wilcoxin rank-sum test for skewed data, t-tests for normally distributed continuous data & chi-squared tests for categorical data). Any variables not balanced by randomization will be controlled for as covariates in subsequent analyses.

To test the primary and secondary study aims, we will examine the effects of the physical activity intervention vs. wellness control on mean neuropsychological testing and mean subjective cognitive concerns over 3 months. To avoid the effect of outliers, we will apply a normalizing transformation (if necessary) to the outcome prior to analysis. A linear mixed effects regression model will be used to simultaneously estimate the treatment effects on outcome (at baseline and 3 months) with a subject-specific intercept included to account for within-subject correlation in the outcome over time. Treatment arm and time (baseline, 3 month), and the treatment*time interaction will be included as fixed effects; a significant interaction will indicate that changes in outcomes differ between treatments. We will control for potential covariates such as time since diagnosis, chemotherapy and hormonal therapy and any variables not equally distributed by randomization. Mixed effects models use a likelihood-based approach to estimation and therefore make use of all available data (on the intent-to-treat sample) without directly imputing missing outcome values.

For the tertiary aim, we will explore the potential mediating effects of biological mechanisms (BDNF, IGF-1, HOMA-IR, CRP) on the relation between treatment assigned and the primary/secondary outcomes (neuropsychological testing and cognitive concerns over 3 months). We will define a mediator as a variable M that is in the causal path between treatment assignment (Z) and outcome (Y= change in neuropsychological testing for example). We will employ the methods outlined by Kraemer et al.^{52,53} and MacKinnon et al.⁵⁴, which does not require a significant main effect of treatment on outcome (although we will be testing this as part of the Primary and Secondary Aims above). Rather, we must show that Z has a “causal” effect on M and M has a “causal” effect on Y. These analyses yield two path coefficients (one from Z to M and the other from M to Y). Taken together, the path coefficients are the indirect effect of treatment (product of coefficients). We will test this effect using Sobel’s variance formula⁵⁵ or via a bootstrap (Efron⁵⁶ or other methods that are less sensitive to normality assumptions)⁵⁷. We will keep in mind that in most cases mediation will be partial and individual mediators might not meet the criterion of strict statistical significance. If partial mediation is found to hold, we will also evaluate the ratio of the mediated to direct effect (path from Z to Y) as outlined in MacKinnon, Warsi and Dwyer.⁵⁸ Although we recognize that the sample size may not provide sufficient power to simultaneously test for all possible mediators, information gathered from the individual mediation analyses will provide important data for generating new hypotheses about the mechanisms through which a physical activity intervention vs. wellness control can influence outcome.

As a final step, we will explore the potential moderating effects of breast cancer variables (stage at diagnosis, time since diagnosis, cancer treatment) on the association between treatment and primary/secondary outcomes (neuropsychological testing and cognitive concerns). We will use a similar approach to analysis as that described for the primary and secondary aims; however, models will now include a main effect of the potential moderator,

as well as an interaction between treatment assigned, time, and the moderator of interest. A significant interaction will be considered evidence for potential effect modification.

DISCUSSION

To our knowledge, Memory & Motion is one of the first intervention trials with breast cancer survivors to test whether increasing exercise will improve cognitive functioning. By using the latest technological in wearable activity devices, we will have objectively measured, continuous monitoring of physical activity to assess physical activity adherence. This detailed data may provide us with important insights into the necessary dose of physical activity to impact cognitive functioning. In addition, by obtaining a variety of biological measures this study will be able to explore mechanisms of change. Our findings will potentially be complementary to another randomized trial conducting fMRI on their sample of breast cancer survivors (n=30) to examine physical activity-associated changes in brain activation.⁵⁹

Currently there are few evidence based interventions for cancer patients experiencing cognitive impairments.⁶⁰ Physical activity may be an effective intervention as it has been shown to improve cognitive functioning in both healthy and cognitively impaired populations.^{8,9,12,13} The recent Institute of Medicine's report on Cognitive Aging⁶¹ primary recommendation for reducing risk of cognitive decline is to be physically active. Consistent with this, a Cochrane review found that regular physical activity can slow down or prevent functional decline associated with aging.⁸ Emerging research with cancer survivors suggests that physical activity may also be effective for some domains of cognitive functioning.^{14–17} However, it is currently unknown whether breast cancer survivors have the same benefits to their cognitive functioning from increasing physical activity as other populations or if the impact of having cancer and undergoing cancer treatments outweigh the benefits of physical activity.

In addition, physical activity has the potential to impact an important aspect of quality of life: self-reported cognitive problems. These concerns refer to the amount of cognitive problems (memory, learning, language, and concentration) that patients perceive in their daily life and their satisfaction with their cognitive functioning.^{19,62} These self-perceived cognitive concerns are often associated with psychological factors^{18,19} for which there is good support that increasing physical activity can positively impact these factors in cancer subjective cognitive concerns reflect different aspects of cognition, measuring both provides a fuller picture of the cancer patients' experience and provides different potential intervention targets.

To enhance the ability to intervene to prevent or improve cognitive impairments, we need to understand the underlying mechanisms that link physical activity with neuropsychological outcomes and subjective cognitive concerns. Several biological mechanisms, including brain-derived neurotrophic factor (BDNF), measures of metabolism, and measures of inflammation have strong potential to link physical activity with neuropsychological outcomes^{25,26,28,63–68} and cognitive concerns.^{69,70} BDNF mediates the effects of physical activity on neuropsychological outcomes in non-cancer populations²⁷ and is related to

neuropsychological outcomes in breast cancer patients.²⁹ Therefore, BDNF is a highly probable mechanism through which physical activity may improve neuropsychological outcomes in cancer survivors. BDNF is regulated insulin and cytokines; therefore, measures of metabolism and inflammation may be mechanisms as well. This is consistent with research reporting that measures of metabolism (IGF-1, HOMA-IR),^{71,72} and measures of inflammation (CRP) are associated with physical activity^{7,9} and with neuropsychological outcomes.^{7,73} Additionally, all of these biological measures are associated with psychological variables,^{69,70} suggesting they could also be mechanism linking physical activity with cognitive concerns. Expanding what is known about potential mechanisms of physical activity-induced changes in neuropsychological outcomes and cognitive concerns in breast cancer survivors is an important step in developing targeted interventions.

To summarize, this study will provide a rich data set that includes neuropsychological testing, objective physical activity, quality of life including cognitive concerns, and a wide array of biological assays. The randomized controlled trial, with the transdisciplinary set of data, will for a novel and innovative investigation of the relationships between physical activity and neuropsychological outcomes and cognitive concerns in breast cancer survivors. Results from this study will inform a large scale fully powered trial and may help to guide development of interventions to improve cognitive functioning in breast cancer survivors.

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