Sedentary Behavior Interrupted:

A Randomized Trial of 3-Month Effects on Biomarkers of Healthy Aging and Physical Functioning in the Real World (P2)

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Overview

Rise for Health is a 3-arm RCT of 2 interventions that address changing sitting in overweight, postmenopausal women over a 3-month period, compared with an attention control condition. This study is one of the three projects within the National Institute on Aging Program Grant named *Sedentary Time and Aging Mortality and Physical Function* (STAR). The program grant proposes a paradigm shift away from energy expenditure as the primary mechanism for improving health outcomes to investigate potentially feasible behaviors such as brief sit-to-stand transitions that expend little energy but engage muscles, improve postural blood flow, and may impact physical functioning in older adults. The STAR program includes 3 projects and 2 cores for studying postmenopausal women at risk of chronic diseases. In addition to the RCT described here (project 2), STAR includes a 3-condition randomized crossover laboratory trial of strategies to interrupt sitting time (n=78; project 1) and a study that optimizes new computational techniques for objectively measuring sedentary behavior to apply to existing prospective hip-worn accelerometer data from the Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) cohort of the Women Health Initiative (N>6000, project 3). All projects are investigating the consequences of sitting and brief sit-to-stand transitions on the mechanisms of healthy aging, including glucose regulation and endothelial functioning. The STAR program will provide a comprehensive evidence base that can inform public health guidelines on sitting behaviors and healthy aging.

Study Objectives

Rise for Health will examine 3-month changes in biomarkers of healthy aging and physical, emotional, and cognitive functioning across a 3-arm randomized trial: (1) healthy living attention control (Healthy Living), (2) reduce sitting time (Reduce Sitting), and (3) increase sit-to-stand transitions (Increase Transitions). The study aims to enroll 405 postmenopausal women into the 3-month trial. The primary aim is to compare changes in glucoregulatory biomarkers (fasting plasma insulin and glucose, HbA_{1c}, and HOMA-IR) and blood pressure over 3 months for the 2 intervention arms compared with the attention control condition. We hypothesize that, compared with those allocated to the attention control arm, participants in the 2 intervention arms will have greater improvements in glycemic control and blood pressure. In addition, we will evaluate the dose-response effects of sitting behavior changes on glucoregulatory biomarkers and blood pressure. We hypothesize that greater improvements in the target behavior will be associated with greater improvements in glucoregulatory biomarkers and blood pressure. The secondary aims of the study are to examine the effects of the intervention on physical, emotional, and cognitive functioning. This project will also explore (1) the modifying effects of age on the relationship between the 3 conditions and primary and secondary outcomes, (2) the psychosocial and mediators and moderators of changes in sitting behaviors, and (3) the differences in outcomes between the 2 sitting interruption intervention arms. The purpose of this paper is to describe the study protocol of Rise for Health, a 3-arm randomized trial, to assess ways of interrupting sitting in postmenopausal women.

The institutional review board of the University California San Diego (UC San Diego) approved all study procedures, and all participants will provide written informed consent. Study recruitment, participant safety, and progress are reviewed semiannually by an external independent data safety monitoring board appointed by the National Institutes of Health (NIH).

Participants

Eligibility

To be eligible, participants must be female and meet the following inclusion criteria: (1) currently 55 years or older; (2) sit for more than 7 hours on a majority of device-measured days, as assessed by activPAL (as given in the *Screening Visit* section); (3) do 70 or fewer sit-to-stand transitions on a majority of device-measured days, as assessed by activPAL; (4) no health conditions that would inhibit standing; (5) able to read and write fluently in English; (6) postmenopausal, defined as no menstrual period in the last 12 months; (7) BMI≥25 kg/m^2 and <45 kg/m^2; (8) able to walk, stand, and perform sit-to-stand transitions without a high risk of falling, determined by the Short Physical Performance Battery (SPPB); and (9) able to travel to study visits. Exclusion criteria include (1) the use of insulin, (2) uncontrolled diabetes defined as HbA_{1c}>10%, (3) uncontrolled blood pressure defined as systolic blood pressure>180 or diastolic blood pressure>110, and (4) participation in another research study or program that would impact the outcomes of this study.

Recruitment and Screening

The primary methods of recruitment are contacting UC San Diego patients identified through electronic health records and contacting women in San Diego through marketing lists. Women are mailed a letter and a flyer to explain the study. Prospective participants are informed that the study staff would contact them or they could call to opt out. Additional recruitment methods include advertisements on social media platforms, such as Facebook and Instagram, flyers and listserv postings, and ResearchMatch.

Trained recruiters describe the study activities and conduct phone eligibility screening with potential participants. After phone screening, eligible women are scheduled for an in-person screening visit at UC San Diego.

Screening Visit

At the initial visit, study requirements are reviewed and signed informed consent is obtained. Next, participants complete a medical history questionnaire and self-report their current medication and supplement use to confirm they do not have a medical condition that would inhibit standing or sit-to-stand transitions and do not use insulin. Measurements of height, weight, and blood pressure are taken to screen for BMI and blood pressure. Hip and waist circumference measurements are also recorded. Participants perform SPPB to assess physical functioning and the ability to safely stand and perform sit-to-stand transitions. If all the preliminary screening criteria are met, participants complete a battery of cognitive tests and questionnaires on self-reported demographics and PA. Participants are given an activPAL, a thigh-worn accelerometer that objectively measures sitting time and number of sit-to-stand transitions, and an ActiGraph GT3X+ (ActiGraph, LLC) accelerometer, a waist-worn device that objectively measures minutes of PA. Participants are shown how to attach activPAL using waterproof Tegaderm dressing so that it does not have to be removed, and replacement waterproof dressing is provided. Participants are asked to wear these devices for 24 hours continuously, except they are asked to remove the ActiGraph GT3X+ accelerometer before bathing or swimming for the next 7 days.

Baseline Visit

Participants return to the clinic after at least seven days of wearing the two devices. Data from activPAL are screened for sitting time (more than 7 hours on a majority of measured days) and sit-to-stand transitions (70 or fewer transitions per day on a majority of measured days) to confirm eligibility. Participants provide fasting blood samples via a finger prick to screen for HbA_{1c}. Those who pass these final eligibility criteria then have a venous blood draw taken by a certified phlebotomist and complete additional questionnaires. Participants receive a total of US $35 for completing baseline measures. After all baseline assessments are complete, the participants are then randomized.

Randomization is stratified by BMI (overweight vs obese) and employment status (full-time vs nonfull-time employment). A computerized randomization scheme was created using the STAR program grant Biostatistics Core, using a random number generator. A stratified permuted block design is used in this study. After randomization, the participants review the expectations and requirements of their study group assignment (details given in the *3-Month Intervention* section). Data collectors and the principal investigator are blinded to the study group assignment.

3-Month Final Visit

Before their final visit, participants are mailed the accelerometer and activPAL and asked to wear both devices continuously for 7 days before the visit. At this visit, participants repeat the same measures collected at the screening and baseline visits, including blood draw, anthropometric measures, battery of cognitive tests, SPPB, and questionnaires. Participants receive up to US $110 for completing the final measures.

3-Month Intervention (Rise for Health)

Reduce Sitting and Increase Sit-to-Stand Transitions

The primary goal of the respective intervention arms is to interrupt the current sitting patterns by targeting 2 specific behavior changes: reducing the amount of time spent sitting (Reduce Sitting) or by increasing the number of sit-to-stand (STS) transitions each day (Increase Transitions). Both interventions, Reduce Sitting and Increase Transitions, use habit formation, social cognitive theory, and motivational interviewing techniques to support behavior change.

Health Coaching Sessions for Reduce Sitting and Increase Transitions

Participants in both intervention arms receive 5 in-person, individual coaching sessions (weeks 1, 2, 3, 4, and 8) and 2 individual phone coaching sessions (weeks 6 and 11) over the course of the 12-week program. Participants

are asked to wear activPAL on their thigh continuously for the first 4 weeks of the study and then again during weeks 7 and 8 to help with self-monitoring, goal setting, and personalized feedback.

During the first 60-minute in-person session, the health coach provides an overview of the intervention and gives participants a binder of printed educational materials and safety tips, printed action plan forms, and tracking logs. First, participants are asked to share their motivation to join the study. Next, they review reasons for sitting, dangers of prolonged sitting, and benefits of breaking up sitting. Tips for safely reducing sitting or increasing sit-to-stand transitions based on group assignments are reviewed. The health coach models the target behavior by having participants in the Reduce Sitting arm practice standing for up for 5 minutes in the middle of the session, and participants in the Increase Transitions arm perform 3 brief sit-to-stand transitions in a row, holding each for 5 seconds, twice during the session. Participants are then given a wrist-worn activity band that is programmed to prompt sitting breaks based on group assignment (refer to the *Toolbox* section). Participants are shown graphs from activPAL data, either of time spent sitting or sit-to-stand transitions, depending on the group assignment (Figures 1 and 2). The health coach and participants use the graphs to (1) review a typical day and identify times during the day when participants may be able to take sitting breaks or perform sit-to-stand transitions, (2) set behavior change goals for the next week, and (3) create a specific action plan. Participants complete an action plan by identifying the specific strategy, location, days of the week, time of day, and tailored goals for the participant (number of minutes to reduce sitting by or number of transitions to complete). Participants brainstorm potential obstacles to following the action plan and solutions for overcoming each obstacle. Using motivational interviewing techniques, confidence is assessed and supported using a 0 (very low confidence) to 10 (very high confidence) scale (*ruler*). To further support behavior change, participants are provided with several tools they can choose to use. As people vary in their preferences and needs, a toolbox approach allows participants to select tools they want to try (refer to the *Toolbox* section). At the end of the session, participants are given an activPAL to wear for the next 7 days and bring in the following week so that they can review their behavior with their health coach. If the participant provides consent, the health coach sessions are audio recorded for quality checks and training.

At each subsequent coaching session, the health coach starts by assessing the adverse events that may have occurred since the last session. Then the health coach and the participant model the respective behavior, gradually increasing the number of minutes of standing or number of transitions each week until week 4, when standing time may be up to 10 minutes and the number of transitions at the beginning of the session may be 5. The health coach reviews any key topics from the previous session before introducing the new behavior change topic (Figure S1 in Multimedia Appendix 1). When worn, the previous week's daily activPAL data are reviewed using daily graphs of data (Figures 1 and 2), as described above for week 1. Graphs of weekly data are shown to discuss progress toward the target behavior (Figures 3 and 4). At each session, the health coach supports the updating of personalized goals and action plans. There is a second break to model the target behavior before completing the action plan. Discussions on barriers and solutions and the confidence to meet the goal are addressed. Weeks 2, 3, 4, and 8 sessions are carried out in person and last approximately 60 minutes each. Weeks 6 and 11 sessions are carried out over the phone and last approximately 30 minutes each. Participants are given activPAL to wear in weeks 1, 2, 3, 4, 8, and 9.

Intervention Toolbox

Participants are provided with a toolbox of options to help with their personalized behavior goals. Participants can choose different tools at each in-person session and can keep tools for the duration of the study or trade them in for new tools as desired. All participants are encouraged to use a wrist-worn device (eg, Watchminder) that provides reminders to engage in the behavior. The wrist-worn device is programmed to vibrate and display the message *Rise Up* periodically from 8 AM to 9 PM every day; however, participants have the option to change these times to match their personalized action plan. For participants in the Reduce Sitting arm, the reminder is set to once an hour. For participants in the Increase Transitions arm, the reminder is set to every 20 minutes. Other tools offered to help prompt behavior change include lists of computers, tablets, and phone apps that prompt sitting breaks; egg timers; and visual reminders (cue cards and a study-branded bracelet). Participants in the Reduce Sitting arm have the option of a standing desk to use at home or work starting in week 2, and participants in the Increase Transitions arm have the option of a tally counter to count transitions throughout the day.

Healthy Living

Participants in the healthy living attention control (Healthy Living) condition receive an equal number of contacts as those in the 2 intervention arms. The first session (week 1) is delivered in-person, whereas the remaining

sessions (weeks 2, 3, 4, 6, 8, and 11) are delivered over the phone. During the first session, the health coach provides an overview of the study group and gives the participant a folder that includes information, worksheets, and resources on various healthy aging topics that may be discussed throughout the study. A new healthy aging topic is discussed at each session, with sleep and aging as the first topic. For all future phone sessions (weeks 2, 3, 4, 6, 8, and 11), the participant chooses which healthy aging topic to discuss. Example topics include safe driving, stress reduction, and healthy bones (Figure S1 in Multimedia Appendix 1). At each session, the health coach first provides an introduction to the selected topic. The health coach then reviews the learning objectives for the session, provides additional information about the health topic, and prompts the participant to complete the topic's worksheet. Then, the health coach and participant set the goal of the participant's choice related to the topic for that session and develop a related action plan. Using motivational interviewing techniques, confidence is assessed and supported using a 0-10 ruler question. At the end of each session, the health coach summarizes the session and confirms the date and time of the next session. The initial in-person session lasts 60 minutes, and subsequent phone sessions last 30 minutes.

COVID-19 Considerations

Owing to the COVID-19 pandemic, temporary pauses in enrollment of new study participants and in-person sessions occurred and may continue to occur consistent with UC San Diego research policies and San Diego County health orders. To minimize data loss during the pause of in-person visits, enrolled participants whose final 3-month assessment visits are scheduled during office closures will be asked to complete measures remotely. For remote measures, the participants are mailed an automated blood pressure machine and a measuring tape. A Zoom videoconferencing session is scheduled to obtain the blood pressure, waist and hip circumferences, balance tests, chair raises (as part of the SPPB), and NIH Toolbox measures (oral symbol digit test and the list sorting working memory test) using the NIH Toolbox recommendations for remote delivery]. Participants are mailed activPAL and ActiGraph to objectively measure sedentary time and sit-to-stand transitions per protocol on the due date. Survey measures through REDCap (Research Electronic Data Capture) are emailed to participants on the due date. Participants are offered extended phone coaching with continued behavior change support until they are able to complete a blood draw either via mobile phlebotomy that goes to their home or upon our ability to conduct in-person assessments. Additional measures of anxiety (PROMIS Bank v.10–Anxiety and Cognitive and Affective Mindfulness Scale–Revised [CAMS-R]) have been added to better understand how anxiety and stress during this period relate to behavior change.

The study protocols may continue to shift to support remote delivery and to respond to the changing requirements related to the COVID-19 pandemic to maintain safety for participants and study staff.

Measures and Outcomes

Primary Outcomes

Glucose Regulation and Blood Pressure

The primary outcomes are glucose regulation and blood pressure assessed at baseline and at 3 months. Glucose regulation will be assessed by fasting plasma insulin and glucose, HbA_{1c}, and HOMA-IR. Fasting blood (45 mL) is collected in EDTA and Li-Heparin vacutainers. Frozen processed samples will be stored in locked freezers at −80 °C. Plasma and whole blood samples will be used for glucose and HbA_{1c} assays, and all analyses will include normalization and quality control standards. HbA_{1c} is measured in whole blood in real time (DCA Vantage, Siemens). After blood sample collection is complete, fasting plasma glucose will be measured using the standard glucose oxidase method (YSI Bioanalyzer) and fasting plasma insulin will be measured using an immunoassay kit (Meso Scale Discovery, catalog #K151BZC). Standard curve samples and quality control replicates (minimum of 2 per plate) will be run on each assay plate. Linear dilution and spike-in controls will also be included in each assay run. Additional aliquots of samples will be stored at −80 °C should repeat analyses be required and also for future ancillary analyses. Blood pressure is measured using the Dinamap or Accutor 7 or Dinamap V100 blood pressure monitor after participants have rested while seated for at least 5 minutes. Measures are taken at least three times, and the mean of the second and third readings will be calculated.

Objective Measure of Sitting Time and STS Transitions

Measures used to examine the dose-response effects of behavioral changes on glucoregulatory biomarkers and blood pressure are activPAL and ActiGraph GT3X+. For 7 days before the baseline and 7 days before the 3-month final visit, participants are asked to wear the 2 devices for 24 hours a day. activPAL is a small and

lightweight accelerometer worn on the anterior aspect of the thigh that produces a signal related to thigh inclination, which is used to estimate the time spent in different body postures (sitting and standing) and the number of sit-to-stand transitions. activPAL has demonstrated good reliability and validity. activPAL data will be downloaded using activPAL Professional Research Edition software package using the 15-second Epoch. To filter nighttime sleeping, participants are asked to keep a sleep log each night they wear the activPAL. ActiGraph GT3X+ is a small device attached to a belt, positioned over the right hip. The ActiGraph collects data on 3 axes at 30 Hz to estimate the minutes spent in sedentary, light, moderate, and vigorous activity using calibration thresholds. ActiGraph has been validated against heart rate telemetry and total energy expenditure. Nonwear time will be classified using Choi algorithm with 90 consecutive zero counts on the x-axis. We will use the newly validated OPACH cut points to assess moderate PA. In addition, data will be provided to the Biostatistics Core and project 3 for further analysis of bouts, time of day, and clustering with sleep and to validate the machine-learned algorithms.

Secondary Outcomes

Secondary outcomes focus on physical, emotional, and cognitive function and will be measured at baseline and at 3 months. Objective lower extremity functioning will be measured using the SPPB to measure balance, gait speed (4 meters course), and chair stand. Self-report physical functioning will be measured using 6 items from the Activities of Daily Living Survey, which focuses on the ability to perform basic tasks of everyday life, such as eating, bathing, or dressing with or without assistance. Physical and emotional functioning will be measured using the Physical Functioning Survey (SF-36). It comprises 36 items that assess 8 health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy or fatigue, pain, and general health perceptions. SF-36 has been found to be reliable, valid, and responsive for a variety of medical diagnoses. Depressive symptoms will be measured using the validated 10-item Center for Epidemiologic Studies Depression Scale short form. These outcome measures were selected for consistency with the outcome measures used in the cohort for project 3 of the STAR program.

Objective cognitive functioning will be measured using the Dimensional Change Card Sort, List Sorting Working Memory, and Oral Symbol Digit from the NIH Toolkit. These tests assess executive function, memory, and processing speed, respectively. These 3 tests take about 17 minutes to administer via an iPad (Apple Inc) app and have been validated and normed in individuals aged 3-85 years. Self-report cognitive functioning is assessed using the 8-item Cognitive Function Questionnaire from the Patient-Reported Outcomes Measurement Information System (PROMIS).

Additional Measures

As psychosocial factors may mediate and moderate sedentary behavior changes, these domains are also measured. Self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep are measured using the NIH PROMIS Sleep Disturbance 8a Short Form. Self-reported barriers and benefits related to sitting are assessed on a 9-item, 5-point Likert scale assessing the mental and physical factors that affect their ability to sit adapted from a scale for PA. Participants are asked to rate their confidence in performing the targeted sedentary behaviors (sitting reduction and increase in sit-to-stand transitions) on a 2-item confidence scale, which is modeled after a PA self-efficacy scale. Self-reported PA is measured at baseline using the Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults, which asks about weekly frequency and duration of a variety of lifestyle physical activities that are meaningful and appropriate for older adults. CHAMPS was selected for measurement consistency across all the STAR projects. Anxiety will be assessed using the NIH PROMIS computer-adaptive version of their anxiety measure. CAMS-R is a 12-item measure that captures mindful approaches to thoughts and feelings. Pain will be measured using the PROMIS pain interference NIH PROMIS pain interference and intensity short forms and modified items recommended by the NIH Task Force for Research Standards for Chronic Low Back Pain. Additional measures that were adapted from validated measures to specifically address sedentary behavior include the Self-Report Behavioral Automaticity Index and habits and perceptions.