Study Title: Effects of combined exercise training and Ketone ester on muscle strength and cardiovascular response in Parkinson's disease

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Effects of combined exercise training and ketogenic diet on muscle strength and cardiovascular response on Parkinson's disease

Background: Most of the research emphasis in Parkinson's disease has been on the basal ganglia and dopamine. This research paradigm has led to the successful introduction of dopaminergic drugs in clinical practice. Although L-DOPA remains the mainstay of PD management to date, this drug fails to prevent disease progression. In contrast, accumulating evidence has shown that exercise may be the only therapy with disease-modifying effects in PD. The ability to exercise optimally declines with disease progression due to systemic frailty and sarcopenia in advancing PD. In other words, those persons with PD who need exercise the most may be the least able to reap its benefits. Previous work on ketone supplementation has established an improvement in endurance cycling performance in persons with Parkinson disease (PwPD) (Norwitz et al., 2020) and elite athletes (Cox et al., 2016).

Critical Knowledge Gap: Although exercise is known to have effective disease-modifying effects on PD progression, there are no standard therapies to improve muscle bioenergetics so that biological effects of exercise can be better exploited over time in people with PD. A prior study showed that one-time consumption of a ketone ester supplement boosted endurance exercise in PwPD. Effects of ketone supplementation on cumulative exercise sessions, and benefits to strength versus cardiovascular endurance remain unknown.

Problem to be solved: A critical but unmet need in exercise management of PD is the lack of an effective therapy to improve muscle bioenergetics during exercise so that biological effects of exercise can be better exploited in people with PD over time. Repeated dietary supplementation with a ketone ester presents a promising, incompletely understood potential intervention.

Specific Aim: To explore the effect of ketone ester supplementation on aerobic exercise tolerance in persons with Parkinson's disease.

Hypothesis: Ketone ester will help improve exercise performance on endurance cycling at 80 rpm at a personalized fixed-wattage, and improve performance on the quadriceps maximal strength test when compared to exercise alone.

Background

<u>Ketone supplementation in neurodegeneration and exercise</u>:

Ketone ester supplementation, and the ketogenic diet (consisting of preferential intake of predominant medium and long-chain fatty acids and minimization of carbohydrates) have become a subject of recent research in metabolic and neurodegenerative disorders. Preliminary positive findings have been reported mainly from short-duration studies. Both the ketone supplementation and the ketogenic diet are meant to induce a state of ketosis, characterized by elevated levels of ketone bodies in the blood.

Ketones levels in blood are naturally elevated during a fasting state, or during a low glycemic state which may brought on by performing a prolonged bout of exercise. The exogenous C8 ketone di-ester used in this study is a naturally occurring molecule in the body and is converted to ketone bodies by the liver by the same mechanisms as endogenously produced ketone esters.

KE supplementation in elite athletes has previously been shown to enhance endurance exercise performance in elite cycling endurance (Cox et al.,2016). In addition, a proof of principle study from Oxford demonstrated that one-time KE supplementation improved aerobic exercise endurance in participants with PD (Norwitz et al., 2020) on a maximal endurance cycling test.

Exercise interventions and Parkinson's disease:

There are currently no disease-modifying drug therapies for PD. Standard treatment involves dopamine replacement with levodopa, a medication that has a temporary window of efficacy, can induce dyskinesia, and does not address the non-motor symptoms of PD (Hinnel and Ray, 2009). Moderate to high-intensity exercise may be the only therapy with disease-modifying effects in PD. A comprehensive review of PubMed literature from the Mayo clinic concluded that there is compelling evidence of midlife cardiovascular exercise slowing the disease progression of PD (Ahlskog., 2018). Research in animal models has shown that exercise has neuroprotective effects against dopaminergic toxins such as 6-OHDA and MPTP (Tajiri et al., 2010). Retrospective study of the interaction of exercise and incidence of Parkinson's (Chen et al., 2005; Thacket et al., 2008; Xu et al., 2010) demonstrates that vigorous exercise in midlife reduces the risk of developing PD. When assessing exercise history, engaging in moderate to high-intensity exercise was associated with a 38% reduced risk of developing PD.

In addition**,** cycling is known to be an accessible and beneficial exercise mode even for PD patients who exhibit freezing of gate (FOG), who may not be able to exercise effectively through walking or running. FOG is associated with abnormal beta-band oscillations in the cortico-basal ganglia loop during walking, and these abnormal oscillations are reported to be weaker and briefer upon initiation of cycling movements. This is suggested to be due to the continuous nature of cycling, and the lower amount of proprioception required to maintain balance as compared to walking (Licen et al., 2022). Previous interventional exercise studies have also emphasized the cadence of cycling as a critical factor for therapeutic benefit to PWPD. Cycling at 80 RPM conferred benefits to motor symptoms of PD on the UPDRS that last for at least a month, and such improvements were not seen at lower cycling cadences (Ridgel et al., 2009, 2015, 2019). No significant reduction was shown for participation in light physical exercise. In addition, the Study in Parkinson's Disease of Exercise (SPARX) reported that high-intensity treadmill exercise but not moderate-intensity exercise, prevented progression of motor symptoms of PD over 6-months (Schenkman et al., 2018). These data suggest that vigorous exercise is disease-modifying in PD.

Overall strategy

General Overview: Sixteen patients with Parkinson's disease (PD) will be recruited to participate in this exploratory clinical study with a randomized, placebo-controlled, double-blind design. Patients will be randomized into one of two groups: (1) Group A (experimental): consuming ketone ester (KE) beverage before each of 12 1-hour sessions of aerobic exercise, or (2) Group B (control): consuming placebo electrolyte (EL) beverage before each of 12 1-hour sessions of aerobic exercise. Participants will have 3 testing visits and 12 intervention visits to the laboratory over the course of 4-6 weeks. Patients will undergo physical, cognitive, and metabolic testing before and after the endurance cycling intervention. Prior to exercise testing participants will be cleared for exercise by a resting twelve-lead electrocardiogram and Physical Activity Readiness Questionnaire. Primary Outcomes will consist of the time of 80 rpm endurance test, and VO2 testing during exercise and rest (Cosmed Quark). Additional optional measures of isometric and isokinetic quadriceps muscle strength (Biodex 4 dynamometer) and/or hand grip strength may be collected. Blood levels of glucose, β-HB, and lactate will be sampled and measured throughout each interventional day by fingerstick- up to 3 samples will be taken at each visit. Blood lactate will be measured using a The Edge™ device, and blood glucose and β-HB will be measured using a Keto-Mojo™ device. Participants will be asked to wear a continuous glucose monitor (CGM) during the study. An MRI scan of the brain will be performed pre and post intervention to study network connectivity changes as an exploratory outcome.

Participants and Screening

Human Subjects

Description of subject populations:
PD (net n=24) Diagnosis of PD in PD participants (M/F, age 45 years and over) will be based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Research Criteria (patients with clinically significant dementia will be excluded; Hoehn & Yahr Stages 1-2.5 included)

Exclusion criteria:

1. Any recent changes in EKG, history of myocardial infarction or other cardiac event or other cardiac contraindications to exercise
2. Inability to use a step, stand, walk, or use a stationary cycle ergometer;
3. History of symptoms in exercise that preclude safe and comfortable participation, such as dizziness and lightheadedness, orthostasis, severe symptomatic leg or back musculoskeletal pain, painful neuropathy, significant ankle edema or medication side effects;
4. History of symptomatic cardiovascular or pulmonary disease interfering with exercise;
5. History of active rheumatoid arthritis;
6. History of uncontrolled chronic pain syndrome;
7. Any other history of medical or psychiatric comorbidity precluding safe participation in the project;
8. Poorly controlled diabetes
9. Pregnancy or breastfeeding
10. Clinically significant dementia
11. Any contraindications to MRI (metal implants, severe claustrophobia, inability to lie still for 1 hour, etc.) The MRI portion of the study is optional, so participation in the remainder of the study can occur for individuals with contraindications to MRI.

Study timeline: This study, to be conducted over a 2-year period, will include a net total of n=24 subjects (22 participants + 2 for 10% attrition of drop out).

Subject Recruitment: Prior to any research procedures, written informed consent will be obtained from each subject followed by initial study eligibility screening. PwPD subjects will be recruited from the University of Michigan Functional Neuroimaging, Cognitive & Mobility Laboratory subjects list who have consented to be contacted for new studies.

Study design: Phase 1B randomized controlled clinical trial.

Baseline Testing

After obtaining informed consent and screening for study eligibility, study participants will undergo the baseline clinical assessment. The exploratory motor components of the test battery will be performed in the dopaminergic medication ‘off’ state in the morning after overnight withholding of their dopaminergic medications. Participants will complete the MDS-UPDRS, MINI-BEST & APDM, Biodex strength assessment

followed by the baseline aerobic test, the 80 rpm endurance test, and the anaerobic threshold test. Following the motor testing, participants will take their dopaminergic medication and complete the exploratory neuropsychological evaluations and questionnaires. The exploratory neuropsychological assessments include Judgement of Line Orientation test (JOLO), Parkinson's Disease Cognitive Rating Scale (PD-CRS), Parkinson's Disease Cognitive Function Rating Scale (PD-CFRS), California Verbal Learning Test II (CVLT-II), Delis-Kaplan Executive Function System (D-KEFS), Wechsler Adult Intelligence Scale III (WAIS-III), and Wechsler Memory Scale (WMS-III). The questionnaires include the Parkinson's Disease Questionnaire (PDQ-39), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale, Physical Activity Questionnaire, and the Beck Depression Inventory II (BDI-II).

Baseline Aerobic Test

To determine intensity for the training intervention, participants will engage in a baseline aerobic test (Norwitz et al., 2022). Participants will come in fasted and following overnight withdrawal of dopaminergic medication (levodopa and dopamine agonists), in an "off' state. After being cleared for exercise by a resting 12-lead electrocardiogram, blood glucose test (>70mg/dL), and physical activity readiness questionnaire, participants will be instructed to cycle on a Keiser cycle ergometer at a controlled cadence.

After familiarization with the cycle ergometers, description and explanation of the procedures and adjustments related to body position as well (seat height, seat distance, and handlebar on each cycle ergometer), the test will begin with standardized warm-up at cadence of 80 rpm at 50 watts for 4 minutes. Thereafter, wattage will increase by 10 Watts every 2 min until the participant voluntarily ends the test or is unable to sustain a cadence of >70 rpm at the wattage interval. 30 seconds before the end of each stage participants will be asked to rate their exertion on the Borg RPE scale (6-20). Resting heart rates, heart rates taken at the end of each stage of the baseline test, and approximated maximum heart rate (220 – age) will be used to create a linear regression of wattage as a function of heart rate. Each participant's fixed-Watt value for subsequent tests will be set at 55% of their projected wattage at a maximum heart rate. In order to standardize test length, participants exhibiting lower physical capacity will begin at 25 watts for the baseline test, or cycle at 75% of projected wattage at maximum heart rate on the endurance test. The Keiser™ M3 cycle ergometer, the wattage is calculated as the product of speed (rpm) for the gear (from 1 to 24), considering the time required (in minutes) for its 16.8kg wheel to travel one meter, and is presented on the display (Viega et al., 2020).

80 rpm Endurance Test

The endurance test will be conducted on the same cycle ergometer as the baseline test and begin with the same 4-minute warmup at 50 watts. Thereafter the participants will cycle at their personalized fixed wattage at 80 rpm until failure, defined as the point at which the participant could not sustain a cadence of >70 rpm for a cumulative total of 20 s, or until voluntarily choosing to end the test (Norwitz et al., 2022). Participants will be encouraged verbally throughout the test.

One-Minute Anaerobic Threshold Test

After the 80 rpm endurance exercise test, participants will rest their heart rates return to near baseline and they self-report they feel fully recovered (~5 min rest). Participants will then engage in a 1-min anaerobic threshold test. Participants will be instructed to cycle at as high a cadence as possible at the ergometer resistance that achieves their personalized target wattage (calculated from baseline test) when cycling at 80 rpm (Norwitz et al., 2022). Within 60s, immediate post-exercise, β-HB, glucose, and lactate levels will then be measured.

Biodex Strength Test

Participants will sit (~85° hip flexion) on an ergometer (Biodex System 4). The upper body will be stabilized with straps across the thorax and abdomen. Knee joint axis of rotation will be aligned with the measurement axis of the system. The leg being tested will be strapped around the mid-thigh. The knee angle will be placed at 90° to cancel the effect of gravity on the test. Participants will be instructed to perform maximal effort during a static knee extension and to limit countermovement. At least three maximal voluntary contractions will be recorded. A fourth and possibly fifth trial will be performed if the value reached during the last trial is higher than the preceding ones, or if the difference between trials was greater than 10%. Participants will be encouraged verbally throughout the test. Primary outcome will be the mean torque value for each leg. Biodex testing for isometric strength is established as the gold standard in the field and highly reliable (Feiring et al., 1990). Protocol for Biodex isometric testing on knee extensors taken from prior studies at University of Manitoba (Ogborn et all., 2021)

Magnetic resonance imaging (MRI)

The exploratory MRI scan will be performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands). A 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200x160 slices and reconstructed to 1mm isotropic resolution. Resting-state fMRI scans will be acquired using a 32-channel head coil and multi-band sequence (32), with nominal parameters: (TR/TE/FA = 720/34/52, 2mm isotropic resolution, 72 slices). Data are collected with eyes fixated on a cross for 10 minutes (33). Pre-processing follows our standard pipeline that includes physiologic noise reduction and thorough motion correction (34, 35). Graph theory analysis will be used to identify the most highly connected nodes following published methods. Briefly, ROIs will be represented as nodes and pairwise correlations, based upon the mean time series for each ROI, will serve as weights over corresponding edges, thresholded by FDR correction, $p<0.05$ (34, 35). Change from baseline will serve as the primary measure of interest in this optional assessment.

Intervention

Cycling Intervention

After the baseline cycling test day, the participants will come into the lab to complete twelve 1-hour sessions of cycling on the ergometer, 1-hour exercise per visit across a 4-6week period. On each intervention day, study participants will arrive fasted and 1-hour prior to exercise they will take their dopaminergic medication followed by ketone ester or electrolyte placebo. Physical activity readiness questionnaire and heart rate monitoring will be done before the beginning of each session. Before each exercise session, participants will have their blood glucose measured and assessed to determine if it is within the normal range. Participants displaying hypoglycemia (blood glucose <70mg/dL) will discontinue

exercise for that session and reschedule. Participants displaying hypoglycemia a second time will discontinue the study and be referred to their primary care physician.

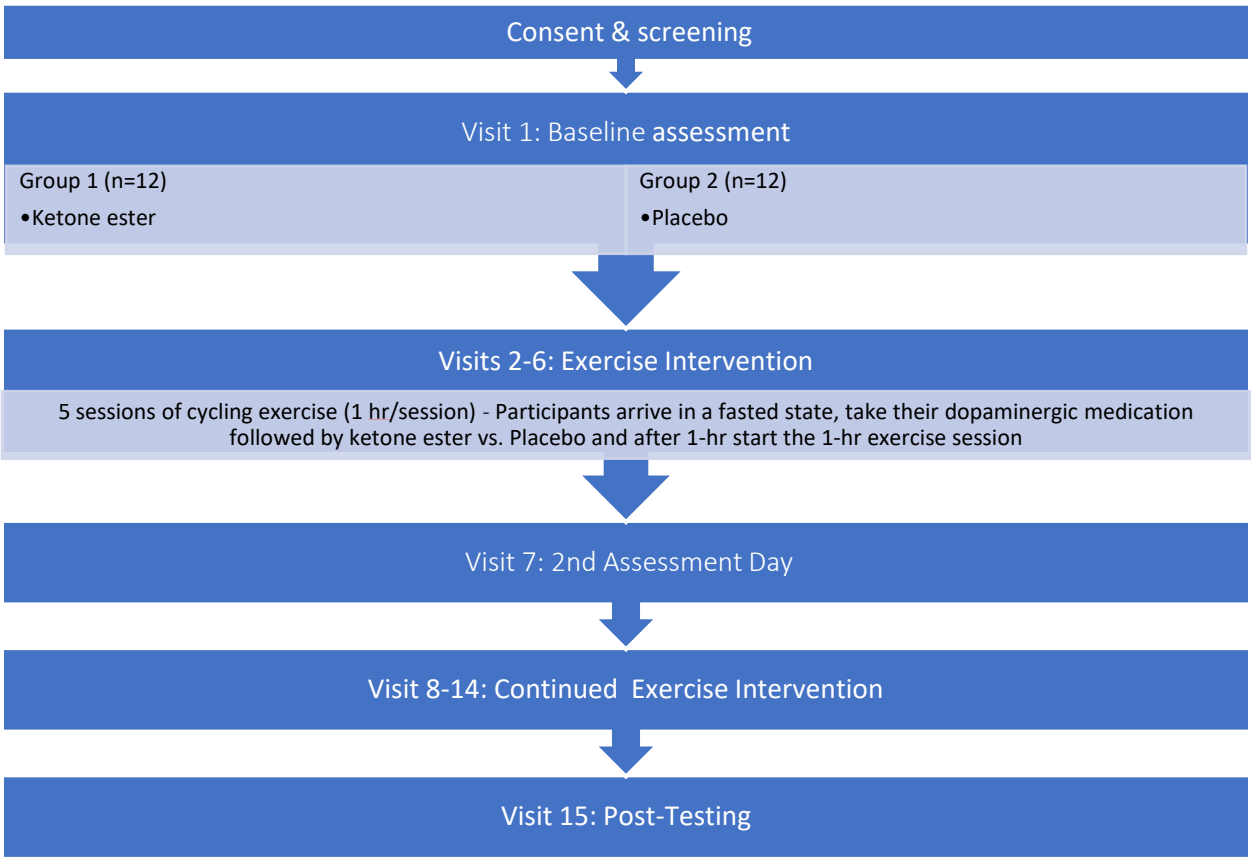
For each session, participants will complete a 10 min warm up followed by 8 intervals consisting of 3 min "fast" cycling at 80-90 PM followed by 2 min of "slow" cycling at ≤60rpm, followed by a 10-minute cooldown. Target HR for "fast" intervals will be 75% estimated max heart rate, measured at the peak HR typically shortly (within ~10s) after each interval. Ergometer resistance will be adjusted throughout the session to allow the participant to consistently reach their target HR. This protocol is based on a study in which PD participants followed these training parameters 3x/wk for 8 weeks and exhibited improved neurological and motor symptoms of PD compared to normal controls (Mariusiak et al, 2019).

To assess the impact of ketone supplementation alone on patients' exercise performance, participants will come into the lab in an "off" (abstaining from dopaminergic medication) and overnight fasted (>8hr) state, in the same fashion as the baseline testing procedure. After arrival, the participant will take their medication and at 1-hr prior to exercise testing participants will have β-HB, glucose, and lactate levels measured by fingerstick. A new lancet will be used to draw blood from either the index or middle finger and the first drop of blood will be discarded prior to measurements. Immediately thereafter, the participants will receive either the KE drink or the EL drink. 1-hr after receiving the study drink, participants will again have β-HB, glucose, and lactate levels measured before beginning the training. These blood values will be measured again immediately following the exercise session.

Drink Preparation and Randomization

The two drink preparations that will be used in this study are a ketone ester plus electrolyte drink (KE), consisting of 2 scoops (=25 g C8-KE) of Quitone Pro-Ketone Powder and electrolyte solution diluted in water, and an electrolyte only drink (EL) consisting of electrolyte solution diluted in the same amount of water. Drinks will be prepared in a room separate from participants and administered in an opaque container. As this is a randomized study, the order in which the drinks are presented to the participants will be determined by a random number generator, with even numbered participants recieving the KE drinks and odd numbered participants receiving EL drink. One study team member will be responsible for mixing all the beverages administered in the study, will maintain the a log indicating which participants were in the placebo arm or the treatment arm, and this team member will not participate in any assessments or data collection in the study. The other study team members will not be unblinded until the conclusion of the entire study.

Study outline:



Assessment Schedule:

	Baseline: Visit 1	Exercise Intervention Visits 2-6, 9-14	2nd Assessment: Visit 7	Post-Testing: Visit 15
Total Time	6 hours	2 hours	6 hours	6 hours
Informed Consent	✓			
Demographic Information	✓			
Inclusion/Exclusion Criteria	✓			
Clinical, Balance & Neurological Assessment[1]	✓		✓	✓
Resting Electrocardiogram	✓			
Blood measurements		✓		
Ketone Ester Supplement or placebo		✓		
Biodex Strength Assessment	✓		✓	✓
Baseline Aerobic Test [1]	✓			
Cycling Intervention		✓		
80 RPM Endurance Test [1]	✓		✓	✓
One-Minute Anaerobic Threshold Test [1]	✓		✓	✓
*MDS-UPDRS I &II	✓		✓	✓
*MDS-UPDRS III[1]	✓		✓	✓
*Mini-BESTest [1]	✓		✓	✓
APDM Mobility assessments[1]	✓		✓	✓
*PDQ-39	✓		✓	✓
Activity questionnaire	✓		✓	✓
*MoCA	✓		✓	✓
*PD-CRS[2]	✓		✓	✓
*PD-CFRS[2]	✓		✓	✓
*JOLO[2]	✓		✓	✓
*CVLT-II[2]	✓		✓	✓
*D-KEFS[2]	✓		✓	✓

*WAIS-III[(2)]	✓		✓	✓
*WMS-III[(2)]	✓		✓	✓
*Epworth Sleepiness Scale	✓		✓	✓
*FSS	✓		✓	✓
BDI-II	✓		✓	✓
Adverse event assessment	✓	✓	✓	✓
DEXA	✓		✓	✓
*MRI	✓		✓	✓
Urine pregnancy test in women of childbearing potential	(Within 48 hours of the dexa scan)		(Within 48 hours of the dexa scan)	(Within 48 hours of the dexa scan)

(1) Performed in dopaminergic "off" state- unless otherwise noted in this table, all assessments performed in "on" state (taking dopaminergic medication); * Exploratory measure.

Statistical analysis:

We will begin by calculating summary statistics (mean, median, SD, range, etc.) as well as plots of all data. All analyses will be performed using SPSS or R software package. The primary aim of this study is to compare the ketone group with the control group prior to and at the end of the 5 sessions . A t-test will be used to determine if the change in duration of 80 rpm endurance test and One-Minute Anaerobic Threshold Test between baseline and after 5 sessions is different between the two groups. Analogously, we will use a t-test to determine the difference in other outcome parameters between the groups (using time points 2 and 3) too. For all aims a 2 tailed t-test will be performed.

Risks

Risks associated with the ketone ester: The risks to participants are low. Studies in humans have shown evidence of nausea, gastro-intestinal discomfort, abdominal distention, diarrhea, dizziness, lightheadedness, sweating, headache, keto flu-like symptoms, heartburn, shakiness, sleep changes, other symptoms of hypoglycemia, and/or increased glucose levels. Poor or bitter taste is a more common side-effect. Therefore, the KE drink may be diluted. Prior work has shown that the 25g dosing regimen proposed in this study has been found to be safe and generally well-tolerated in healthy controls and patients with type 2 diabetes mellitus (Soto-Mota et al., 2019, 2021). A clinician may be recommended by a study-affiliated clinician to study participants who begin developing symptoms of nausea or upset stomach.

Risks associated with exercise testing: There are cardiac risks associated with participating in exercise testing and training. A review of studies documenting the average number of cardiac events per 10,000 exercise test indicates the risk is very low, with approximately 3 cardiac events per 10,000 tests (Goodman et al., 2011). The risk of this happening to participants is very rare, because it occurs in less than 0.001% of people. Other side effects or risks of exercise include an increase in heart rate, an increase in blood pressure, shortness of breath, general fatigue, and in some cases muscle soreness. We will perform a 12-lead EKG assessment of cardiac health and function. In the event that participants experience a serious medical condition during assessment of physical function, research staff will stop the session and appropriate emergency medical care will be provided. This may include providing emergency care until appropriate medical personnel arrive. Exercise-induced hematuria is a rare risk for stationary cycling and

typically resolves within 72 hours without specific treatment. Participants exhibiting exercise-induced hematuria will be monitored and will be referred for their physician if the condition does not resolve within 72 hours of first incidence.

Risks associated with clinical, neuropsychological and behavioral testing: This study involves cognitive tests and questionnaires. The cognitive tests are not harmful, but some people find them frustrating and concerning. Risks regarding the neuropsychological and behavioral assessment are limited to fatigue, frustration, boredom, and momentary embarrassment that may occur when one experiences difficulty performing a task or learning a new skill. Some people may be uncomfortable/embarrassed disclosing personal information or become nervous about memory testing and may experience discomfort or become tired. Study team members are very well experienced in the assessment of older individuals and persons with dementia, understanding the need for breaks, gentle reassurance, or reinforcement. All assessments will be stopped if requested by the participant.

MRI scan: There is a substantial risk to persons who have metallic objects inside their bodies, as the magnet in the MR scanner can cause these to move. Consequently, participants with pacemakers or metallic objects located in the eye, ear, brain or blood vessel walls will be excluded. There is a potential risk of heart rhythm disturbances in patients who have previous heart rhythm abnormalities or in patients who have certain types of heart pacemakers. If an X-ray study is required to rule out the presence of metallic fragments, the maximum radiation dose to the involved body area will be 0.3 rems (a unit of radiation dosage), with minimum exposure of the other areas of the body. Participants who developed claustrophobic anxiety during scanning found that this fear dissipated within 15 min while remaining in the scanner, or as necessary, after exiting the scanner. There also is the potential that imaging could reveal a previously unrecognized but pre-existing abnormality. Many such abnormalities are not clinically significant, but they may cause anxiety or require further investigation by a personal physician. If one of the investigators identifies such an abnormality, they will contact the personal physician, who will arrange for appropriate care.

Data & Safety Monitoring Plan (DSMP)

Dr. Christopher Chauncey Spears, MD and/or Dr. Amelia Louise Heston, MD from Department of Neurology, University of Michigan will review outcomes with the PI on a semi-annual basis. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the study is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed.

A monthly review of study procedures and adverse effects will be performed by the study team. The PI will be responsible for the day-to-day monitoring of any potential breach of confidentiality and for reporting any adverse events (AE) following University of Michigan IRB guidelines.

For purposes of this study, an AE is defined as any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with participation in this study, whether a causal relationship with the study has been established.

Breaches of confidentiality will be considered related to the research whenever they occur and will be reported. Withdrawals from the study and the reason for these withdrawals will also be reported. The PI will be in daily contact with the PT and study research staff. The research staff will test the participants, score, and enter the data and will monitor their procedures to ensure that confidentiality is maintained.

Research staff will be responsible for reporting any significant events to the PI. The PI will ensure that the IRB is notified of any adverse event following the IRB guidelines.

Expected and unexpected serious (including fatal) adverse reactions and major unresolved disputes between the research investigator(s) and the research participant or between research investigator(s) will be expeditiously reported to the IRB of the University of Michigan. At the time of renewal, the IRB will be provided with a summary indicating the frequency of the monitoring, cumulative adverse event data, information regarding participant safety or ethics changes, confidentiality issues, benefit-to-risk changes, and recommendations on continuing, changing, or terminating the study.

For risk of suicidality (if participants select answer responses 2 or 3 for question 9 on the Beck Depression Inventor, i.e. 'I would like to kill myself' (answer 2) or 'I would like to kill myself if I had a chance' (answer 3) then the staff will hand out the UM Depression brochure, refer to the contact information and also inform Dr. Spears or Dr. Heston who will discuss this with the participant. The face-to-face conversation with the physicians must occur during that visit and must not be deferred. There must be a safety plan in place before the patient can leave the building.

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