Author’s response to reviews

Title: Feasibility of a Combined Aerobic and Cognitive Training Intervention on Cognitive Function in Cancer Survivors: A Pilot Investigation

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Version: 2 Date: 06 Oct 2017

Author’s response to reviews:

On behalf of the authors who contributed to this investigation, I would like to express my thanks and gratitude for each of the reviewers who have provided constructive feedback for the improvement of this manuscript. We have responded to all reviewer comments and have completed a more thorough revision that should better reflect the suggestions and comments of the reviewers, thereby improving the quality of the manuscript. Responses to each comment are located directly below each comment.

Gratefully,

Dr. Brent M. Peterson

Reviewer reports:

Reviewer #1: The article presents the results of a trial to test whether aerobic or cognitive training or both provide superior improvements to cognitive function. The article is detailed and well-written. I have a few minor comments to improve the clarity of the manuscript.
Pg 3 - should be "e.g., alkylating agents"

- This has been corrected as suggested.

Pg 4, 10 - please add references to support the following statements "tai chi and Qigong..." and "Qigong was frequently associated ...." and "few studies have evaluated the ...."

- This has been corrected as suggested.

Pg 5 - please include the name of the university review board and the ethics approval number.

- This has been corrected and now reads, “The University of Northern Colorado Institutional Review Board approved [573297-2] all procedures and written informed consent forms were signed by all subjects.”

Pg 5 - the authors note that all groups received the flexibility training intervention, however it is not clear how or when the intervention groups completed this. Was it completed 3 times per week in addition to the 30 minute intervention sessions, which would make intervention sessions 1 hr duration?

- This has been corrected as suggested. It now reads, “A cancer control group (CON) participated in 36 sessions of a 30-minute flexibility only intervention. All interventions were administered to cancer survivors in a one-on-one clinical setting at our facility. Directly following the completion of 30 minutes of AER, COG, or AER + COG training participants completed the 30-minute flexibility training intervention for a total of an hour of training.”

Pg 5 - Was the study protocol registered with a clinical trials registry? The CONSORT checklist states this is N/A, but it's not clear why.

- This is an excellent point. Our group plans to more carefully address this consideration with future studies. From the outset, the design was completely exploratory in nature. In addition, there were no medications being tested nor were there any plans for this intervention to be used as a treatment modality for CRCI. Therefore, we chose not to register with a clinical trials registry.
pg 9 - The following sentences are unclear "...the COG group showed no statistically significant improvements in cognitive function. In contrast, the COG group showed no significant improvements in cognitive function using 12 difference cognitive assessment instruments"

-This has been corrected as suggested. The sentence, “In contrast, the COG group showed no significant improvements in cognitive function using 12 difference cognitive assessment instruments” has been removed.

Table 1: there are 7 participants in the AER group, but only 6 cancer types listed.

-This has been corrected as suggested. It now appears as “breast cancer (3).”

Randomisation: the authors could add more detail about the randomisation process, including whether participants were randomised in a 1:1 ratio, whether there was any block size, did participants know about all of the study group options, were the control group aware that they were in the control group?

-This has been explained further as requested. It now appears as, “Randomization was completed using PROC PLAN (SAS 9.3, Cary, NC), a statistical tool that generates a randomized numerical listing of intervention groups. As participants qualified for the study, they were assigned according to the next available intervention group on the list. All participants in each group were unaware of the number of different intervention groups.”

Reviewer #2: Thank you very much for the opportunity to review this manuscript. The present study represents an area of great interest to researchers, practitioners, and survivors and in which little evidence is available. I commend the researchers for their work in this area. However, while research of this nature is needed, a number of methodological limitations inhibit enthusiasm for this manuscript. These concerns should be addressed before this paper is suitable for publication.

Abstract

* Please consider adding the length of the intervention. The study is described as 36 sessions, but it would be more informative to know over how long these sessions were conducted - e.g., 12 weeks (line 19).
-This has been corrected as suggested. It now appears as A 36-session (approximately 12 weeks) computer-based cognitive (COG), aerobic (AER), cognitive and aerobic (AER + COG), and flexibility (CON) training intervention was completed.

* Please define the group assignments in the abstract by spelling them out and noting that CON refers to flexibility training. Please also note how many subjects were in each group (line 23).

-This has been corrected as suggested. Please see above.

* Delete 's' at the end of the word "variables" in line 30.

-This has been corrected as suggested.

* The conclusion drawn on lines 41-46 seems too assertive. Please modify this interpretation. Given the major limitations in the sample size with a 4-group design, it is difficult to draw such a strong conclusion related to the limited efficacy of AER+COG. At best, the authors might suggest that aerobic training may benefit cognition in cancer survivors; however, larger randomized trials are needed.

-This has been corrected as suggested. It now reads, “Aerobic training for CRCI may positively impact cognitive function. Individually, these methods may appropriately address CRCI, but combined training of this nature may be too demanding for patients undergoing treatment for cancer. However, larger randomized trials are needed to substantiate this protocol among large-scale cancer rehabilitation centers.”

*Please consider noting that the sample was comprised of cancer survivors currently undergoing treatment for cancer.

-This has been corrected as suggested. It now reads, “Purpose: to examine the effects of a quasi-randomized, controlled, exploratory, repeated-measures aerobic and cognitive training intervention on cognitive function in participants undergoing treatment for cancer (N = 28).”
Were all participants currently in treatment? Despite the standard definition of survivor, most studies with survivors include only those who have completed treatment. To avoid confusion, please note the sample included individuals currently undergoing treatment.

-This has been corrected as suggested. Please see above.

Introduction

* Introduction is well-written. However, there are some key studies using human models the authors might mention relative to exercise and CRCI and exercise and age-related cognitive decline. Examples for CRCI include: Zimmer et al., 2016; Marinac et al., 2015; Hartman et al., 2014; Mackenzie et al., 2016; Ehlers et al., 2017; Von Ah et al., 2013. Zimmer et al. at the very least should be included in this manuscript, as it reviews exercise interventions aimed at improving cognitive function in cancer survivors. In relation to cognition in healthy adults, while Chuck Hillman has done commendable work with children and adolescents, older adult research by others in this research group may be more appropriate (i.e., work led by Art Kramer and Edward McAuley).

-This is an excellent point. The authors have added these studies as suggested.

Methods

* Please expand Table 1 to include more participant characteristics broken down by group. Despite the small sample, it would be good to know the mean age and months since diagnosis per group and across the whole sample; and the frequencies for diagnosis stage, cancer site, gender, race/ethnicity, education, income, marital status, treatment(s) received, if participant was in treatment, hadn't started treatment, or completed treatment at time of study, etc.

-This is an excellent point and our group intends on adding these components into the demographic questionnaires for future studies to better describe our participants. Unfortunately, for this particular study, this information was not included in the initial methodology drafting with the exception of time of treatment (either undergoing or have completed within 8 weeks).
Mean age is reported in the Participants section. We have also added individual information on participant gender.

* Please describe what the "first physical assessment" was for (page 5, line 13). Physical assessment for cancer rehabilitation? Or physical assessment for the study? The intake of participants into the study is a bit confusing as written.

    -We apologize for the confusion and this has been corrected. It now reads as follows, “Participant eligibility was initially screened by front office staff prior to arrival at UNCCRI for their first physical assessment. Following initial screening and agreement to participate participants completed the standard UNCCRI comprehensive physiological assessment. This is described in detail below.”

* Similar to the abstract, please note the length of the intervention in weeks or months (page 5, line 18).

    -This has been corrected as suggested. Please see below.

* When were data collected? What was the data collection schedule? (page 5, lines 20-22).

    -This has been corrected as suggested. It now reads, “All training, cognitive and physical assessments, and data collection were conducted at UNCCRI prior to and following the completion of the 36-session intervention.”

* When were data collected relative to participants' treatment for cancer?

    -This is an excellent point and our group plans on including this in future studies. However, for this study, our group only included in the inclusion criteria that participants had to either be currently in treatment or be at most 8 weeks out of treatment. It was not a part of the original study design to collect this particular information.
* To improve the statistical power of this study, the authors might consider using statistical analyses utilized in fractioned factorial designs, which essentially is what the authors have in this study. See work by Linda Collins. Because all participants received flexibility training, the authors may be able to compare ingredients rather than groups (i.e., aerobic v. no aerobic, cognitive v. no cognitive). This would allow them to have larger group sizes without increasing the sample size and would also permit them to better discern the active ingredient(s) contributing to improvements in cognition observed.

- This is an excellent point and our group intends on implementing these suggestions in future studies. However, for the current study, the authors would prefer to follow the guidance of the statistician who helped develop the methodology for this study and leave this section as is.

* Table 2 - should the footnote refer to Table 4 (page 23, line 42).

- This has been corrected as suggested.

* How long was each session (page 4)?

- This has been corrected as suggested. It now reads as, “All interventions were administered to cancer survivors in a one-on-one clinical setting at our facility. Directly following the completion of 30 minutes of AER, COG, or AER + COG training participants completed the 30-minute flexibility training intervention for a total of an hour of training.”

* Please provide citations for the cardiorespiratory fitness and cognitive assessments.

- Citations have been provided for the UNCCRI multistage submaximal treadmill protocol. The review study that guided the methodological design of the cognitive assessments has also been added with the following language, “The cognitive assessment battery was developed based on a review of studies that have implemented similar methodologies and from recommendations from faculty in the Department of School Psychology [41].”

The measures section (page 6, lines 4-18) are lacking critical details. Was the treadmill protocol a submaximal or maximal test? How were cognitive data collected? A computer-based battery, paper-pencil, combination? Who administered the physical and cognitive tests? In what type of setting were participants when completing tests? Were physical and cognitive assessments completed in one appointment or separate appointments? If same, which was completed first or was order counter-balanced across participants?
This has been corrected as suggested. Following agreement to participate and initial screening subjects completed a comprehensive physiological assessment. Initial values for blood pressure (BP), heart rate (HR), oxygen saturation (SpO2), weight, height, body composition (skinfold measurements), circumference measurements, cardiovascular fitness (VO2peak, UNCCRI protocol), balance (Bertec Balance Screener), pulmonary function (spirometry), estimated 1RM (Brzycki equation), muscular endurance (plate loaded cable assisted machines, chair squat test, and plank test), handgrip dynamometry, and flexibility measures (modified Sit and Reach and Shoulder Reach Behind Back) were collected as part of the standard UNCCRI physical assessment protocol. Cardiovascular endurance was assessed using the cancer-specific UNCCRI multistage submaximal treadmill protocol. Cognitive function was evaluated prior to and following the completion of each 36-session intervention. Cognitive assessments were scheduled aside from physiological assessments, often within the same calendar week, so as to maximize participant effort. Trained doctoral candidates from the Department of School Psychology conducted each assessment of cognitive function. A paper and pen-based battery of well-established cognitive assessment tools were administered in a quiet office in the reception area. All cognitive assessments were in a one-on-one setting.

* In subsequent studies, the authors might consider using a cycle ergometer protocol to test cardiorespiratory fitness since the aerobic intervention utilized a cycling protocol.

- This is an excellent point, and we will consider this methodological change in future studies.

* Please include a sentence on the timing and length of flexibility training in the aerobic, cognitive, and combined interventions (page 6)?

- This has been corrected as suggested. It now reads as follows, A cancer control group (CON) participated in 36 sessions of a 30-minute flexibility only intervention. All interventions were administered to cancer survivors in a one-on-one clinical setting at our facility. Directly following the completion of 30 minutes of AER, COG, or AER + COG training (while seated on the Motion Fitness Brain Bike®) participants then completed the 30-minute flexibility training intervention for a total of an hour of training. This was to ensure that any changes in cognitive function were not the result of personal interactions that occurred between subjects and those individuals supervising the intervention.
* Please be clear - participants assigned to COG were seated stationary on the Motion Fitness Brain Bike? Were these sessions 30 minutes as well? Additionally, were the AER + COG sessions 30 minutes also? Table 2 indicates that all participants received flexibility training. Did participants in AER, COG, and AER + COG receive 30 minutes of flexibility training in addition to their assigned protocols?

  - This has been corrected as suggested. Please see above.

* The Methods section overall is a bit confusing to follow. The specifics of each intervention are not clear, making replicability of this study impossible. Please provide more detail on frequency, length, adherence.

  - We believe we have rectified this as a result of addressing all of the previous comments and suggestions provided by all reviewers.

Results

* Please present the limitations at the end of the discussion section. If the limitations described in the results were systematically evaluated, then there is a place for them in the results section. However, these data should be presented as a sort-of process evaluation. For example, are data available on the mean %HRR in each group? Is this information available across groups? Are data available on adherence to each protocol?

  - This has been corrected as suggested. The limitations section has been moved to follow the conclusions section. The limitations section is a process evaluation and is not based on a particular variable or set of variables, and is not available across groups. Unfortunately, there are no data available to explain adherence to each protocol as it was not an intentional component of the methodology.

* It may also be helpful to include effect sizes since the study was not adequately powered.
-The authors currently have referenced tables 5 and 6, which contain effect sizes for these variables explained in the results section. In an effort to preserve data reduction and manuscript brevity, the authors would prefer to leave this as is.

Discussion

* Discussion section addresses findings well and provides nice comparisons with previous studies.

* The conclusion drawn on page 12, line 4-7 should be toned down, as no group differences were observed in this study. The addition of effect sizes may provide the researchers with more empirical backing of these conclusions amidst the study's limited statistical power.

-This has been corrected as suggested and now reads, “The investigators of this preliminary investigation aimed to address a debilitating cancer treatment-related side effect. We attempted to evaluate how two independent interventions may be utilized to reduce CRCI and thereby increase quality of life in cancer survivors. These data provide a framework for future studies aiming to utilize aerobic exercise in the attenuation of CRCI. More research must be done to more fully examine the effects of combined cognitive and aerobic training on cognitive function, but until then aerobic exercise may be as an easily implementable modality to address CRCI in cancer survivors.”