University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS

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Study Title: Acute Exercise Response On Brain Imaging and Cognition

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

SPECIFIC AIMS

We have shown that improved cardiorespiratory fitness following an aerobic exercise program elicits cognitive benefit in elderly subjects and memory improvement in Alzheimer's disease (AD). [1-3] The physiological mechanism may be related to exercise-mediated change in circulating factors that permeate the brain. The response to each individual bout of exercise (i.e. the acute exercise response) may differ between subjects and be key to driving brain benefit. In young populations, the acute response to exercise can last hours [4] and affect brain glucose metabolism. [5, 6] However, we know little about this acute exercise response in AD. Most exercise intervention trials designed to prevent and slow AD, including our own (AG033673; AG034614; AG043962; AG049749; AG053952), assess biomarkers at two fasting time points: pre- and post-intervention. The acute exercise response in the brain and periphery likely varies between subjects and diagnoses and provide key information regarding mechanisms of benefit. Our primary goals are to characterize the acute exercise response to exercise in the brain (glucose metabolism) and periphery (biomarker response) in aging and AD. We will identify relationships between exercise-related factors (i.e. heart rate, biomarkers) and change in brain metabolism and cognition. Understanding these mechanistic relationships will provide specific targets that can be used in future trials to develop individualized exercise prescriptions and maximize benefit.

Accumulating evidence suggests that the exercise-related metabolite lactate is an understudied effector of brain health. Lactate is an essential fuel for neuronal function. [7, 8] It is supplied to neurons through glucose metabolism in nearby glia [9, 10] and from peripheral blood, since the brain is permeable to lactate. [11] A drop in cerebral glucose metabolism is a marker of AD [12]. Thus, supplying neurons directly with lactate for oxidation may supplement energy requirements in AD, as has been suggested with ketones. [13] Importantly, circulating lactate levels rise during exercise [14]. Repeated increases in systemic lactate (acute exercise response) may transiently spare glucose by providing an alternative fuel. With routine exercise, acute responses may elicit adaptations that facilitate the use of lactate beyond that which occurs during acute exercise and contribute to brain benefits observed during chronic exercise interventions. In younger populations, higher exercise intensity evokes a greater lactate response compared to lower intensities [5] and elicits cognitive benefit. [15] Characterizing the acute effects of exercise intensity will greatly inform the design of future trials. We will also characterize diagnostic differences in lactate use. Finally, because acute exercise affects a variety of signaling pathways beyond lactate, we will also characterize the acute exercise response of a selected group of exercise-related biomarkers. We will achieve these goals through the following aims:

Aim 1: Compare the effects of acute, moderate intensity and acute, higher intensity exercise on cerebral glucose metabolism in nondemented (ND) elderly and AD subjects. ND (n=30) and AD (n=30) subjects will undergo a single bout of moderate intensity (45-55% HRR) or higher intensity (65-75% HRR) exercise to assess the effect of exercise intensity on acute change in brain glucose metabolism (rest to exercise). We hypothesize that both moderate and high intensity exercise will elicit a drop in global brain glucose

metabolism compared to quiet rest, but that the effect will be greater with higher intensity vs. moderate intensity exercise, and greater in ND subjects than in AD subjects.
Aim 2: Characterize the effect of both exercise intensities on acute biomarker response and cognition (memory and executive function) in ND and AD subjects. The acute biomarker response to exercise and the effect on cognition has not been examined in aged or AD cohorts. We hypothesize that acute higher intensity exercise will elicit a greater blood lactate response (area under the curve, AUC) compared to acute moderate intensity exercise, and that this response will be greater in ND than in AD subjects. We further hypothesize that lactate AUC will track negatively with change in cerebral glucose metabolism and cognitive performance. Although we will focus on lactate, we will also quantify additional exercise-related biomarkers.

Our overall goal is to characterize the acute exercise response as it relates to brain glucose metabolism in aging and AD. We will also examine lactate metabolism, relationships with cognition, and the effect of exercise intensity. The KU ADC is a recognized leader in the study of exercise and metabolism in aged and AD populations, and puts us in a strong position to successfully achieve these aims.

B. Background and Significance

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting over 5 million Americans, with this number expected to balloon to nearly 14 million by 2050. [1] Annual health care costs associated with AD exceed 200 billion dollars [2] which has led to the formation National Alzheimer's Project Act (NAPA). Goals of NAPA include the creation of a national plan to overcome AD, development of treatments to prevent, halt, or reverse AD, and improvements in early diagnosis and care of AD patients.[3]

Our team has been at the forefront research to characterize the impact of exercise on AD prevention and progression. We have shown that an exercise program improves cognitive (primarily executive) function in nondemented (ND) subjects in an exercise dose-dependent manner. [4] We have further shown that there is a positive relationship between cardiorespiratory fitness change and memory change in individuals with AD who participate in 6 months of aerobic exercise [5] and are currently investigating these effects in subjects with preclinical AD (ClinicalTrials.gov ID NCT02000583). However, not all individuals benefit from exercise, and the precise mechanisms by which exercise elicits a beneficial effect are unclear. We are currently exploring a variety of approaches ranging from molecular to neuroimaging studies to investigate these effects. One of the great knowledge gaps, however, is how little we know about the acute effects of exercise in AD. Most clinical trials, including our own, have been designed to assess metabolic outcomes at two fasting timepoints, before and after the intervention. However, the effects of each acute exercise bout on brain metabolism, and potential mechanisms by which cognition and memory may be affected, remain unclear. We will explore these factors in the current application. *Few groups are as well-positioned as ours to integrate cardiorespiratory fitness measures, acute exercise interventions, and advanced neuroimaging techniques***.**

Exercise benefits the brain: rationale for understanding the acute exercise response in AD

Longitudinal observational studies show a relationship between self-reported exercise and cognitive decline, [6-11] and higher physical activity in midlife and late life is associated with a reduced risk of developing late-onset AD.[12, 13] Furthermore, intervention studies have shown cognitive improvement following exercise in ND and MCI subjects. [4, 14-21] Cardiorespiratory fitness decline tracks with brain atrophy and progression of dementia severity in AD [22] and hippocampal volume has improved with a physical activity intervention in some studies of older adults. [20, 23] In our recent study of exercise in AD subjects, we did not see an overall improvement in memory in the intervention group, but change in cardiorespiratory fitness was positively correlated with change in memory.[24] The finding that cardiorespiratory fitness change is important in achieving memory effects in AD is consistent with work that shows a positive relationship between exercise-related cardiorespiratory fitness change and markers of cortical thickness and brain volume in ND, MCI, and AD subjects. [24-26] It is also consistent with work from our group and others that shows physical activity and fitness levels are associated with larger brain volume.[17, 27, 28]

Importantly, we postulate that cardiorespiratory fitness change is likely driven by the repeated, acute effects of each single, acute exercise bout that is additive over time. These acute effects include changes in peripheral biomarkers that readily cross the blood brain barrier but return to normal within a few hours. However, the effects of acute exercise on the brain are not well understood, especially in aged and AD populations, and at the intensities that are often used in exercise intervention programs. This presents a knowledge gap in the study of the beneficial effects of exercise in aging and dementia populations.

Why study lactate?

The terms "lactate" and "lactic acid" are often used interchangeably and differ by only one proton. Lactic acid is still considered by some to be a waste product generated during exercise, and although controversy still remains regarding the role of lactic acid in muscle acidification,[29-31] there is substantial evidence that lactate plays a critical and beneficial role in a variety of tissues. [32-34] The production of lactate from pyruvate generates NAD+, a necessary intermediate for glycolysis. Peripheral lactate is transported to the liver for regeneration of pyruvate via the Cori cycle; however, lactate is transported throughout the entire body, and during physical exercise, lactate provides a key source of energy for muscle and brain [35-39]. Because lactate is used efficiently by the brain even at rest [40, 41], ***we hypothesize that lactate is a critical energy source for the brain, and that generation of lactate during acute exercise directly impacts glucose metabolism in the brain.*** We will explore the effects of acute exercise on brain glucose metabolism as well as the dynamics of acute exercise biomarkers, including lactate and related substances that may affect brain metabolism.

In 1994, it was shown that that glucose use, lactate production, and lactate release increased with brain activation [42]. This spurred the "lactate shuttle hypothesis" which posits that astrocytes primarily metabolize glucose to lactate, which is shuttled to neurons for use in oxidative phosphorylation (Fig 1A). The concept of metabolic compartmentalization between brain cells is supported by expression of specific monocarboxylate transporter (MCT) isoforms, which transport lactate, in neurons compared to glia. Neurons express MCT2, which is characterized by a high affinity for lactate and limited expression profile, [43] while astrocytes primarily express MCT4, which has low lactate affinity and is implicated in efflux of lactate. [43, 44] It is suggested that astrocytes rely more heavily on glycolysis than neurons [45, 46]. Glycolytic enzyme fructose biosphosphatase is degraded in neurons, suggesting a limited ability of neurons to increase glycolysis and further suggests increased shunting of glucose metabolism towards the pentose phosphate pathway. [47] In short, glycolysis in neurons may be more critical for regeneration of antioxidants like glutathione, rather than generation of pyruvate for oxidation within mitochondria. Finally, studies of mice using FRET technology have shown that lactate can permeate both astrocytes and neurons, with evidence of an astrocyte-neuron lactate gradient. Lactate injection has been shown to increase neuronal lactate uptake relative to astrocytes. [48] Taken together, this molecular evidence suggests that interventions which increase peripheral lactate, such as aerobic exercise, may increase flux into neuronal cells.

Lactate dynamics and exercise

In humans, there is a linear relationship between systemic lactate concentration and brain lactate uptake at physiological concentrations and lactate can contribute to as much as 60% of cerebral metabolism when transporters are saturated. [40] The kinetics of lactate entry into brain indicate the blood brain barrier is about half as permeable to lactate as glucose, but that intracellular uptake of lactate is greater. [49] Recent evidence suggests that the FDG signal is driven by glial glucose use, [50] and that increased supply of peripheral lactate may reduce the FDG-PET signal. [51, 52] Regardless of source, increased lactate supply should drop the FDG signal due to increased availability to both cell types.

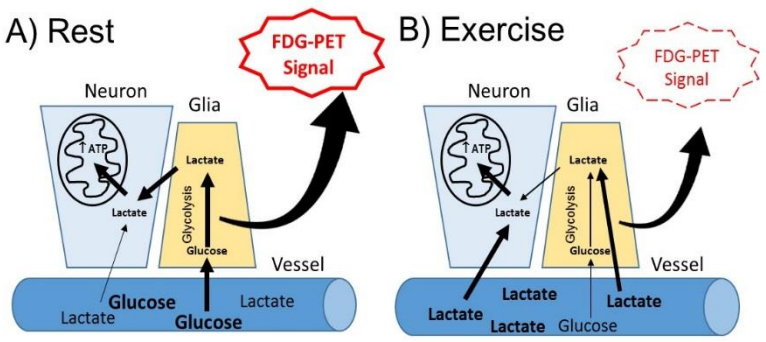


Fig 1. Schematic figure for the effect of exercise on brain glucose metabolism. (A) It has been proposed that glycolysis within glia is a key source for neuronal energy at rest, likely via the intermediate metabolite lactate. B) Acute exercise increases circulating lactate levels, which can permeate the blood brain barrier and freely enter the brain. Lactate can be directly taken up into both neurons and glia, which would spare glucose and decrease the FDG signal.

Human studies: To date, most human studies of lactate and the brain have used lactate infusion and/or exercise, and were performed in healthy young men. A study using a lactate clamp and exercise showed that lactate oxidation during moderate exercise was improved by increasing lactate levels, sparing glucose and decreasing glucose production. [53] Two other studies demonstrated that acute exercise improved cognition, [54] and the cognitive improvement positively correlated with cerebral lactate uptake. [55] Finally, exercise at an intensity which increased circulating lactate levels decreased cerebral glucose metabolism (FDG-PET signal), while lower intensity exercise that did not increase peripheral lactate did not. [51] Although the decrease in cerebral glucose metabolism is proposed to be due to glucose sparing, as energy needs are met by lactate, [51] the cellular fates of glucose and lactate have not been measured directly in humans due to technological limitations. Nonetheless, the acute changes in cerebral glucose metabolism may represent an important measure of **cerebral responsiveness to exercise.** It may also predict changes in resting cerebral glucose metabolism that have been observed in longer exercise intervention studies. [56, 57] However, the effects of acute exercise on brain glucose metabolism have not been assessed in ND elderly or AD populations.

Potential roles of related exercise biomarkers

Although a lactate-specific relationship with cerebral glucose metabolism will be our focus for Aim 1, we will also examine five additional exercise-related biomarkers that affect the brain. These biomarkers will include brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), irisin, and glucose. Our rationale for the selection of these specific exercise-related biomarkers follows. BDNF is a potential mediator of exercise-related brain benefit [20], but its acute response has not been analyzed in AD. Studies in human cell lines suggest that short-term lactate exposure increases BDNF expression in both cortical astrocytes and SY5Y cells. [58] Lactate is positively linked to both BDNF and VEGF levels following exercise, [59, 60] although it is unclear whether lactate drives these responses. In addition, in rodents, exercise-induced elevation of blood lactate increases TGF-β in brain CSF [61, 62]. This may be of relevance as TGF-β is implicated in the mobilization of fat-related energy substrates. We have indirect evidence that energy substrate use during fitness tests may differ based on AD diagnosis, which is discussed later (Fig 4). Furthermore, in rodents, inhibition of TGF-β signaling decreased memory performance and long-term potentiation. [63, 64] Another modulator of fat metabolism and signaling is irisin. [65] Irisin is a relatively newly-recognized hormone that is induced during moderate intensity exercise [66] and has been linked to cognition in older adults at risk for dementia [67].We and others have linked glucose to progression of AD and AD-related neuropathology, [68, 69] and in pilot studies we have observed that glucose and insulin are both acutely responsive to exercise, with large variation between individuals. Quantification of these important exercise- and cognition- related biomarkers will enhance our understanding of the acute exercise response in aged and AD populations.

Acute vs. Chronic effects of exercise on brain glucose metabolism

The directionality of change in brain glucose metabolism following acute exercise likely will not reflect the directionality of change in brain glucose metabolism following chronic exercise. While we expect to observe a decrease in glucose uptake following acute exercise due in part to the availability of lactate for oxidation, it has been shown that a 12wk exercise *intervention* is associated with an increase in brain glucose metabolism post-intervention. [56] Likewise, inactive individuals show reduced FDG signal with age, while active individuals do not, suggesting lifestyle attenuates the age-related drop in brain glucose metabolism.[70] Interestingly, pre-clinical studies have shown that acute exercise modulates a region-specific upregulation of monocarboxylate (lactate/pyruvate/ketone) and glucose transporters that remain elevated at least 18-24 hrs post-exercise [71]. Other work that examined immunostaining patterns of the glucose transporter isoform 1 (GLUT1) showed upregulation in motor cortex following exercise. [72] Although the effect on other transporter isoforms is unclear, this suggests that plasticity in GLUT1 expression may be related to neuronal activity. Over time, acute exercise-related effects may elicit changes in metabolic transporter expression and localization, and thus predict longer-term outcomes. For example, larger acute drops in brain glucose metabolism due to strenuous exercise may elicit greater/longer term change in expression of transporters and increased resting glucose metabolism, although this remains to be

tested. These ideas are outside of the scope of the current proposal, but the current work will lay the foundation for future investigations and trials to explore such mechanisms.

II. Research Plan and Design

Study Objectives:

Aim 1. Compare the effects of acute, moderate intensity and acute, higher intensity exercise on cerebral glucose metabolism in nondemented (ND) elderly and AD subjects. ND (n=30) and AD (n=30) subjects will undergo a single bout of moderate intensity (45-55% HRR) or higher intensity (65-75% HRR) exercise to assess the effect of exercise intensity on acute change in brain glucose metabolism (rest to exercise). *We hypothesize that both moderate and high intensity exercise will elicit a drop in global brain glucose metabolism compared to quiet rest, but that the effect will be greater with higher intensity vs. moderate intensity exercise, and greater in ND subjects than in AD subjects.*

Aim 2. Characterize the effect of both exercise intensities on acute biomarker response and cognition (memory and executive function) in ND and AD subjects. The acute biomarker response to exercise and the effect on cognition has not been examined in aged or AD cohorts. *We hypothesize that acute higher intensity exercise will elicit a greater blood lactate response (lactate area under the curve; AUC) compared to acute moderate intensity exercise, and that this response will be greater in ND than in AD subjects. We further hypothesize that lactate AUC will track negatively with change in cerebral glucose metabolism and cognitive performance.* Although we will focus on lactate, we will also quantify additional exercise-related biomarkers.

A. Study Type and Design:

This is a cross-sectional, observational study to determine the effect of acute exercise on cerebral glucose metabolism in cognitively healthy elderly (n=30) and Probable AD (n=30). There will be 4 study visits. Individuals will be recruited from the KU Alzheimer's Disease Center (KU ADC) Clinical Cohort and Eligibility Database. The study visits are explained below, and a timeline for the FDG-PET scan visits is given in Figure 2.

Figure 2A. Resting Visit Timeline

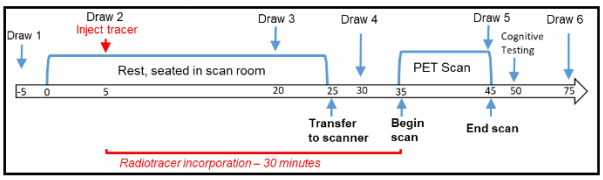
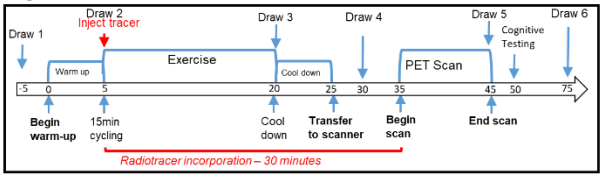


Figure 2B. Exercise Visit Timeline



Study visit summary

Visit 1 (~ 90 mins): Participants will be consented. An exercise test will be administered to determine VO_2 peak, a standard, quantitative measure of cardiorespiratory fitness.[4, 5, 73] Subjects will be called following the visit to complete a CDR evaluation with a clinician and neuropsychometric test battery (UDS 3.0).

Visit 2/3 (~90 mins) V2 will consist of an FDG-PET scan in early morning, after an overnight (8hr) fast, following a period of rest. Six small blood draws will occur during the visit, equaling approximately 40cc total. During radiotracer uptake, the subject will sit quietly. Background factors (lighting, noise, etc.) will be identical between V2 and V3, with the only difference being the acute exercise bout (Fig 2, A-B). We will adhere to strict timing regarding blood draws, tracer injection, and scan time. Following the scan, a short battery of executive function tests (see detailed methods) will be administered (Table 2). **V2 and V3 will be counterbalanced.*

Visit 2/3 (~90 mins): V3 will consist of an FDG-PET scan in early morning, after an overnight (8hr) fast, following exercise. The timing for blood draws and PET scan will match V2. *For both visits we will inject the radiotracer at the timepoint that corresponds to completion of the 5 min warm-up*. In pilot work, we showed that blood lactate levels are elevated at this time using this exact exercise protocol (Fig 3). Following the scan, a short battery of executive function tests (see detailed methods) will be administered. **V2 and V3 will be counterbalanced.*

Visit 4. (~30 mins): We will obtain a structural MRI, which will enhance the analysis of the PET images.

B. Subject Criteria (See Vulnerable Populations appendix, if applicable):

1. Inclusion criteria:
    - Age 60 and older
    - Stable medication doses (>1month)
    - Post-menopausal
    - Diagnosis of either Nondemented (CDR 0) or Probable AD (CDR 0.5 or 1 only)
2. Exclusion criteria:
    - Inability to provide consent
    - Diagnosis of insulin-dependent (Type 1) Diabetes Mellitus
    - Recent ischemic heart disease (<2 years)
    - Diagnosis of an clinically significant chronic disease including CVD, other metabolic diseases (e.g., thyroid), cancer, HIV, or acquired immunodeficiency syndrome
    - Excluded from or unable to complete an MRI scan
    - Any Neurological disorders that have the potential to impair cognition or brain metabolism (e.g., Parkinson's disease, stroke defined as a clinical episode with neuroimaging evidence in an appropriate area to explain the symptoms).
    - Clinically significant depressive symptoms that may impair cognition, abnormalities in B12, RPR, or thyroid function that may impair cognition, use of psychoactive and investigational medications, and significant visual or auditory impairment
3. Withdrawal/Termination criteria: If the participant has a serious AE during the maximal cardiorespiratory fitness test (Visit 1) we will not have the participant return for the rest of the study. Participants are allowed to participate in other observational studies during their enrollment period but not interventional trials.

E. Specific methods and techniques used throughout the study

1. Laboratory tests:

A catheter will be placed to facilitate multiple blood draws. We will draw ~10cc of blood into an EDTA vacutainer tube at 6 timepoints throughout Visit 2 and Visit 3. Lactate levels will be analyzed immediately in whole blood using a Lactate Meter (Nova Biomedical). Blood will be processed for platelet rich plasma (PRP) and platelet free plasma (PFP) and will be stored for analysis. After initial analyses, remaining PRP and PFP will be stored in a locked freezer in Dr. Morris' laboratory (2nd floor Hemenway, badge access area).

2. Study Procedures:

Diagnostic assessment (Visit 1): We will leverage established KU ADC criteria for diagnosing subjects as ND or AD. A clinician evaluates all participants with the Clinical Dementia Rating (CDR) [74, 75] and a standard physical and neurological examination using UDS 3.0 Forms and Scales. The UDS 3.0neuropsychological test battery is then administered. Due to COVID-19, we will be administering the CDR and neuropsychological testing (T-Cog) by telephone to reduce the amount of time spent in the clinic during Visit 1.

To participate in the study, participants will meet criteria for etiologic diagnosis of probable AD (any age, CDR 0.5 or 1) or normal aging (ND, 60 years and older). All participants are required to have a study partner (someone who routinely interacts with participant > 5 times a week) to be available to speak with the clinician via telephone. The study partner will be consented over the phone and will not be required to accompany the participant to any visits. Their involvement in the clinical evaluation will be explained by study staff and will be allowed to ask questions. The study partner will be sent a form from REDCap to add

digital signature. Exclusion criteria include significant neurological disease other than AD that may affect cognition (e.g., stroke, major depression, etc.) history of cancer within the last 5 yrs (except non-metastatic basal or squamous cell carcinoma), history of drug/alcohol abuse (DSM-IV criteria) within the last 2 yrs, and visual or auditory limitations that will interfere with the cognitive assessments. Any available clinical imaging data is also reviewed for abnormalities that may explain cognitive complaints (such as multiple lacunar infarcts or a single infarct > 1 cm^3, prior hemorrhage > 1 cm^3, or evidence of structural damage).

Cardiorespiratory Fitness Testing (Visit 1): Subjects will be tested for VO_2 peak using a Bruce protocol on a treadmill as previously described [76]. Relative ($ml/kg^{-1}/min^{-1}$) and absolute (L/min^{-1}) VO_2 peak and treadmill time to exhaustion will be used as determinants of aerobic capacity. Our ADC has validated VO_2 peak testing in AD patients [76, 77] and in older control adults [4] and currently uses the same assessment in 3 ongoing clinical exercise intervention trials. Subjects are attached to a 12-lead electrocardiograph and wear a non-rebreathing facemask to assess heart rate, blood pressure, and expired air (oxygen, carbon dioxide) using a Parvomedics system. VO_2 peak is the highest observed value during the test[78, 79] and maximal effort is defined as meeting 3 of 4 criteria: a plateau in O_2 consumption, a respiratory exchange ratio (RER) ≥1.0, a maximal heart rate within 90% age-predicted maximum, or volitional fatigue.[80] If the medical monitor detects abnormalities during the ECG, physician's clearance will be required prior to PET scans. This form will be faxed to primary care or cardiologist with ECG and medical monitor's notes.

FDG-PET imaging: FDG PET images will be obtained at a satellite location of the University of Kansas Hospital, the KU Cancer Center – Overland Park (KUCC-OP). The scanner is accredited by the American College of Radiology (ACR), and our physicists perform annual required testing by scanning an Esser PET phantom with 18F to assess SUV range, contrast resolution, spatial resolution, and uniformity. In addition to the ACR annual testing, the nuclear medicine department routinely performs quality control procedures on a daily, weekly, and quarterly basis. Frames are reconstructed to a single PET image in native space. Adverse events will be continuously monitored during the imaging session. The radiation dose from the two FDG PET scans will not exceed 2100 mrem. While this exceeds the amount obtained through normal background exposure, it is considered by Radiation Safety to be well below the risk levels acceptable in research and medical practice. PET images will be analyzed using custom software written for Statistical Parametric Mapping (SPM12). Pre- and post-intervention P images will be co-registered. A priori regions of interest masks from the Automated Anatomic Labeling series will be inverse warped to match native space images. The PET images will be standardized to the uptake value of the cerebellum and standardized uptake value ratios (SUVR) will be calculated from native-space ROIs as determined by MRI. Regional SUVR will be compared using paired t-tests or linear mixed models as appropriate.

Resting Protocol (Visit 2 or 3 – counterbalanced between subjects)
Participants will arrive for FDG PET after having fasted for a minimum of 8 hours and will have a catheter placed for IV administration of FDG. Draw 1 will be performed right before FDG bolus is administered. Subjects will begin resting and will receive a single IV bolus of FDG minutes into resting. Draw 2 will be taken after 5 minutes of rest. Draw 3 will be taken after 20 minutes of rest. The participant will be moved to the PET scanner at minute 25 and Draw 4 will be taken at 30 minutes. The scan will start immediately at minute 35. After the scan is complete a blood draw will be taken at minute 45 and a short cognitive performance test (NIH Toolbox Cognition Battery) will be performed. The final blood draw will be taken after the testing is complete, at approximately minute 75.

Acute Exercise Protocol (Visit 2 or 3 – counterbalanced between subjects): Participants will report to the scan room for the baseline blood draw. After mounting the bicycle, subjects will be asked to begin exercise (warm-up) 5 min before the injection of FDG. One minute prior to warm up, while the subject is resting and sitting on the bicycle, Draw 1 will be taken. At time T0 the subject will pedal at 60-70 revolutions per minute at an equivalent of 40W for 2 minutes. The study coordinator will oversee the workload and provide instruction to the participant as needed. Over the next 3 minutes, the study coordinator will increase the workload to either 45-55% or 65-75% of HRR (depending on randomization group). Blood pressure will be

monitored during the warm up. Four minutes after the warmup begins (1 min prior to FDG injection), Draw 2 will be taken. Immediately following the 5 min warm up, FDG will be injected through the IV catheter that was placed prior to exercise. Following injection, participants will maintain cycling at either 45-55% or 65-75% of their HRR for 15 min. We will use an electronically-braked cycle ergometer (Lode, Groningen, Netherlands) to precisely control HR and workload. Rating of perceived exertion (RPE) will be collected every 2 minutes to assess effort. Participants will maintain a consistent pedaling rate (60-70 rpm) as this may affect physiological variables. [111] Immediately following the 15 min exercise at the target intensity, Draw 3 will be taken. At this time, the participant will begin a cool down period that lasts 5 min. Blood pressure will be monitored during the cooldown. The participant will dismount the bicycle and move to the scanner table. Draw 4 will be taken at 30 minutes before the scan. After the scan is complete a blood draw will be taken at minute 45 and a short cognitive performance test (NIH Toolbox Cognition Battery) will be performed. The final blood draw will be taken after the scan is complete, at minute 75. We will provide up to 120mL of water as needed to account for any dehydration that may affect blood volume during exercise. The amount of water consumed by each participant during exercise will be noted by the study coordinator.

Cognitive performance analyses (Visits 2 and 3): Most work assessing acute cognitive change following exercise has focused on executive function testing. We will administer a short battery of cognitive tests using the NIH Toolbox Cognition Battery on an iPad 5 minutes following the end of the FDG-PET scan at minute 50. These will assess executive function, attention, processing speed and episodic memory, given data linking these domains with exercise and physical activity.[1, 112] Different versions of these tests will be used between the resting and exercise visits where available.

MRI Scan (Visit 4): Structural MRI will use a Siemens 3.0 Tesla Skyra MRI scanner. We will obtain high resolution T1 weighted (MPRAGE) images following the ADNI2 standard. High-res T1 weighted anatomic images provide gross anatomy with high gray-white matter contrast (MP-RAGE; 1x1x1mm voxels; TR=2300, TE=2.98, TI=900, FOV, 1mm thickness, flip angle 9°). Neuroimages will be processed via Freesurfer. [81]

F. Risk/benefit assessment:

Blood draw. This risk is very minimal. However, certain risks including discomfort, blood clot, minor bleeding, bruising, infection, and redness can occur. Aseptic techniques will be used to minimize such risks.

Fitness testing. Some risks are associated with the exercise testing used to assess maximal aerobic capacity. Maximal cardiorespiratory fitness testing is safe in elderly participants[4, 5, 22], but adverse events are possible . Because risks could be serious, initial screening by maximal stress test will be performed in a clinical setting under the direction of a physician. Muscle soreness and strain are possible with exercise testing, but these are not a serious risk. The maximal aerobic capacity test represents greater risk of cardiovascular events than the acute exercise stimulus because of the increased intensity of the exercise. However, events are extremely rare, and participants will be screened for risk of cardiovascular disease and symptoms. Emergency equipment, including defibrillator, and ambulance plan are available for all participants.

Genotype. APOE e4 genotype data will be requested from the KU ADC (HSC #11132) for subjects who participate in the KU ADC clinical cohort and will be generated from all other participants. There is potential negative impact if this information were to become known. Thus, this information will be stored electronically in a secure password protected RedCAP database and any paper copies of records will be filed by number in accordance with professional standards of privileged information in a secure badge-access file room at the KU CRC.

PET/CT Risks. PET/CT scans include exposure to radiation. This radiation exposure is not needed for your medical care. The amount of radiation you receive annually in this study is about the same amount that you receive in 166 months (14 years) from background radiation. The long-term effect of concern from exposure to radiation is an increase in the risk of getting cancer. Most cancers caused by radiation develop

20 or more years after the exposure to radiation.

Adequacy of Protection Against Risk
Protection Against Risk: All research data are maintained confidentially by numerical code in password-protected databases. All paper copies are filed by number in accordance with professional standards of privileged information. Confidentiality is strictly safeguarded by HIPAA-compliant standards. Protected health information is not divulged to any outside party or the subject's personal physician unless requested in writing by the subject after full disclosure of risks related to divulging protected health information. To minimize venipuncture-related discomfort, an experienced nurse clinician performs venipuncture. Maximal exercise testing will be performed in the KU CTSU with the supervision of a medical monitor. A clinician will also be available for the exercise sessions at KUCC-OP.

Potential Benefits of the Proposed Research to the Subjects and Others
The mechanisms that underly exercise-mediated improvement in cognition are not well understood, but may involve peripherally-released factors that are best detected acutely following exercise. Repeated, transient increases in certain biomarkers in response to exercise - the "acute exercise response" could over time provide physiological benefit. Moreover, identifying specific acute effects of exercise on the brain (i.e. changes in cerebral glucose metabolism) may help to quickly identify training modalities/intensities that are most likely to elicit long-term benefit.

G. Location where study will be performed:

Performance sites: Visit 1: KU Medical Center Clinical Research Center (CRC) Clinical and Translational Science Unit (CTSU). Visits 2 and 3: KU Cancer Center Overland Park (KUCC-OP). Visit 4: KU Medical Center, Hoglund Brain Imaging Center (HBIC). Study records will be kept at the KU CRC.

H. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s):

Visit 1: CTSU Exercise Physiologist, Study Coordinator, CTSU Medical Monitor. Visits 2 and 3: KUCC-OP Radiology staff and nurse, PI, Study Coordinator, Visit 4: HBIC MRI Technician

2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Study Coordinator
    b. Obtaining informed consent: Study Coordinator
    c. Providing on-going information to the study sponsor and the IRB: PI
    d. Maintaining participant's research records: Study Coordinator
    e. Completing physical examination: CTSU nurse
    f. Taking vital signs, height, weight: CTSU nurse
    g. Drawing / collecting laboratory specimens: CTSU nurse, KUCC-OP nurse, PI and study coordinator
    h. Performing / conducting tests, procedures, interventions, questionnaires: Exercise Physiologist, CTSU nurse, PI, study coordinator
    i. Completing study data forms: Study Coordinator
    j. Managing study database: PI, Study Coordinator

I. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

Study personnel and/or nursing staff will continually monitor participants for adverse events. Cardiorespiratory fitness testing will be scheduled when a CTSU safety monitor is available. In accordance to the Data Safety Monitoring Plan (DMSP), there will be Data Safety Monitoring Committee (DSMC) assigned to evaluate safety concerns quarterly. A report will be provided to the DSMC with enrollment, adverse event, and protocol deviations. All serious adverse events will be reported to safety DSMC within 48 hours. The PI and other study staff will be examining research data on a subject to subject basis to ensure that it is accurate and to address any problems that may arise with the protocol. In addition Drs. Morris and Perry will meet at least once per month to discuss data collection and any issues that may arise.

Plan for Adverse Event Reporting: Adverse events will be defined as any untoward medical occurrence in study participants or others immediately involved in the performance of the protocol, which does not necessarily have a causal relationship with the study treatment, but results in a change in intervention, daily function, hospitalization or rated category 3 or above using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Expected events such as minor bruising following the blood draw will not be considered an AE. Staff will continually monitor participants for adverse events throughout each study visit and reported to the DSMC on a semi-annual basis

III. Subject Participation

A. Recruitment:

The KU ADC has an excellent history of recruitment. We will leverage the KU ADC Outreach and Recruitment (OR) Core, which reaches more than 2000 individuals annually. The OR Core supports and maintains Eligibility Database, which contains demogrpahic and health information for all individuals who contact the ADC or are referred from clinic (n>7000, ~5000 without cognitive complaints). Recruitment will also leverage the ADC Clinical Cohort, which is comprised of 400 individuals who are characterized annually with clinical and cognitive testing. The OR core has created a novel reruitment model, which consists of a centralized, dedicated team staffed by a lead recruitment coordinator and 4 recruitment specialists. This team supports recruitment and pre-screening. These efforts have improved enrollments and efficiency, receiving national attention as a novel model for approaching recruitment.[82]

B. Screening Interview/questionnaire: N/A

C. Informed consent process and timing of obtaining of consent

The consent form will be mailed to the participant at the time that they are scheduled for the study visit to allow adequate time for review prior to the visit. The participant will be given a phone number to reach the PI and study coordinator if they have any questions prior to the visit. The study coordinator and/or PI will go over the consent form in person the morning of the first study visit and answer any additional questions at that time. If a participant is deemed unable to provide consent for themselves by study staff, they will be excluded from the study.

D. Alternatives to Participation: N/A

E. Costs to Subjects: There is no cost to subjects for participation in this study.

F. How new information will be conveyed to the study subject and how it will be documented: If they wish, we will provide the participant with their VO2 max score from the fitness test. No information regarding brain imaging will be conveyed to the subject.

G. Payment, including a prorated plan for payment:

Subjects will receive a one-time compensation of $200 for participating in this study. They will be given a ClinCard which works like a debit card. At Visit 3, payment will be added to the card by computer. The money will be available within 1 business day. Subjects can use the ClinCard at an ATM or at a store. They will be given one card during the study. The KUMC Research Institute will be given their name, address, social security number, and title of this study to allow them to set you up in the ClinCard system. Study payments are taxable income. A form 1099 will be sent to the subject and the Internal Revenue Service if your payments are $600 or more in a calendar year. The subjects' personal information will be kept on a secure computer. It will be removed from the computer after the study is over and the money on the card has been used. The information will not be shared with other businesses. It will be kept confidential.

Payment for a research-related injury:
We will include the following text in the consent form: "All forms of medical findings, whether routine or experimental, involve some risk of injury. In spite of all safety measures, you might develop medical problems from participating in this study. You must report any suspected illness or injury to the study coordinator immediately. If such problems occur, you will be provided with emergency medical treatment and the investigator will assist you in getting proper follow-up medical treatment. Neither the investigator nor the sponsor will provide compensation for research-related injuries. Payment of lost wages, disability or discomfort is not available. You do not give up any of your rights by signing this form."

IV. Data Collection and Protection

Data Management and Security: Information from these tests will be entered into a research database. The PI and Co-I's together with the study coordinator will supervise the data acquisition. Data will be coded for confidentiality and only the PI, study coordinator, and statistician will have access to the code. Hard copies of study files are kept in a dedicated, locked cabinet in a badge-access area. Subject data will be coded prior to sending it to the statistician for statistical analyses.

Sample / Specimen Collection: Samples will be labeled with a data code, and blood and tissue samples will be labeled with this code and stored in a locked freezer in a badge-access area. Blood and tissue samples will be stored indefinitely.

A. Tissue Banking Considerations: N/A

Procedures to protect subject confidentiality: All outcome measure data will be direct entered onto custom developed electronic source document forms created in Research Electronic Data Capture (REDCap). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap on the KUMC campus sits on a HIPAA compliant, password protected server. The KU ADC has extensive experience building and maintaining REDCap databases, including those used for the preliminary data in this application. Confidentiality is strictly safeguarded by HIPAA-compliant standards.

Quality Assurance / Monitoring

The study team will perform biannual source data verification and self-assessment of records to ensure that data are accurate.

V.Data Analysis and Reporting

A. Statistical and Data Analysis:

The primary statistical analyses for Aims 1-2 utilize paired, pre-, post- acute exercise measurements. As such, we will analyze the data using the two-sample, paired t-tests. This will contrast overall changes in

brain metabolism following acute exercise (i.e., pre- vs. post-exercise differences) and between the intensity groups (moderate vs. higher intensity). We will conduct residual analyses to assess the appropriateness of this methodology to evaluate assumptions of common variance, normally distributed errors, etc. In the event any of the measures do not conform to these foundational assumptions, the nonparametric analogs will be used instead, such as the Wilcoxon rank sum test of the within-subject pre- vs. post-exercise measures. These measures will follow the intent-to-treat principals. Though a randomized design, we will also construct exploratory analyses that incorporate other adjustments using ordinary least squares (OLS) regression on the change scores as the outcomes, also with residual analysis and modified approach if indicated. This will allow for model adjustment to further examine these relationships. One further relationship will involve combining the results of the AD and ND subjects in a single model as described in our Aims. We will use OLS in this context to test for interactions between AD and ND subjects with respect to the acute exercise response (moderate vs. higher intensity) for these pre-/post-exercise change score outcomes. Finally, we will model change score outcomes as functions of the various other change score measures. This approach will enable us to observe how changes in cerebral glucose metabolism are driven by acute-exercise influenced changes in circulating biomarkers. We will conduct similar residual analyses appropriate to the regression models utilized to ensure appropriate inferences are drawn. While descriptive and exploratory in nature, we anticipate that this approach will illuminate and/or confirm our pre-conceived metabolic processes that are related to the acute exercise response, and that it will help identify likely reasons for prior exercise trial successes and failures through mechanistic discovery. We believe this study fits perfectly within the study paradigm for PAR-18-877 by the NIA, which states that identifying precise cellular mechanisms will provide important therapeutic targets.

Sample size justification. We powered our study based upon our primary variable of interest, cerebral glucose metabolism. Based on previous literature [6], the cerebral metabolic rate of glucose following acute exercise at (70% VO2max) (3.18 ± 0.68) was significantly lower compared with that of resting controls (4.25 ± 0.27). This study produced an effect size of 2.07 based on the independent t test design. However, given the small sample size of that initial study, we conservatively use much lower effect sizes. A two sample paired t test design with an effect size of 1.25 and a sample size of 15 AD subjects allocated to high intensity and 15 AD subjects allocated to moderate exercise would yield an estimated power of 91% using a conservative estimated effect size of 1.25. Dropping down to less than half the effect size produced in the preliminary data to 1.00 still provides 75% power, and using a still conservative 1.50 for the effect size indicates >95% power. (Power calculations were produced by nQuery Advisor® 7.0, 1995-2007.) We plan to recruit the same number of elderly healthy patients in the study. Accounting for a possible 10% attrition rate over the course of the study visits, we propose a total sample size of 60 (30 subjects in each diagnosis group with 15 individuals assigned to moderate and higher intensity acute exercise) Thus, we anticipate recruiting the sample size of 66, which will provide over 90% power based on a conservative estimate of the effect size from the literature and the use of paired difference scores for the primary endpoint, which should reduce variation in the response.

B. Primary Outcome:

We expect that the global FDG-PET signal will decline following a single bout of acute exercise in AD and ND subjects, and that the drop will be greater from rest to higher intensity exercise compared to the drop from rest to moderate intensity exercise. We further expect that individuals who have a greater lactate AUC in the exercise compared to resting condition (i.e. greater “lactate response”) will have greater drop in cerebral glucose metabolism. This likely means that they are exercising closer to their lactate threshold – the point where blood lactate concentrations begin to increase exponentially. Thus, we expect to see a negative linear relationship between change in lactate AUC and change in cerebral glucose metabolism, and a positive relationship between change in lactate AUC and change in cognitive performance.

C. Study results to participants:

If participants request, we will provide them with their maximal VO2 value. Some participants find this data interesting. This value does not have any clinical or diagnostic implications so we do not expect any harm to come from providing this information.

D. Publication Plan:

Publication of the results of this study will be governed by the policies and procedures developed by the study team.

APPENDIX I: VULNERABLE POPULATIONS

Cognitively or decisionally impaired individuals: Any individuals with moderate or severe dementia be excluded from this study. Only individuals with very mild or mild dementia will be screened and scheduled. During Visit 1, the clinician will verify (based upon their full clinical examination) that participants can consent for themselves. If the clinician determines that the individual requires a surrogate decision maker, they will be excluded from the study. We will only enroll individuals deemed able to consent for themselves. In our experience, individuals with very mild or mild dementia (CDR 0.5 or 1) are able to consent for themselves while individuals with moderate or severe dementia (CDR 2 or 3 based on clinical examination) require surrogate consent.

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