University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS

Study Title: Intervention to Reduce Sitting Time in Mild Cognitive Impairment (ReST-MCI)

NCT#: 02878486

Principal Investigator: Amber Watts

Co- Investigator(s): John Thyfault, Christie Befort

Version date: May 5, 2016

I. Purpose, Background and Rationale

A. Aim and Hypotheses

Older adults are highly sedentary, spending more than 60% of waking time sitting. Independent of physical activity, daily sitting time is a risk factor for poor glycemic control and type 2 diabetes. Glycemic control and insulin sensitivity are inexorably linked to Alzheimer's disease (AD) and cognitive decline. Individuals with mild cognitive impairment (MCI) and AD display physiological differences in insulin and glucose regulation compared to older adults without cognitive impairment. Reducing sitting time and taking frequent breaks from sitting have resulted in improved glycemic control and insulin sensitivity within hours. Studies are beginning to suggest that time spent in seated activities (e.g., TV) is associated with poorer global cognitive function and risk of AD independent of physical activity.

The proposed study directly addresses the recommendations of an NIH sponsored workshop on "Physiology of Sedentary Behavior and its Relationship to Health Outcomes." 1) We will investigate the physiological correlates of sedentary behavior by assessing glycemic control and insulin sensitivity. 2) We will focus on the impact of lack of movement as distinct from the effects of movement by objectively measuring both simultaneously. In individuals with MCI, we will evaluate whether a behavioral intervention to reduce sitting can alter physiological processes known to contribute to disease pathology.

Cardiorespiratory fitness changes that occur with moderate or vigorous aerobic exercise may not be essential for improving brain health and cognition, as demonstrated by studies of activities that do not robustly improve fitness (Tai Chi, resistance training, Wii fit), but still show improvements in brain health and cognition. Even low intensity, non-exercise activity is associated with reduced risk of cognitive decline and healthier cardiometabolic measures. In fact, non-exercise activity accounts for the vast majority of daily activity, while exercise accounts for only 2-5%. More evidence is needed to determine whether reductions in sitting time are sufficient to produce changes in cognitive performance, brain volume, or neurogenesis as seen in aerobic exercise interventions.

Interventions targeting sedentary behavior can effectively reduce sitting time (average 42 min/day), but few studies have evaluated whether these reductions result in clinically meaningful outcomes and none have been conducted in older adults with MCI. **We propose a <u>feasibility</u> study of a 12-week home based behavioral intervention to reduce sitting time among sedentary older adults with MCI and their caregivers.** The intervention is designed to break up prolonged bouts of sitting and replace sitting behavior with standing and light or moderate intensity activities associated with improved cognitive performance among people at risk for AD. Our proposed intervention adds innovative elements that are empirically rigorous compared to previous studies: 1) it uses objectively assessed electronic postural monitoring, 2) it provides electronic feedback to promote sitting times <30 minutes, 3) it assesses insulin sensitivity and glycemic control which are sensitive to changes in sitting after a short duration and which few previous interventions have measured, 4) it is conducted in the home and targeted to individual habits and physical environments that reinforce sitting behaviors, 5) it targets sedentary older adults with MCI, which has not been done before, and 6) it capitalizes on the caregiver/patient dyad to help improve adherence to the behavioral change regimen.

Specific Aim 1: Determine feasibility of a 12-week home and telephone based intervention in older adults with mild cognitive impairment targeting both the impaired individual and their study partner to help initiate and maintain behavior change. We will recruit KUADC registry participants with MCI and their caregivers (as study partners). Behavioral interventions are more effective when there is built in social support. We will evaluate feasibility in terms of successful recruitment and retention of participants, 10% or less of technological failures, rate of participant concerns addressed by phone and at home visits, acceptability of the intervention to participants (measured by questionnaires during home visits).

Specific Aim 2: Determine whether a 12-week home and telephone based intervention results in reduced total sitting time and shorter bouts of sitting in older adults with MCI and their caregivers. Electronic postural monitors will record sitting time for a duration of one week at three time

points (pre-intervention, mid-intervention, and post-intervention). The intervention includes 1) feedback from baseline monitoring, 2) educational and goal setting session with the participants and research staff, 3) wrist worn monitors that alert wearers to sitting times >30 minutes, 4) home and telephone visits to address physical, psychological, and home environment barriers to behavior change. Changes in sitting time and breaks from sitting will be compared between baseline, mid-intervention, and post-intervention measurement occasions.

Specific Aim 3: Determine whether sedentary behavior intervention results in improved insulin sensitivity and glycemic control. To evaluate whether reduced sitting results in meaningful metabolic changes, we will measure postprandial insulin and glucose, and body composition, and evaluate changes from pre- to post- intervention adjusting for relevant covariates.

The PI is an early-career investigator who has completed KU-ADC funded pilot work using objective activity monitoring and has the necessary foundation for the proposed research on physical activity and sedentary behavior in older age and AD. She has several published papers on biomarkers associated with cognitive decline and dementia. She has successfully collaborated with the KU-ADC since 2008 to build a program of research measuring physical activity in naturalistic settings in older adults with and without AD. She has experience in use, interpretation, and analysis of objective activity monitoring data in ADC participants. Her pilot work found that participants with mild AD did not differ from older adult controls in their levels of moderate physical activity, but differed in sedentary and light intensity activities. This supports the idea that sedentary behavior is a valuable target for this population.

B. Background and Significance

Older adults are highly sedentary, spending more than 60% of waking time sitting.[1,2] Independent of physical activity, daily sitting time is a risk factor for poor glycemic control, unhealthy body composition, elevated lipid levels,[3–5] and Type 2 diabetes.[6,7] An NIH sponsored workshop identified research priorities and recommendations for understanding the "Physiology of Sedentary Behavior and its Relationship to Health Outcomes."[8] The proposed study addresses these recommendations directly. 1) We investigate the physiological correlates of sedentary behavior by assessing glycemic control and insulin sensitivity. 2) We focus on the impact of lack of movement as distinct from the effects of movement by accurately and objectively measuring both simultaneously. In individuals with mild cognitive impairment (MCI), we will evaluate whether a behavioral intervention can alter physiological processes that contribute to disease pathology.

Glycemic control and insulin sensitivity are highly modifiable through changes in activity and sitting[9] and are inexorably linked to Alzheimer's disease (AD) and cognitive decline.[10,11] Individuals with MCI and AD display physiological differences in insulin and glucose regulation compared to older adults without cognitive impairment.[12] Reducing total sitting time and taking frequent breaks from sitting have resulted in improved glycemic control and insulin sensitivity.[4,13] Reduced insulin sensitivity has been shown to occur within hours after a transition to sedentary behavior.[14] Time spent in seated activities (e.g., TV) is associated with poorer global cognitive function[15] and risk of AD[16] independent of physical activity.

Cardiorespiratory fitness changes that only occur with moderate or vigorous aerobic exercise may not be essential for improving brain health and cognition, as demonstrated by studies of activities that do not robustly improve fitness (Tai Chi, resistance training, Wii fit), but still show improvements in brain health and cognition.[17,18] Even low intensity, non-exercise activity is associated with reduced risk of cognitive decline[19,20] and healthier cardiometabolic measures.[21,22] In fact, non-exercise activity accounts for the majority of daily activity, while exercise accounts for only 2-5%.[23,24] More evidence is needed to determine whether reductions in sitting time are sufficient to produce changes in cognitive performance and neuroanatomy as seen in aerobic exercise interventions.[18,25]

A recent meta-analysis reports that interventions targeting sedentary behavior can effectively reduce sitting time in adults (average 42 min/day), but few studies have evaluated whether these reductions result in clinically meaningful health outcomes.[26] Furthermore, few interventions have been conducted in older adults. One intervention to reduce sitting time in older adults included one on one goal setting and individualized feedback on objectively derived sitting time.[27] Participants successfully reduced sitting time, increased breaks in sitting, and increased light and moderate intensity activities. Our 12 week intervention

adds new elements to strengthen this design: 1) objective *postural* monitoring, 2) electronic reminders when sitting >30 minutes (real time reminders are more effective than education alone in reducing sitting[28]), 3) assessment of insulin sensitivity and glycemic control which are sensitive to changes in sitting after a short duration.

The proposed intervention is ecologically valid—it can be done in any setting. It uses participants' goals and preferences to guide behavior changes instead of defining goals for them.[29] The intervention is designed to break up bouts of prolonged sitting and replace sitting behavior with standing, light and moderate intensity activities (e.g., walking, household activities, and resistance exercise) which have been associated with improved cognitive performance among people at risk for AD.[25]

Preliminary Results: The PI is an early-career investigator with a foundation for the proposed research on physical activity, sedentary behavior, and associated biomarkers in older age and AD.[21,30–42] Pilot research allowed us to establish expertise in use, interpretation, and analysis of activity monitoring data. In 100 participants, we had excellent retention (99%) and low rates of technological problems that prevent valid data collection (5%). We found that participants with mild AD did not differ from older adult controls in their levels of moderate physical activity, but differed in sedentary and light intensity activities.[42] This supports the idea that sedentary behavior is a valuable target for this population. We discovered that patterns of activity variability differ between men and women (i.e., women are more consistently active across days), but did not differ by dementia status.[35] Understanding within-individual variability helps target interventions toward individual habits to result in tailored behavior change approaches. We conducted a focus group with the KU-ADC Ambassadors and consulted with experts (Gardiner, Befort, Thyfault, Rosenberg, & Carlson) to develop our intervention.

C. Rationale

Our proposal is innovative in 6 ways compared to previous studies: 1) it is conducted in the home and targeted to individual habits and physical environments that reinforce sitting behaviors, 2) it uses objectively assessed electronic postural monitoring, 3) it provides electronic reminders to reduce sitting, 4) it targets sedentary older adults with MCI, which has not be done before, 5) it assesses glycemic control and insulin sensitivity which are sensitive to changes in sitting after a short duration and which few previous interventions have measured, and 6) it capitalizes on the caregiver/patient dyad to help improve adherence to the behavioral change regimen.

II. Research Plan and Design

A. Study Objectives:

We propose a **feasibility** study of a 12-week home based behavioral intervention to reduce sitting time among sedentary older adults with MCI and their caregivers.

B. Study Type and Design:

The proposed pilot study will include individuals with MCI and their caregivers as a dyad. We will use a multi-level model to evaluate the change in our outcome variables across three time points. Level 1 is time of observation (baseline, mid-study, follow up). Level 2 is the individual (with or without MCI), and Level 3 is the level of the dyad. This model includes the non-independence in the estimation of the two members of the dyad as well as repeated observations for each individual. This model also allows us to compare whether individuals with MCI are equally or less responsive to the intervention than the study partners within the context of the dyadic relationship. Future funding applications will include an RCT design with a control group of dyads who do not receive the intervention or a double baseline design to establish within person change with and without the intervention. We chose an intervention duration of 12 weeks. A previous intervention study in middle-aged adults observed changes in glucose and insulin within 2 hours of reduced sitting replaced by light walking.[13] A 6-month intervention in adults improved insulin levels and waist circumference.[43]

Sample Size, Statistical Methods, & Power

We will enroll 15 dyads of older adults (N=30 individuals; 15 with MCI and 15 non-impaired caregivers).

Aim 1: We will evaluate feasibility in terms of 1) successful recruitment and retention of participants, specifically how many months did it take to recruit an adequate sample of participants, 2) 10% or less of technological failures, calculated as the number of failures divided by the total number of participants enrolled, 3) rate of participant concerns addressed by phone and at home visits, as measured by numerical counts of concerns successfully or unsuccessfully addressed and percent of participants having concerns, and 4) acceptability of the intervention to participants (measured by questionnaires during home visits), we will describe these data using descriptive statistics.

Aims 2 and 3: Our proposal is underpowered to detect significant effects, however we will focus on finding a meaningful effect size for the treatment (which is not affected by sample size). We feel this is acceptable given the **feasibility** focus of our pilot study. A previous RCT of an intervention to reduce sitting in multiple sclerosis[47] reported a statistically significant main effect, Cohen's d = 0.49, for intent-to-treat analysis.

We will use a multi-level model to evaluate the change in our outcome variables across three time points. Level 1 is time of observation (baseline, mid-study, follow up). Level 2 is the individual (with or without MCI), and Level 3 is the level of the dyad. This model includes the non-independence in the estimation of the two members of the dyad as well as repeated observations for each individual. This model also allows us to compare whether individuals with MCI are equally or less responsive to the intervention than the study partners within the context of the dyadic relationship. Constraining estimates to be equivalent provides a test of the significance of the difference in the estimates between the MCI patients and the study partners. We are primarily interested in the change in outcome measures (listed below) from pre-intervention to post-intervention (i.e., is the intervention effective), thus we are testing for a growth model with an intercept change, indicating a mean change after the intervention, this type of model can estimate discontinuous processes with longitudinal data. With regard to the multiple time points, we hypothesize an improvement in outcomes from baseline to mid-point and a maintenance effect from mid-point to follow up. Outcomes are (1) average daily sitting time (2) number of sitting bouts >30 min (3) insulin and glucose, adjusting for baseline values and relevant covariates (disability status, medications, age, education, etc.). Data will be validated for wear time (i.e. remove periods of sleep or monitor removal). A valid day of wear is $\geq$ 10 hours of waking wear time and a valid week of wear includes $\geq$ 4 valid days of wear ($\geq$1 weekend day).

D. Participant criteria. We will enroll 15 dyads of older adults (N=30 individuals; 15 with MCI and 15 non-impaired caregivers) per Table 1 criteria. We will recruit additional participants in the event of screen failure or technological problems to reach our enrollment goal. MCI status will be determined by CDR in the most recent KU Alzheimer's disease center (ADC) Registry visit (See Appendix I: Vulnerable Populations). Inactive status will be determined by the Measure of Older Adults' Sedentary Time (MOST), a 7-item questionnaire about sitting activities common in older adults.[27] There is no guidance from the literature for cutoffs for self-reported sitting times. Self-reports consistently underestimate sitting times compared to objective measures and we do not wish to exclude the majority of individuals screened. Thus, we will use a cutoff of self-reported sitting time of ≥7 hours per day not counting time spent sleeping or napping. This is roughly the average time spent sitting per self-reports using this questionnaire in a previous study of older adults (Gardiner et al. 2011). The MOST scale can be found in Appendix II. We will include individuals with glucose in the normal or pre-diabetic range. No participant who is eligible to participate based on inclusion/exclusion criteria will be denied based upon race, gender, or ethnicity.

Table 1.

Inclusion Criteria	Exclusion Criteria
1) Person with MCI enrolled in KU ADC Registry	1) Unable to stand or walk unassisted
2) Clinical Dementia Rating (CDR) = 0.5 for the impaired partner	2) Inadequate visual, auditory, or English language capacity
3) Inactive status on MOST questionnaire (both partners)	3) Adhesive allergy
4) Retired or <20 hrs/wk in an office (both partners)	4) Current Type 2 diabetes
5) Live together in a a community dwelling setting (both partners)	5) Unwilling to change sitting behavior

E. Methods

Measures

Sitting. Our primary outcome measures are the average number of minutes sitting per day and the number of sitting bouts >30 minutes during waking hours over one week measured with activPAL (PalTechnologies, Glasgow, Scotland). ActivPAL is superior in estimation of postural changes (sitting vs. standing) compared to other monitors[44] partly due to thigh placement. It is waterproofed for 7+ days by placing in a nitrile sleeve and wrapping in medical adhesive before attaching to the thigh with medical adhesive (i.e., can be worn while bathing). The device estimates time in sitting, standing, or stepping postures and transitions (sit-to-stand, stand-to-sit) in 15 second epochs. It is small, lightweight, and unobtrusive. Its rechargeable batteries last up to 14 days. We have successfully collected pilot data from 100 older adults establishing safety and **feasibility** including adhesive integrity for the study duration. Participants will be educated on use of the device before recording data. Logs will be used to record waking/sleeping times and problems with or removal of monitors (see appendices).

Biomarkers. Fasting and postprandial glucose and insulin will be collected to determine whether changes in sedentary behavior impact glycemic control and insulin sensitivity. Postprandial glucose and insulin responses will be determined as reported previously.[45] Briefly, an IV catheter will be placed for sampling by a nurse. Fasting baseline blood will be drawn. Subjects will then consume a liquid mixed meal (Ensure drink containing 57% carbohydrate, 28% fat, and 15% protein). Blood will then be collected at 15, 30, 45, 60, 90, and 120 minutes after consumption of the drink. The total amount of blood will not exceed 92 cc which is safe for adults over 100 lbs. Glucose will be measured in all samples immediately after collection with a glucose analyzer (YSI 2300 Stat plus). Remaining blood will be processed with centrifugation and serum separated and stored at -80 until time of analysis. Insulin will be measured in serum using Enzyme-Linked Immunosorbent Assay (ELISA; Alpco Diagnostics). Glucose and insulin area under the curve calculations will quantify postprandial responses. We will calculate insulin sensitivity via the Matsuda index as reported previously.[9,45] Body mass will be measured using a digital scale. Height will be measured by stadiometer with shoes off. Waist circumference will be reported as the average of 3 measures.

Covariates. Covariates include age, sex, education, marital status, physical functional limitations, health history, self-reported pain, and medications that may influence insulin sensitivity and glycemic control. We will classify medications into categories of drugs used to treat diabetes or to induce weight loss, and use them as covariates in the model to determine the effect of the intervention on biomarkers after adjusting for use of these classes of medications.

Procedures

Pre-Intervention (T0). Eligibility will be determined via chart review and telephone screening.

Baseline Visit (V1). Participants (both the individual with MCI and the study partner) will arrive fasting for baseline insulin and glucose testing. Weight, height, and waist circumference will be measured for both partners. Postural monitors will be attached by study staff to participants' dominant thigh. Participants will be asked not to remove the monitor for 7- 24 hour periods. They will receive instructions on use of the monitors and sleep/wake logs.

Table 2.	Pre-	Pre-	Pre-	Int	Int	Int	Int	Int	Int	Post-	Post-
			Wk0	Wk1	Wk2	Wk5	Wk 6	Wk8	Wk12	Wk13	Wk14
Study Timeline	T0	V1	BL	HI1	TI1	HI2	M	TI2	HI3	FU	V2
Eligibility Screening	X										
Insulin & Glucose		X									X
Postural monitoring			X				X			X	
Postural feedback				X							X
Education & goals				X							
Wrist worn alert				X	X	X	X	X	X		
Intervention Visit				X	X	X		X	X		
T- telephone; V- clinic visit; BL- Baseline; HI- Home intervention visit; M-Mid-Study; FU- Follow up											

Baseline Postural Monitoring (BL). Participants will wear monitors for 1 week and return it at the home visit (HI1). They are encouraged to call the clinic regarding questions about monitors or sleep logs.

Home and Telephone Intervention Visits (HI1-3, TI1-2). A series of home visits and telephone calls will be used to administer the behavioral intervention for both members of the dyad together. Study staff will be trained on intervention procedures by Dr. Gardiner via two 1-hour Skype training sessions and a written handbook based on his expertise in sitting reduction interventions. At the first intervention visit **(HI1)**, participants will receive preliminary feedback on baseline monitoring (i.e., graphical & verbal feedback, attention to times of day when sitting occurred), and will be mailed a more detailed account of their sitting behavior to review at **TI1**. The education and goal setting session will consist of 1) education on demographic trends, harms of sitting, contexts in which prolonged sitting occurs, recommendations for reduced sitting, 2) guided completion of a workbook that: a) asks participants to reflect on their habits, b) sets realistic and measureable goals, describes expectations for change in sitting and barriers to reducing sitting, c) evaluates perceived benefits of reducing inactivity, reinforcement strategies for rewarding change and enjoyable nonsedentary activities to pursue, ratings of confidence in ability to make changes, d) tips for ways to reduce sitting time (targeted to individual habits and home environments), and ways to make sitting time more active when sitting cannot be avoided.[30] In the home, interventionists and participants will identify specific environmental cues that promote sitting and devise plans to integrate nonsedentary activity into typical routines. The workbook was originally developed by Gardiner et al.[27] based on Social Cognitive Theory[46] and Behavioral Choice Theory.[29]

Both members of the dyad will receive a water resistant activity monitor to wear on the non-dominant wrist (Jawbone Up, San Francisco, CA). Monitors will be programmed to provide vibrations ("idle alerts") to encourage activity after inactive periods of >30 minutes and to shut off during hours when participant is normally asleep. We chose Jawbone for programmability and vibration reminders (vs. auditory). Jawbone batteries last 10 days. Participants and study partners will be trained in their home on how to recharge them and can be assisted via telephone and during home visits if needed. Participants and study partners will indicate in logs during which activities they most frequently received alerts to assist in goal setting during subsequent visits.

TI1 (wk2) will focus on problems and adherence with idle alerts, monitor wear, success of limiting sitting to 30 minutes, and goals for other cues to limit sitting. HI1 (wk5) will focus on setting goals for replacing sitting with standing/light activity, maintenance of goals, and reduction of barriers. Study staff will attach activPAL monitors for mid-intervention assessment of changes in sitting time in both partners **(M)** measured during week 6 of the intervention. After the weeklong assessment, participants will mail monitors in a pre-addressed stamped padded envelope. TI2 (wk8) will check on success of goal maintenance and barrier reduction. HI2 (wk12) will be the final follow up visit to address barriers and discuss progress toward

maintaining goals. Questionnaires will be used to assess the acceptability of the intervention to participants. Study staff will attach activPAL monitors for post-intervention assessment of changes in sitting time (measured week 13).

Follow up (V3). Participants will return monitors to the clinic and complete follow up biomarker testing (glycemic control, insulin resistance, BMI, and waist circumference). Participants will receive feedback from postural monitoring during the waiting period of glucose testing.

F. Risk/benefit assessment:

Physical risk: Blood tests usually result in some discomfort during the blood draw and may result in mild bruising at the site of the blood draw. Fasting before blood testing may result in some discomfort and feeling hungry. Some people experience dizziness or feel faint after having blood drawn. The medical tape used to attach the monitor to the thigh may cause redness or stick to leg hair.

Psychological risk: It is possible that wearing activity monitors, keeping a diary, or filling out questionnaires will be tiring or annoying.

Social & Economic risk: We do not foresee any social or economic risk to participating in the study.

Potential benefit of participating in the study

a. Individual subject: The participant may learn about his/her own activity and sedentary habits and they may learn strategies to make them healthier. This information may benefit health and well-being.
b. Study Population: We do not expected to the population from which the subject is drawn to benefit in any particular way.
c. Science, society, and humanity in general: The new information that will be obtained may benefit future patients by providing new insights into healthy aging and prevention of Alzheimer's disease or Mild Cognitive Impairment (MCI).

G. Location where study will be performed: Participants will visit the Clinical Translation Science Unit in Fairway, KS for study visits. Activity monitoring, home visits, and telephone calls will take place in the participant's home and community environment. Data will be stored at the KU Alzheimer's Disease Center and the PI's research lab at the University of Kansas in Lawrence.

H. Collaboration (with another institution, if applicable): NA

I. Single IRB Review for a Multi-site study (if applicable): NA

J. Community-Based Participatory Research (if applicable): NA

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): Study Coordinator, Research Assistants
2. Primary responsibility for the following activities, for example:
    a. Determining eligibility: Study Coordinator, PI, Research Assistants
    b. Obtaining informed consent: Study Coordinator, Research Assistants
    c. Providing on-going information to the study sponsor and the IRB: NA
    d. Maintaining participant's research records: Study Coordinator, Research Assistants, PI

e. Completing physical examination: N/A
f. Taking height, weight: CTSU staff
g. Drawing / collecting laboratory specimens: CTSU staff
h. Performing / conducting tests, procedures, interventions, questionnaires: Study Coordinator, Research Assistants
i. Completing study data forms: Study Coordinator, Research Assistants
j. Managing study database: PI, Research Assistants

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

1. Elements of the plan include:
    a. **Persons/groups who will review the data:** CTSU and research staff
    b. **Data/events that will be reviewed:** Reports from participants to study staff will be recorded during study visits and telephone calls.
    c. **Frequency of review:** quarterly
    d. **Types of analyses to be performed:** assess frequency and severity of reported events
    e. **Safety-related triggers that would cause the PI to stop or alter the study:** No anticipated safety-related events

Eligibility criteria screen for health risks prior to study enrollment, and we will immediately report to PI any adverse events. Postprandial glucose and insulin testing is the only procedure that increases risk to participants above the risks in daily life and that portion will be continuously monitored in the CTSU. Home visits and telephone calls to study participants from study staff occur frequently during the study period to monitor any additional unforeseen problems. We will record and review any reported adverse events for severity. If deemed, severe, participation will be discontinued.

III. Subject Participation

A. Recruitment:

1. We will recruit and collect data from participants currently participating in the KU-ADC Registry. This is a large registry of well characterized patients that has demonstrated an excellent ability to identify, recruit, and characterize individuals with mild AD and healthy older adults and retain them for investigator initiated research studies. Participants with MCI have had a full physical and neurological examination and review of medical history as part of the Alzheimer's Disease Center Registry evaluation before being recruited into the present study. No subject who is eligible to participate based upon the inclusion/ exclusion criteria; desires to participate is this study; is eligible for the study will be denied based upon race, gender or ethnicity.
2. The study coordinator and/or research assistants will identify potential participants via chart review and telephone screening.
3. Recruitment letters will be mailed to potentially eligible participants. Copies of recruitment letter, website description, and pocket card for recruitment are attached. The pocket card is used as a tool for study coordinators to have handy information to inform participants they contact in person or over the phone about the study.

B. Screening Interview/questionnaire: As members of the KU Alzheimer's Disease Center Registry, potential participants have previous consented to being contacted for future research. During eligibility screening, the study coordinator or research assistants will contact potential participants by telephone. They must meet the inclusion/exclusion criteria given in Table 1. Clinical Dementia Rating scores will have been determined in a previous registry visit for those with MCI. Additional questions will include work/retirement status, availability of a willing study partner, able to stand or walk unassisted, adequate English language, auditory, and visual capacity, adhesive allergy, current uncontrolled Type 2 diabetes, and willingness to change sitting behavior. To evaluate eligibility for sedentary behavior, we will use the MOST questionnaire which is shown in Appendix II below.

C. Informed consent process and timing of obtaining of consent

1 The study coordinator who is experienced in working with participants from the KU-ADC participant Registry, will give subjects detailed and comprehensive information about the study and obtain their written consent.

2 For all study participants, consent forms will be reviewed and signed in a private, clinic room at the Alzheimer's Disease Center or CTSU/GCRC. The potential subjects will be given the consent form to fully review prior to signing.

3 Both caregivers and persons with cognitive impairment who are potential participants for the study will be given details about the study as stated in the consent form. Both the caregiver and the person with impairment will be asked to describe what they will do to participate in the study, the risks and benefits of participation, and what they would do if they decided they wanted to discontinue participation in the study. Their ability to relay back key information about the study will be used to determine whether they have capacity for consent. We will not enroll participants who are unable to consent for themselves. We will obtain written consent from all participants.

D. Alternatives to Participation: Participation in the study is entirely voluntary. Participants may withdraw at any time and no care or services will be denied on the basis of participation or lack thereof.

E. Costs to Subjects: There are no costs to participants.

F. How new information will be conveyed to the study subject and how it will be documented: Participants will be notified verbally and in writing if any new information is determined that might alter the participant's wish to participate in research.

G. Payment, including a prorated plan for payment: Participants will not be paid to participate in the study. Upon study completion they will be able to keep their wrist worn activity monitors (value about $100).

H. Payment for a research-related injury: If participants have research-related injuries, they will be provided treatment at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to their health insurance policy, government program, or other third party, but they will be billed for the costs that are not covered by the insurance.

IV. Data Collection and Protection

A. Data Security

Data Sharing, Management, & Quality Control: We have signed a formal data use agreement specifying the terms of data use and protection. Data collection and sharing for this project was funded by the KUADC (NIH P30AG035982). KUADC has a designated Data Management Core that provides support for data collection, management and secure storage. All data are entered on standardized forms during the clinical visits and entered into a central database. Data are doubly entered to minimize data entry errors. Upon completion, we conduct logic, edit, and range checks. Queries are sent to the study coordinator for resolution. Data are downloaded and locked in a secure dataset. The database is backed up in an off-site location. Data security is ensured by managing all data on a secure server that has role-based access that is password protected. All files that are modified are backed up daily, with complete backups of the server on a weekly basis. Confidentiality is strictly safeguarded by HIPAA-compliant standards and all data are stored in a HIPAA compliant manner. All paper records will be kept in locked files in the research offices to which only our research personnel have access and filed by number in accordance with professional standards of privileged information. Any information on the subjects which may be shared will only be identifiable through a code number and will not have any personal information attached. Empathetic and professional staff mitigates risk of embarrassment. There are no plans to have ongoing third party monitoring.

B. Sample / Specimen Collection: At the CTSU, fasting and postprandial glucose and insulin will be collected to measure glycemic control and insulin sensitivity. An IV catheter will be placed for sampling by a nurse. Fasting baseline blood will be drawn. Subjects will then consume a liquid mixed meal (Ensure drink containing 57% carbohydrate, 28% fat, and 15% protein). Blood will then be collected at 15, 30, 45, 60, 90, and 120 minutes after consumption of the drink. Glucose will be measured in all samples immediately after collection with a glucose analyzer (YSI 2300 Stat plus). Remaining blood will be processed with centrifugation and serum separated and stored at -80 until time of analysis. Insulin will be measured in serum using Enzyme-Linked Immunosorbent Assay (ELISA; Alpco Diagnostics). Samples will be stored in a secure location within the CTSU to which only CTSU and study staff have access. The samples will not be shared outside this research, but will be sent to an external site for processing.

C. Tissue Banking Considerations: NA

D. Procedures to protect subject confidentiality: The researchers will protect the participant's information as required by law. Researchers cannot guarantee absolute confidentiality. Efforts will be made to keep your personal information confidential. If the results of this study are published or presented in public, information that identifies participants will be removed. The privacy of health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). By signing this consent form, you are giving permission ("authorization") for KUMC to use and share health information about the participant for purposes of this research study. If you decide not to sign the form, you cannot be in the study. The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities and from your medical record that relates to study participation. You may be identified by information such as name, address, phone, date of birth, or other identifiers. Your health information will be used at KUMC by Dr. Watts, members of the research team, The University of Kansas Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC who oversee research including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. By signing this form, you are giving the research team permission to share information about you with persons or groups outside KUMC. Your information will be shared by Dr. Watts with KU Lawrence campus, and U.S. agencies that oversee human research (if a study audit is performed). These groups or agencies may make copies of study records for audit purposes. The purpose for using and sharing the information is to make sure the study is done properly. The HIPAA privacy law may not apply to everyone who receives your health information. Your

health information might not be protected by HIPAA if persons outside KUMC disclose it. In some cases, there may be other laws that protect your information from improper use. Your permission to use and share the participant's health information will not expire unless you cancel it. No research information will be placed in your medical record. Some research-specific information is kept only by the researcher. Access to all of the research-specific information may not be available until the end of the study.

E. **Quality Assurance / Monitoring**

We have signed a formal data use agreement specifying the terms of data use and protection. Data collection and sharing for this project was funded by the KUADC (NIH P30AG035982). KUADC has a designated Data Management Core that provides support for data collection, management and secure storage. All data are entered on standardized forms during the clinical visits and entered into a central database. Data are doubly entered to minimize data entry errors. Upon completion, we conduct logic, edit, and range checks. Queries are sent to the study coordinator for resolution. Data are downloaded and locked in a secure dataset. The database is backed up in an off-site location. Data security is ensured by managing all data on a secure server that has role-based access that is password protected. All files that are modified are backed up daily, with complete backups of the server on a weekly basis. Confidentiality is strictly safeguarded by HIPAA-compliant standards and all data are stored in a HIPAA compliant manner. All paper records will be kept in locked files in the research offices to which only our research personnel have access and filed by number in accordance with professional standards of privileged information. Any information on the subjects which may be shared will only be identifiable through a code number and will not have any personal information attached. Empathetic and professional staff mitigates risk of embarrassment.

There are no plans to have ongoing third party monitoring.

V. Data Analysis and Reporting

Statistical and Data Analysis:

Data Analysis: We will use a multi-level model to evaluate the change in our outcome variables across three time points. Level 1 is time of observation (baseline, mid-study, follow up). Level 2 is the individual (with or without MCI), and Level 3 is the level of the dyad. This model includes the non-independence in the estimation of the two members of the dyad as well as repeated observations for each individual. This model also allows us to compare whether individuals with MCI are equally or less responsive to the intervention than the study partners within the context of the dyadic relationship. Constraining estimates to be equivalent provides a test of the significance of the difference in the estimates between the MCI patients and the study partners. We are primarily interested in the change in outcome measures (listed below) from pre-intervention to post-intervention (i.e., is the intervention effective), thus we are testing for a growth model with an intercept change, indicating a mean change after the intervention, this type of model can estimate discontinuous processes with longitudinal data. With regard to the multiple time points, we hypothesize an improvement in outcomes from baseline to mid-point and a maintenance effect from mid-point to follow up. Outcomes are (1) average daily sitting time (2) number of sitting bouts >30 min (3) insulin and glucose, adjusting for baseline values and relevant covariates (disability status, medications, age, education, etc.). **Outcome**: Milestones for achieved **feasibility** include successful recruitment and retention of participants, 10% or less of technological failures, rate of participant concerns addressed by phone and at home visits, acceptability of the intervention to participants (measured by questionnaires HI3), and few adverse events. Effectiveness of the intervention will be evaluated based on change of moderate effect size in the average amount of time spent in sitting and duration of sitting bouts as demonstrated in previous studies. Two previous intervention studies reported a decline in sitting time of about 3 - 4%.[27,43] We will use this range as our target for success.

Study results to participants: Participants will learn their individual results from activity monitoring as part of the intervention at home visit 1 and clinical visit 2. These results are used as educational and motivating agents to modify the participants' behavior.
Publication Plan: Our plan is to use the results from this pilot study to support an NIH R21 application to fund a larger RCT of our intervention to reduce sitting time. We will publish results in a peer reviewed manuscript.

VI. References

1. Harvey, J. A., Chastin, S. F. & Skelton, D. A. Prevalence of sedentary behavior in older adults: a systematic review. *Int. J. Environ. Res. Public. Health* **10,** 6645–6661 (2013).
2. Matthews, C. E. *et al.* Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am. J. Epidemiol.* **167,** 875–881 (2008).
3. Owen, N., Healy, G. N., Matthews, C. E. & Dunstan, D. W. Too Much Sitting. *Exerc. Sport Sci. Rev.* **38,** 105–113 (2010).
4. Hamilton, M. T., Healy, G. N., Dunstan, D. W., Zderic, T. W. & Owen, N. Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior. *Curr. Cardiovasc. Risk Rep.* **2,** 292–298 (2008).
5. Mikus, C. R. *et al.* Lowering physical activity impairs glycemic control in healthy volunteers. *Med. Sci. Sports Exerc.* **44,** 225 (2012).
6. Booth, F. W., Roberts, C. K. & Laye, M. J. Lack of exercise is a major cause of chronic diseases. *Compr. Physiol.* (2012).
7. Hu, F. B. *et al.* Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch. Intern. Med.* **161,** 1542–1548 (2001).
8. Thyfault, J. P., Du, M., Kraus, W. E., Levine, J. A. & Booth, F. W. Physiology of sedentary behavior and its relationship to health outcomes. *Med Sci Sports Exerc* (2014).
9. Mikus, C. R. *et al.* Lowering physical activity impairs glycemic control in healthy volunteers. *Med. Sci. Sports Exerc.* **44,** 225 (2012).
10. Yaffe, K. *et al.* Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* **63,** 658–663 (2004).
11. Luchsinger, J. A. Type 2 diabetes and cognitive impairment: linking mechanisms. *J. Alzheimers Dis.* **30,** (2012).
12. Morris, J. K. *et al.* Cognitively impaired elderly exhibit insulin resistance and no memory improvement with infused insulin. *Neurobiol. Aging* **39,** 19–24 (2016).
13. Dunstan, D. W. *et al.* Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care* **35,** 976–983 (2012).
14. Heath, G. W. *et al.* Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J. Appl. Physiol.* **55,** 512–517 (1983).
15. Hamer, M. & Stamatakis, E. Prospective study of sedentary behavior, risk of depression, and cognitive impairment. *Med. Sci. Sports Exerc.* **46,** 718 (2014).
16. Lindstrom, H. A. *et al.* The relationships between television viewing in midlife and the development of Alzheimer's disease in a case-control study. *Brain Cogn.* **58,** 157–165 (2005).
17. Mortimer, J. A. *et al.* Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *J. Alzheimers Dis.* **30,** 757–766 (2012).
18. Lövdén, M., Xu, W. & Wang, H.-X. Lifestyle change and the prevention of cognitive decline and dementia: what is the evidence? *Curr. Opin. Psychiatry* **26,** 239–243 (2013).
19. Buchman, A. S. *et al.* Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* **78,** 1323–1329 (2012).
20. Middleton, L. E. *et al.* Activity energy expenditure and incident cognitive impairment in older adults. *Arch. Intern. Med.* **171,** 1251–1257 (2011).

21. **Watts, A. S.,** Vidoni, E. D., Loskutova, N., Johnson, D. K. & Burns, J. M. Measuring physical activity in older adults with and without early stage Alzheimer's disease. *Clin. Gerontol.* **36,** 356–374 (2013).
22. Gando, Y. & Muraoka, I. in *Physical Activity, Exercise, Sedentary Behavior and Health* 51–61 (Springer, 2015).
23. Craft, L. L. *et al.* Evidence that women meeting physical activity guidelines do not sit less: an observational inclinometry study. *Int J Behav Nutr Phys Act* **9,** 122 (2012).
24. Dunstan, D. W., Howard, B., Healy, G. N. & Owen, N. Too much sitting–a health hazard. *Diabetes Res. Clin. Pract.* **97,** 368–376 (2012).
25. Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T. & Kramer, A. F. Exercise, brain, and cognition across the life span. *J. Appl. Physiol.* **111,** 1505–1513 (2011).
26. Martin, A. *et al.* Interventions with potential to reduce sedentary time in adults: systematic review and meta-analysis. *Br. J. Sports Med.* bjsports–2014 (2015).
27. Gardiner, P. A., Eakin, E. G., Healy, G. N. & Owen, N. Feasibility of reducing older adults' sedentary time. *Am. J. Prev. Med.* **41,** 174–177 (2011).
28. Evans, R. E. *et al.* Point-of-choice prompts to reduce sitting time at work: a randomized trial. *Am. J. Prev. Med.* **43,** 293–297 (2012).
29. Rachlin, H. *Judgment, decision, and choice: A cognitive/behavioral synthesis.* (WH Freeman/Times Books/Henry Holt & Co, 1989).
30. Rhyner, K. T. & **Watts, A.** Exercise and depressive symptoms in older adults: A Systematic Meta-Analytic Review. *J. Aging Phys. Act.* (2015).
31. **Watts, A.**, Ferdous, F., Moore, K. D. & Burns, J. M. Neighborhood Integration and Connectivity Predict Cognitive Performance and Decline. *Gerontol. Geriatr. Med.* **1,** 2333721415599141 (2015).
32. **Watts, A.** *et al.* A combined measure of vascular risk for white matter lesions. *J. Alzheimers Dis.* **45,** 187–193 (2015).
33. **Watts, A. S.,** Loskutova, N., Burns, J. M. & Johnson, D. K. Metabolic syndrome and cognitive decline in early Alzheimer's disease and healthy older adults. *J. Alzheimers Dis. JAD* **35,** 253 (2013).
34. Burns, J. M., Johnson, D. K., **Watts, A.**, Swerdlow, R. H. & Brooks, W. M. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. *Arch. Neurol.* **67,** 428–433 (2010).
35. **Watts, A**., Walters, R., Hoffman, L. & Templin, J. Intra-individual variability of physical activity in older adults with and without mild Alzheimer's disease. (under review).
36. Vidoni, E., **Watts, A.** & Burns, J. Feasibility of a memory clinic-based physical activity prescription program. (under review).
37. **Watts, A.**, Ferdous, F., Diaz Moore, K. & Burns, J. Neighborhood Spatial Configuration and Metabolic Function in Older Adults with and without Alzheimer's Disease. (under review).
38. **Watts, A.**, Ferdous, F. & Diaz Moore, K. Perceived neighborhood characteristics differentially impact sedentary behavior in older adults with and without Alzheimer's disease. (Nov 2016). Paper to be presented at the annual meeting of the Gerontological Society of American, New Orleans, LA.
39. **Watts, A.**, Anstey, K., Andrews, S. & Dixon, R. BDNF interacts with physical activity to predict cognitive function and declines. (in preparation).
40. Breda, A., Liebmann, E., Ferdous, F., Diaz Moore, K. & **Watts, A.** Neighborhood Characteristics and Dementia Status Predict Physical Functioning in Older Adults. (Nov, 2015). Paper presented at the annual meeting of the Gerontological Society of American, Orlando, FL.
41. Khou, C., Rendzia, B., Bevan, A. & **Watts, A.** Evaluation of waist-worn actigraphy monitors for the assessment of sleep and physical activity in older adults with and without Alzheimer's disease. (Oct, 2015). Poster presented at the Berg Symposium, St. Louis, MO.
42. Varma, V. & **Watts, A.** Differences in accelerometer-derived peak physical activity between older adults with and without mild AD. (in preparation).
43. Aadahl, M. *et al.* Motivational counseling to reduce sitting time: a community-based randomized controlled trial in adults. *Am. J. Prev. Med.* **47,** 576–586 (2014).
44. Kozey-Keadle, S. *et al.* Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc* **43,** 1561–1567 (2011).

45. Young, C. N. *et al.* Influence of endurance training on central sympathetic outflow to skeletal muscle in response to a mixed meal. *J. Appl. Physiol.* **108,** 882–890 (2010).
46. Bandura, A. *Social foundations of thought and action: A social cognitive theory.* (Prentice-Hall, Inc, 1986).
47. Klaren, R. E., Hubbard, E. A. & Motl, R. W. Efficacy of a behavioral intervention for reducing sedentary behavior in persons with multiple sclerosis: a pilot examination. *Am. J. Prev. Med.* **47,** 613–616 (2014).

APPENDIX I: VULNERABLE POPULATIONS

Both caregivers and persons with cognitive impairment who are potential participants for the study will be given details about the study as stated in the consent form. Both the caregiver and the person with impairment will be asked to describe what they will do to participate in the study, the risks and benefits of participation, and what they would do if they decided they wanted to discontinue participation in the study. Their ability to relay back key information about the study will be used to determine whether they have capacity for consent. We will not enroll participants who are unable to consent for themselves. We will obtain written consent from all participants.

Measuring Older Adults Sedentary Time (MOST) Questionnaire

I am going to ask you about activities you did over the ***last week while sitting or lying down***. Don't count the time you spent in bed.

Today is _____. I want you to think about the time from last _____ to yesterday.

For each of the activities only count the time when this was your main activity. For example if you are watching television and doing a crossword, count it as television time or crossword time but not as both.

*During the last week, how much time in total did you spend **sitting or lying down** and……*

SEDENTARY ITEM	TIME	
1. Watching television or videos/DVDs	_____ hours	_____ minutes
2. Using the computer/Internet	_____ hours	_____ minutes
3. Reading	_____ hours	_____ minutes
4. Socializing with friends or family	_____ hours	_____ minutes
5. Driving or riding in a car, or time on public transport	_____ hours	_____ minutes
6. Doing hobbies, e.g. craft, crosswords	_____ hours	_____ minutes
7. Doing any other activities	_____ hours	_____ minutes