2022

Physical Exercise for Augmenting Cognitive Health (PEACH)

NCT Number: NCT04922710

JAN 3, 2022

Reversibility Network Pilot of Home-Based Aerobic Exercise among Adults Exposed to Threat-related Adversity

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1.0 Background and Aims:

Early life adversity (ELA) encompasses a range of negative experiences during childhood and adolescence, including poverty, abuse, parental maladjustment, and inadequate nutrition, which interfere with neurocognitive and socioemotional development. Unfortunately, ELA is common in both economically distressed and wealthy countries, though the specific nature of ELA may differ by country. It is estimated that 40-60% of individuals are exposed to at least one form of ELA, and a quarter of individuals experience multiple adversities[1–3]. Exposure to ELA exerts profound and long-lasting effects on health and well-being that persist into late adulthood. Globally, ELA accounts for up to 30% of incident psychiatric disorders in adulthood[3], and increases risk for the development of numerous chronic health conditions such as Type II diabetes, obesity, and cardiovascular disease[4,5]. More recent evidence suggests that ELA also negatively impacts brain health in mid- and late life, accelerating the rate of age-related cognitive decline and heightening susceptibility to neurological illnesses such as Alzheimer's Disease[6]. Further, retrospective studies have observed a link between ELA and brain structure and function in adulthood[7–10]. These data suggest that the effects of ELA on brain health are enduring and may underlie ELA-related susceptibility to psychological, cardiometabolic, and neurocognitive illness. In order to improve the health and well-being of the millions of individuals impacted by ELA, it is necessary to establish whether it is possible to reverse or mitigate the effects of ELA through interventions delivered in adulthood. Yet, despite this pressing need, there is a paucity of research exploring this question.

Physical activity (PA), particularly aerobic exercise, may be an effective, low-cost approach to remediate the long-term negative health consequences of exposure to ELA. In addition to the well-documented benefits of PA for reducing chronic disease risk[11], there is growing evidence that PA improves cognitive and brain health[12], even among adults experiencing illness or aging[13–17]. Numerous randomized controlled trials in adults have demonstrated PA-related benefits in a number of cognitive domains, including memory[18], attention and processing speed[17] and executive functions[19]. Crucially, PA also modulates structure and function of brain regions that support cognitive and psychological processes influenced by ELA, most notably the hippocampus and prefrontal cortex[20–23].Thus, PA holds great promise as a means of improving brain health among adults who have experienced ELA.

Despite the promise of PA, few studies have examined whether ELA exposure moderates the impact of PA on brain health. This is driven in part by the unique challenges associated with conducting research among individuals who have been exposed to ELA. Adverse childhood experiences increase vulnerability to adversities in adulthood, including lower socioeconomic status and higher risk of work disability[24,25]. The socioeconomic and socioemotional consequences of ELA are significant barriers to participation in research, particularly time intensive clinical trials of PA that may require numerous in-person visits each week over the course of several months. Therefore, to better serve this population, the format in which PA is delivered must be adapted to accommodate the challenges associated with ELA. The proposed research aims to address this issue by conducting a pilot 12-week PA intervention delivered remotely using aerobic exercise bikes

programmed to connect users with a trainer via an app. We will recruit individuals between the ages of 30-55 years (*N* = 20) from a well-characterized cohort of adults in Jamaica with early-childhood exposure to malnutrition and other forms of ELA (e.g., poverty) confirmed by contemporaneous medical records who continue to participate in research led by Co-Investigators and Reversibility Network members Terrence Forrester and Kirk Erickson. A comparison sample (*N* = 20) of age, sex, and race matched adults with an ELA history will be recruited in Pittsburgh, and a harmonized battery of cognitive, fitness, and psychosocial measures will be collected in both samples at baseline and following the 12-week intervention.

We have assembled a highly creative, productive, and interdisciplinary team with extensive experience conducting exercise interventions and evaluating indicators of brain health in multiple vulnerable populations (e.g., older adults with cognitive impairment, adults with a history of malnutrition). We will test the following aims:

Aim 1: Determine the feasibility and acceptability of a remote PA intervention among adults exposed to threat-related ELA living in Pittsburgh and Jamaica It is hypothesized that the remote format of the intervention will enhance the feasibility of conducting a PA trial among individuals with a history of threat-related ELA.

Aim 2: Determine whether the remote PA intervention promotes improvements in cognitive and psychological functioning. It is hypothesized that cognitive and psychological functioning will improve over the course of the intervention and improvements will be greatest among those with the highest adherence rates.

The proposed research addresses the central goal of the NIA Reversibility Network to develop and test feasible interventions that may mitigate ELA-related risk for adverse health outcomes in adulthood. This pilot feasibility trial will set the groundwork for a larger-scale future R01 application that will test the efficacy of a remote PA intervention for improving brain health among adults who have been exposed to ELA. Further, the proposed research will provide an initial test of the impact of country-level factors (e.g., poverty rates, prevalence of more severe ELA such as malnutrition) on ELA-related disease burden in adulthood, information which may be leveraged to tailor interventions to meet the specific needs of the target population.

1.1 Overview of Methods:

1.1.1. Subject recruitment, Pittsburgh: We expect to advertise through numerous outlets in order to enhance our ability to successfully recruit for the study. Participants (*N*=20) will be recruited via methods found to be effective in other studies, including the University of Pittsburgh online research registry (Pitt+Me) and community presentations at local community centers. We will also advertise on the Brain Aging and Cognitive Health (BACH) lab website (http://bachlab.pitt.edu/), lab social media accounts (Facebook & Instagram), and will post flyers and other ads around the Pittsburgh community.

1.1.2. Subject recruitment, Jamaica: Participants (*N*=20) will be recruited from across Jamaica, particularly from the areas within and surrounding Kingston, Jamaica where the University of the West Indies is located. Participants will be age, sex, and race matched across sites.

1.1.3. Eligibility criteria: Inclusion criteria will be as follows: 1) adults aged 30-55 years, 2) exposure to at least one form of threat-related ELA (e.g., exposure to violence; physical abuse) prior to the age of 10 as documented by retrospective self-report (described in detail below), 3) self-identified Black or African American race, 4) access to high-speed internet, and 5) sedentary lifestyle (<60 minutes of PA/week). Exclusion criteria will include: 1) psychosis, 2) significant suicide risk (i.e., current, active suicidal ideation with a plan), 3) engaging in moderate-intensity exercise >=20 min per day, >=3 times per week, 4) current treatment for cancer, 5) neurological condition (e.g., MS, Parkinson's, Dementia, MCI) or brain injury (e.g., stroke), 6) substance use disorder in the past 3-months, 7) current treatment for congestive heart failure, angina, uncontrolled arrhythmia, DVT or other cardiovascular event, 8) myocardial infarction, coronary artery bypass grafting, angioplasty or other cardiac condition in the past year, 9) sensory impairment that would preclude neuropsychological testing, 10) not fluent in English, 11) travelling consecutively for 2+ weeks during the study, 12) uncontrolled hypertension, 13) insulin-dependent Diabetes Mellitus, and 14) self-identified as any race other than Black or African American.

1.1.4. Phone screening: When a prospective participant indicates interest in the study, a brief phone screening will be conducted to determine provisional eligibility. The total time to administer phone screening questions is ~15-20 minutes. The phone screening process will also provide details of the study and participants will have the opportunity to ask questions about these details during this phone call. Staff will also confirm with the participant that they will not be travelling for two or more consecutive weeks during their participation period. If individuals are deemed provisionally eligible based on the phone screen, they will be scheduled for a videoconference call via the HIPAA-compliant version of the Zoom software, during which informed consent will be obtained.

1.1.5. Informed Consent: Informed consent will be obtained remotely over a video conference call, during which a staff person will go through the details of the consent form and answer any questions posed by the participant. The consent document will be signed electronically using REDCap, a secure data management platform licensed by the University of Pittsburgh. This system enables participants to review and sign the consent form electronically, and the signed document is then stored in the REDCap system in a secured archive. Participants will have the ability to download an electronic copy of their signed e-consent form and investigator contact information will be listed on the e-consent form in the event that participants wish to ask further questions. After informed consent has been obtained, self-reported history of adversity and health history/current health (measures described below), will be evaluated via REDCap. These measures, described in detail below, will be used to determine full eligibility.

1.1.6. Secondary screening for eligibility determination:

1.1.6.1. ELA will be evaluated via several well-validated retrospective self-report measures that capture complementary information about childhood adversity, including type, timing, and severity of adverse experiences. We will administer the Childhood Trauma Questionnaire (CTQ)[26], a 28-item survey which assesses the severity of five domains of childhood maltreatment, including emotional neglect, physical neglect, emotional abuse, physical abuse, and

sexual abuse. We opted to use the CTQ because, unlike other ELA measures, it has been validated in numerous countries and cultures[27,28]. In addition, participants will complete the Maltreatment and Abuse Chronology of Exposure (MACE) scale[29], a 52-item self-report measure of the timing and severity of multiple forms of ELA, some of which are not covered by the CTQ, including bullying and intra-parental violence. Finally, to evaluate childhood socioeconomic disadvantage, participants will be asked to estimate childhood household income and report parent/guardian occupation and education. Childhood socioeconomic status will not be used as an index of adversity but will be collected for the purpose of fully characterizing participants' childhood context. Responses on these assessments will be used to form a composite score reflecting degree of ELA exposure. Exploratory analyses that decompose the specific types of ELA will also be performed.

1.1.6.2. Health history will be evaluated to determine whether an individual has a history of or is currently experiencing any health conditions that may preclude them from participating in a physical activity intervention. This information will be obtained via the phone screening as well as through a Health History Questionnaire administered electronically with the CTQ and MACES. This questionnaire asks questions about medical symptoms participants have experience in the past 6 months related to cardiovascular disease and musculoskeletal injuries as well as other related measures (e.g., alcohol consumption).

1.1.7. Remotely administered questionnaires. Those deemed eligible based on responses to the above measures will then be provided with secure links to complete a number of questionnaires via REDCap. Questionnaires will evaluate psychological functioning and behaviors such as physical activity. The following questionnaires will be administered via survey link:

1.1.7.1. Psychological Functioning:

- Perceived Stress Scale (PSS): a 14-item measure that assesses experiences of daily life stress. The PSS is an instrument on which respondents use a 0 ("never") to 4 ("very often") Likert scale to rate the degree to which daily life events are perceived to be uncontrollable, unpredictable, or unmanageable. Responses are summed to form a total score (maximum possible score of 56; ~3 min)

- State Trait Anxiety Inventory (STAI): a 40-item measure with two subscales assessing state and trait anxiety symptoms rated along a 1 ("Almost Never") to 4 ("Almost Always") scale. Higher subscale scores indicate more severe anxiety. (~5 min).

- Center for Epidemiological Studies Depression Scale (CES-D): a measure of the frequency of 20 common depressive symptoms rated along a 0 ("rarely or none of the time") to 3 ("most or all of the time") Likert scale. Responses are summed to yield a total symptom score (maximum possible score of 60) with higher scores reflecting more severe depressive symptoms (~3 min).

- Positive Affect Negative Affect Schedule (PANAS): This scale consists of a number of words that describe different feelings and emotions. Participants are instructed to rate the degree to which each word describes them. State negative and positive affect are assessed (~ 5 min).

- Index of Race Related Stress-Brief: This inventory consists of 17 items that measure stress associated with common, day to day racial hassles experienced by Black Americans, emphasizing the ubiquitous and chronic presence of racism in the United States. Participants are asked to indicate their experience with and reaction to the events depicted in each item using a 5-point Likert-type scale (0 = this never happened to me; 1 = this event happened but did not bother me; 2 = this event happened, and I was slightly upset; 3 = this event happened, and I was upset; 4 = this event happened, and I was extremely upset). Items are summed to yield a total score (range 0-68), and higher scores indicate respondents endorsing a greater degree of stress because of their encounters with racism. The IRRS-B is one of the most widely used measures to assess race-related stress among Black Americans (~5 min).

1.1.7.2. Other assessments:

- MacArthur SES Questionnaire: This scale includes 12 questions regarding perception of subject's status relative to their community and the country as a whole, their living situation, level and degree of education obtained, job status, income and debt (~3 min).

- Exercise Self Efficacy (EXSE): a questionnaire measuring participant's confidence in their ability to complete the exercise intervention (~5 min).

- Exercise Benefits/Barriers Scale: a 43-item questionnaire assessing perceived barriers and benefits to engaging in physical activity. The benefits subscale is composed of 29 items, while the barriers subscale is composed of 14 items. Respondents rate their agreement with each statement on a 4-point scale from 1 (“Strongly Disagree”) to 4 (“Strongly Agree”). A total score can be derived by reverse coding barrier items, or individual subscale scores for benefits and barriers can be obtain by summing the items of each subscale (~4 min).

- Paffenbarger Physical Activity Questionnaire (PPAQ): a seven-day activity recall survey that evaluates the amount of physical activity due to activities of daily living (e.g., walking) and leisure activity that involves physical exertion (e.g., gardening, jogging). The PPAQ is a widely used instrument for assessing habitual PA that exhibits good reliability and has been shown to correlate highly with objective measures of body composition and physical activity. (~10 min)

- Childhood socioeconomic status: participants will be asked to estimate childhood household income and report parent/guardian occupation and education. Childhood socioeconomic disadvantage will not be used to evaluate inclusion or exclusion on the basis of ELA exposure, but will be

collected for the purpose of fully characterizing participants' childhood context.

- We will also collect basic demographic information, including current and childhood socioeconomic status.

1.1.8. In-person assessment. Participants will then be invited for an in-person visit that will last approximately two hours, during which they will complete assessments of cognitive and psychological functioning. This session will be completed in person at the Brain Aging and Cognitive Health Lab in a private room that will be occupied by the study staff and subject only. Cognitive tests and questionnaires will be scored after the session is completed by the staff who administered the visit. A second staff member will also score the tests to ensure reliability and validity of the session. All measures described below will be completed at baseline and post-intervention. A description of the proposed assessments and questionnaires are provided as follows:

1.1.8.1. Cognitive functioning:

1.1.8.1.1. The Cognitive Portion of the NIH toolbox is a computer-based program that assesses Executive Function, Attention, Episodic Memory, Language, Processing Speed and Working Memory. This computer program was designed by NIH for the purpose of collecting standardized cognitive data in studies like this and takes approximately 30-40 minutes to complete. Some of the tasks that may be completed as part of the toolbox:

- Dimensional Card Sort: (6 minutes) A task that measures cognitive flexibility and attention. Two target pictures are presented that vary along two dimensions (e.g., shape and color). Participants are asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). The relevant dimension for sorting is indicated by a cue word (e.g., "shape" or "color") that appears on the screen for all participants.

- List Sort Working Memory: (10 minutes) This task assesses working memory and requires the participant to recall and sequence different visually and orally presented stimuli. Pictures of different foods and animals are displayed with both an accompanying audio recording and written text that name the item. The participant is asked to say the items back to the examiner in size order from smallest to largest.

- Picture Sequence: (5 minutes) In this measure of episodic memory, sequences of pictures objects and activities are presented in a particular order. The participants are asked to reproduce the sequence of pictures that is shown on the screen.

- Flanker: (4 minutes): This is a measure of inhibitory control and attention. The task requires the participant to focus on a particular stimulus while inhibiting attention to the stimuli flanking.

- Picture Vocabulary Test (4 minutes): Measures receptive vocabulary administered in a computer-adaptive test (CAT) format. Respondents select the picture that most closely matches the meaning of the word.

- Pattern Comparison (3 minutes): Assesses the amount of information that can be processed within a certain unit of time. Items are simple so as to purely measure processing speed.

1.1.8.2. Height and weight will also be measured using a calibrated stadiometer and digital scale respectively. These values will be used to calculate body mass index (BMI).

1.1.9. Activity monitoring: At the end of the baseline assessment visit, eligible participants will be fitted with a commercially available physical activity monitoring device (ActiGraph Link), worn on the wrist. ActiGraph Link provides information about movement, rotation, and body position, that is used to determine intensity and amount of physical activity. Activity monitoring will be completed one-week prior to and one-week after completion of the intervention.

1.1.10. Exercise training session: After completion of the initial assessment visit and the activity monitoring period, two study team members will schedule a time to transport a study stationary bike to the participant's home via a university-owned vehicle, set-up the bike in the participant's home, and monitor the participant's first home-based exercise session in-person. Participants will also be provided with a study-owned tablet loaded with the application (described below) that will be used to administer and monitor their exercise regimen throughout the intervention.

1.1.11. Participants will complete one onsite exercise session, during which they will work with the exercise physiologist to determine the appropriate peddling speed corresponding to a moderate-intensity exercise zone based on the American College of Sports Medicine Guidelines. Heart rate and blood pressure will be monitored during this session to ensure that the participant does not exceed ACSM guidelines for safe activity.

1.1.12. Exercise intervention: The intervention will use personalized physical activity regimens that are remotely administered by exercise staff using an application called Neotiv. Neotiv has been programmed by a research group in Germany who have agreed to make it freely available for this pilot study. Neotiv is integrated with the stationary bike, allowing for the collection of data about speed, resistance, and duration of cycling. We will use Neotiv to monitor adherence to the intervention protocol and to adjust the protocol as needed. The participant will complete three exercise sessions per week on the bike at home for 12-weeks, which will gradually increase in duration from 15- to 50-minutes over the first month of the intervention. The final weekly exercise goal will be set to 150 minutes.

Prior to initiating each exercise session, the participant will wear a Polar heart rate monitoring band around their chest, open the Neotiv application on the study tablet, at which time they will be prompted to rate their current mood using the Exercise

Induced Feeling Inventory (EFI)[30], which prompts respondents to rate the extent to which 12 different emotion words describe how they feel in the moment on a scale from 0 (“Do not feel”) to 4 (“Feel very strongly”). Example words include “Calm”, “Tired”, “Revived”, “Happy”, and “Fatigued”. The participant will then press the start button on the tablet application and begin exercise, at which time data from the exercise bike and the heart rate monitor will begin continuous transfer to the tablet in one-second intervals, via Bluetooth and ANT+ technology. Pleasant and relaxing images will be presented via the tablet during the exercise sessions to maintain interest and adherence. At the end of each exercise session, participants will be prompted to again rate their mood on the EFI and to rate their perceived exertion using the Borg scale from 6 to 20. After completion of the session the participant will press the end button on the tablet application and put the tablet in standby mode, unplug the stationary bike, and engage in 10-minutes of a stretching regimen taught by the exercise physiologist during the training session.

After completion of each exercise session, the following data will be sent to a subject-folder (named by study id) on a secure cloud-based platform (google firebase database set up for the study), which will be accessible to study staff: 1) heart rate per second 2) bike resistance per second, 3) peddling speed (rotations per minute), and 4) duration of exercise session. Study exercise staff will review these exercise data on a daily basis to monitor intervention adherence and will modify the exercise regimen (i.e., bike resistance) as required to ensure the participant is engaging in moderate-intensity exercise for the majority of each exercise session.

A study team member will check-in with participants via weekly emails or calls with participants via phone or HIPAA-compliant videoconferencing software to troubleshoot issues that arise during exercise, discuss participants' subjective exercise experience, and problem-solve barriers to adherence. The format of these check-ins will be determined by the participant’s preference, progress, and needs, and may change over the course of the intervention as warranted. Exercise safety will also be reviewed during these weekly check-ins and participants will be encouraged to reach out to the study staff if any safety-related concerns arise. Participants will also be asked about whether there have been any issues with their bike or other equipment. Should damage occur, two staff people will schedule a time to visit the participants home to fix the issue(s) noted or to collect the bike to be returned to the manufacturer for repair. In the event that the bike must be returned to the manufacturer for repair, participants will be furnished with a replacement bike within 5 days of the removal of the original bike, and any exercise sessions missed as a result will either be made up within the following week or marked as absences that will not be counted toward the participant's attendance/adherence bonus numbers.

1.1.13. Follow up assessment: All of the baseline assessments will be repeated at follow-up after completing the 12-week intervention, including cognitive and psychological functioning, and physical activity monitoring (see descriptions above). We will not administer CTQ or MACE questionnaires at follow-up given that scores on these questionnaires should not change.

1.1.14. Bike return: Following the completion of the 12-week intervention, the study PI and a staff member will return to participants' homes to collect the study-issued

stationary bike, tablet, and heart rate monitor. Any needed repairs will be made and equipment will cleaned for use by another participant.

1.2. Statistical Analysis Plan: This intervention is a pilot feasibility investigation. Therefore, the primary focus is on evaluating how successful we are at recruitment and retention, and whether we are able to keep participants engaged in the intervention. Although we will evaluate the effect of the intervention on cognitive and psychological functioning, is not intended to be statistically powered to address questions regarding the effectiveness of the intervention for improving the outcomes among adults exposed to early life adversity.

Aim 1a. The feasibility of this intervention will be assessed by examining average adherence rate over the course of the intervention, operationalized as a combination of number of sessions attended and average duration of each session. Average number of minutes spent in the 'moderate-intensity' heart-rate zone per session will also be examined. Threshold analysis will be conducted to understand whether exercise adherence declines after a certain time point in the intervention (e.g., 6-weeks). In an exploratory analysis, ActiGraph data will be used to assess whether engagement in the intervention results in an increase in physical activity from pre- to post-intervention.

Aim 1b. Intervention acceptability will be assessed through a self-report questionnaire completed post-intervention, including questions about satisfaction with various aspects of the intervention (i.e., intervention duration, interaction with study staff, use of technology to remotely guide intervention, overarching feedback about intervention, willingness to continue engaging in exercise).

Data related to 1) study enrollment and 2) summaries of weekly video/phone calls to monitor exercise adherence and engagement will be documented. The recruitment process (e.g., proportion of participants screened who enrolled in the study) and participants' experience in the intervention based on weekly phone sessions and the satisfaction questionnaire at the completion of the study will be qualitatively examined.

Aim 2. Paired sample T-tests will be used to assess change in cognitive and psychological functioning over the course of the 12-week intervention.

Aim 3: Attendance and adherence rates, as well as participant satisfaction ratings, will be compared using Paired sample T-tests to determine whether there are differences in these metrics across sites. Statistical tests performed to assess Aim 2 will be repeated separately for each site to evaluate whether effect sizes differ by site.

1.3. Minimization of Risks:

1.3.1. To reduce the risk for breach of confidentiality we will separate all information obtained during the screening period from identifying documents. All research data will be de-identified. These documents will be stored in a separate location from the data and the screening information in locked filing cabinets in a locked and secure room that only lab personnel have access to. Data that is saved electronically (computer system) is protected by the University of Pittsburgh firewalls. Regarding heart rate data collected via the Polar app, these data will only

be stored on the app temporarily (i.e., during the exercise session) in order to continuously monitor safety. This information will be transferred to our secure server as soon as possible after each session to minimize risk of breached confidentiality.

1.3.2. Subject privacy will be maintained in this research study by having all participants answer questions and perform cognitive tasks in an isolated and private room. All of the information that we will collect in this protocol is essential for the research questions we are posing. In this way, there will be no unnecessary personal information collected from these participants.

1.3.3. We will ensure participant confidentiality by coding all participants' data according to a numbering system and separating it from the informed consent and other documents that contain personal information. All informed consent documents and other forms with personal information (such as payment receipts) will be kept in a locked cabinet in a locked room that only researchers involved in the project will have access to. All data collection pertaining to the individual will be stripped of all identifying information. Data files (paper based) pertaining to subject data collection will be kept in a locked cabinet in a separate locked room that only researchers involved in the project will have access to. For data records that are computer based, multiple levels of password protection (e.g., record, file, directory, server, and computer levels) are employed to ensure data security. All personnel involved in the study will be approved through the IRB and will sign a statement agreeing to protect the security and confidentiality of identifiable information.

1.3.4. Regarding exercise procedures, the most common injuries resulting from exercise are strained ligaments, muscles and joints along with delayed onset of muscle soreness. An exercise physiologist with a Master's degree in Exercise Science (George Grove) and who has extensive experience monitoring exercise behaviors in normal and at risk populations will remotely monitor participants during all scheduled exercise sessions. Data to be monitored include heart rate (as collected via the Polar heart rate monitor), speed of pedaling, duration of exercise session, and ratings of perceived exertion. To avoid injuries, participants will gradually increase their exercise session duration and study intervention staff will be made fully aware of any pre-existing physical conditions that would require careful monitoring. All exercise sessions will be programmed to include a warmup and cool down period. Participants will also be reminded and encouraged to wear proper footwear and comfortable and appropriate workout attire for their exercise sessions. Potential problems such as dehydration, heat exhaustion and heat stroke are very uncommon and usually occur in athletes and others involved in extremely vigorous exercise. To prevent heat related illnesses, participants will be encouraged to regularly hydrate during exercise sessions, wear appropriate clothing, to open windows or turn on fans as needed, and to cease exercising if they feel they are becoming overheated. Prior to the start of the intervention, participants will be instructed about signs and symptoms of overexertion so that they can appropriately self-monitor during exercise sessions and stop exercising if needed.

1.3.5. With regards to exercise equipment malfunctions, these will be minimized by the fact that stationary bikes will only be used by on person for the duration of time that person is involved in the intervention. Staff will also be made available to complete repairs as needed and will query participants about any repair needs during weekly check-in calls.

1.3.6. Occasionally someone may develop heart trouble during exercise. Occurrence of such an event is extremely rare (as described in potential risks section above).

However, to reduce the risk of heart troubles during exercise, participants with a history of heart disease will be ineligible to participate in this study. The study will follow ACSM guidelines in regards to contraindications to perform exercise, including systolic blood pressure > 190 mm Hg, diastolic blood pressure > 100 mm Hg, or heart rate > 100 beats per minute. These parameters will be evaluated during the exercise training session prior to the start of the intervention and participants will be disqualified if they exceed these recommendations. Once the intervention has begun, heart rate will be routinely monitored by exercise staff. If heart rate is observed to be abnormally high during home-based exercise sessions, exercise staff will contact the participants to discuss concerns and modify the exercise protocol as appropriate. If excess heart rate continues after modifications, exercise may be discontinued until the participant has been evaluated by a physician and has provided documentation of medical clearance to continue.

1.3.7. Exercise staff have completed a degree in Exercise Science or related field (e.g., kinesiology) and / or have a fitness certification from a reputable organization. All staff will have a minimum of 2 years of experience in exercise supervision and prescription. The exercise prescription level is moderate in intensity and the risk of a cardiac event occurring during exercise is 1 in 400,000 – 800,000 hours of exercise. Given this low level risk, it is not feasible to have a physician on site at each exercise session. All staff involved in the exercise intervention will review the emergency protocol of the hosting community centers. In addition, each session is staffed by individuals who are trained and certified in First-Aid, CPR, and AED use and oxygen administration. Both centers have first-aid kits, AED's and oxygen available at all times. Subjects will start with 10 - 15 minutes of moderate exercise and gradually increase as they can tolerate more. Level of increase will be individually based. This gradual increase is done to prevent injury. If subject becomes injured, they will need clearance from their physician in order to return to the intervention.

1.3.8. Regarding use of the physical activity monitoring device, participants will be guided through the use of the device at the exercise testing session. We will help participants through the fitting process of the device and alert them to the sound the device will make when it is properly adjusted and ready to collect data. We will ensure that participants understand how the device works and how to correctly wear it so as to avoid any discomfort or incorrect usage. We will also instruct participants to notify us if any discomfort occurs. If any discomfort does arise as a result of wearing the physical activity monitoring device, we will instruct participants to discontinue use of the device.

1.3.9. Cognitive and psychological assessments: In order to alleviate any fatigue which may occur, participants will be offered breaks during testing periods. Any person scoring highly on the depression or anxiety items or those who report childhood trauma will be provided with referrals to local treatment providers, including free and reduced cost options, and offered additional consultation with Dr. Donofry (Co-PI), a licensed clinical health psychologist.

1.4. Data Management:

We appreciate the challenges associated with the organization, execution, management, and analysis of a study of this kind and recognize the importance of frequent communication between staff, students, analysts, and investigators. Protection of subject privacy and safety, meticulous quality control, and prudent organization is the bedrock for success of a study like this. For this study, PI Stillman will maintain overall responsibility for data management and quality

control but we have constructed a plan that distributes database and analysis workload across labs and specialization. IT staff will control permissions to the database to ensure proper access and DM by staff, students, and investigators. We will store and link all behavioral and assay data on a HIPPA secure cloud-based server (REDcap). REDcap allow investigators at all sites to access data and coordinate analyses. Data entry to the REDcap database will be completed at the University of Pittsburgh. The data forms in REDcap are similar to the actual paper version of the forms that will be completed by participants and staff. All participant data will be stored and archived on a secure server at the University of Pittsburgh. By having the data base on REDCap, all data is secure is case of a natural disaster in which the server would be completely undamaged.

1.5. Dissemination Plan:

1.5.1. ClinicalTrials.gov. The University of Pittsburgh is strongly committed to supporting compliance with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial information. As such, the University of Pittsburgh Office for ClinicalTrials.gov (http://rcco.pitt.edu/clinicaltrialsgov) provides resources and procedures to assist Responsible Parties with fulfilling the requirements for submission of clinical trial information to ClinicalTrials.gov. Monitoring by the University of Pittsburgh Institutional Review Board (IRB) and Research Conduct and Compliance Office (RRCO) ensures that all clinical trial registrations and results information are obtained in compliance with NIH policy requirements and reported on ClinicalTrials.gov. Per NIH's requirements, the PI will register the proposed clinical trial on ClinicalTrials.gov no later than 21 days after the first participant is enrolled. The PI will also ensure that summary results from the proposed clinical trial are submitted to ClinicalTrials.gov for public posting no later than one year after the trial's primary completion date. Per NIH's policy, this summary information will include participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol, statistical analysis plan, and administrative information. Clinical trial information submitted to ClinicalTrials.gov will be verified, updated, and corrected in accordance with all applicable deadlines established in the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR 11.64). Informed consent documents will also include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov.

1.5.2. Publications. Findings from the proposed study, including baseline observations and intervention outcomes, will be published to scientific journals with broad audiences. I will specifically target journals specializing in health psychology, sports medicine, behavioral medicine, and clinical science. Examples include Psychosomatic Medicine, Health Psychology, Translational Behavioral Medicine, and Clinical Journal of Sports Medicine.

1.5.3. Presentations at meetings. Results from the proposed study will be presented at annual scientific meetings of the Society for Behavioral Medicine, American Psychosomatic Society, and American Psychological Association. I will also present findings at local conferences and symposia, such as the Health Psychology brown bag series at the University of Pittsburgh. As appropriate, findings may also be shared at public community events in an effort to engage the public in scientific discussions and provide information about research activities occurring at the University.

1.5.4. Websites. The Department of Psychology maintains an active website where faculty research findings and accomplishments are highlighted, and announcements for scientific presentations are posted. As findings emerge from the proposed study, they may be featured on the departmental website. In addition, in collaboration with staff members in Dr. Kirk Erickson's lab with web programming experience, I will create a website dedicated to the proposed study. This website will serve as a public access point for information about the study, including details about the study protocol, any publications or presentations based on findings obtained from the study, and information about how to participate.

1.6. References

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