Title: EMPOWER (Empowered with Movement to Prevent Obesity & Weight Regain)
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Background, Rationale and Context

The latest obesity treatment guidelines for all ages recommend an intensive lifestyle intervention involving behavioral counseling, caloric restriction, and regular exercise to achieve weight loss.[1] While this approach elicits moderate weight loss over a short period of time (typically 6-12 mos), weight regain is the norm.[2] Regain of lost weight may be especially detrimental for older adults who are prone to preferentially store excess calories as fat, rather than lean mass;[3-5] thus, it is imperative that WL interventions for older adults focus on the challenge of weight regain.

The current recommendation to prevent weight regain is performance of a high volume of physical activity/exercise (200-300 min/wk),[1,6] an approach that has not been highly successful, especially in reduced-weight older adults as they are likely less able to adhere to this recommendation.[7,8] A key biological adaptation to weight loss is a decrease in total energy expenditure, mainly through declines in non-exercise activities of daily living (spontaneous physical activity, SPA).[9-11] SPA does not include structured exercise and is primarily influenced by sedentary behavior (SB; defined as ***sitting or lying down[12])***. Both the duration and the number of breaks in SB are consistently associated with multiple adverse health outcomes, including weight gain, independent of exercise behavior.[13-30] This study will test an innovative, scalable, and acceptable behavioral intervention that targets this known risk factor for weight gain. We found that this intervention is feasible and well-tolerated by older adults; if proven to be effective against weight regain, it would add important scientific input for advancing treatment guidelines.

We hypothesize that, in older adults, intervening on SB will be more effective for preventing weight regain than the conventional approach of intervening on exercise behavior. This is supported by evidence showing: 1) decreased SPA/increased SB is a consistent biological adaptation to weight loss[31-39] and this adaptation predicts weight regain;[40] 2) as our data show, reducing SB with a self-monitoring intervention enhances weight loss and may prevent weight regain[41]; 3) interventions targeting increased exercise are less tolerated and sustained over time in older, obese adults[42-50] who may be more likely to adhere to a SB intervention; 4) initiation of exercise in older adults can lead to compensatory increases in SB,[51-66] thus reducing total energy expenditure and limiting its efficacy for preventing weight regain; and 5) compensatory eating occurs in many individuals who exercise,[56,67,68] though the effects of altering SB on appetite and energy intake are not known.

Objectives

Our pilot data provide evidence that a novel, highly acceptable, behavioral intervention (SitLess) that focuses on increased awareness of SB employing accelerometry-based self-monitoring, that is reinforced with other self-regulatory strategies, improves weight loss during treatment and prevents weight regain during a short (5-month) follow-up.[41] **The main goal of this study is to definitively test the efficacy of this intervention for longer-term maintenance of lost weight**. This will be an 18-month trial in up to 189 obese (BMI=30-45 kg/m^2) older (65-85 years) adults randomized to one of three treatment arms, all with a caloric restriction intervention for weight loss (WL) plus: 1) moderate-intensity aerobic exercise (WL+EX); 2) a SB intervention (WL+SitLess); or

3) (WL+EX+SitLess). Participants will undergo a 9-month weight loss intervention involving a 6-month intensive phase with decreasing contact from months 7 to 9, and a minimal contact, self-managed, 9-month follow-up phase to address these **aims and hypotheses**:

Aim 1: To determine whether addition of an intervention that targets sedentary behavior to a standard WL intervention that only targets EX results in a larger 18-month reduction in body weight in older, obese adults.
Primary hypothesis: WL+EX+SitLess will have lower 18-mo body weight than either WL+EX or WL+SitLess.
Secondary hypothesis: WL+SitLess will have lower 18-mo body weight than WL+EX.

Aim 2: To compare the effects of the interventions on volume and pattern of sedentary behavior and physical activity and determine if these factors predict weight regain during the 9-month follow-up phase.
Hypothesis: WL+EX+SitLess will have higher total physical activity energy expenditure, less sedentary behavior, more breaks in sedentary behavior, and more minutes of light and moderate-vigorous activity averaged across follow-up than either WL+EX or WL+SitLess.
Hypothesis: Irrespective of treatment arm, greater activity energy expenditure and fewer minutes of sedentary behavior after the WL phase will be predictive of less weight regain during follow-up.

Aim 3: To evaluate treatment effects on clinical outcomes (body composition, functional fitness, cardiometabolic risk, fatigue, appetite) and social cognitive measures.
Hypothesis: WL+EX+SitLess will improve these tertiary outcomes more than either WL+EX or WL+SitLess.

Methods and Measures
Study Overview: We will use a 3-group design in up to189 older (65-85 years), obese (BMI=30-45 kg/m^2), sedentary men and women, all of whom will undergo a 9-month WL intervention (6-mo intensive phase and 3-mo reduced contact phase), followed by a 9-month self-managed follow-up phase with minimal contact, to test our overall hypothesis that intervening on SB will enhance long-term WL in this age group. The diet element of the intervention is identical across groups, but groups differ by activity intervention: 1) structured, moderate-intensity, aerobic exercise (WL+EX); 2) intervening on SB throughout the day (WL+SitLess); or 3) (WL+EX+SitLess).

Recruitment of study participants: Our recruitment goals include: 50% women and 20% minority. We will recruit these individuals using community-based recruitment strategies, including newspaper and radio advertisements, and mass mailings. **Specific inclusion/exclusion criteria (see table) are in place to eliminate those that may be adversely affected by the interventions or that are not able to comply with the interventions**. To reduce adverse effects of dietary WL we exclude individuals that are non-obese, those with recent WL, those who have low bone density, are being treated for osteoporosis, or taking medication that may affect bone density, and/or those who have deficient levels of vitamin D (25 hydroxyvitamin D level < 20 ng/mL) who are not taking a calcium/vitamin D supplement. We also exclude anyone who cannot walk unassisted.

Participant screening and randomization: All individuals who respond to our recruitment strategies will call a toll-free phone number and a recruiter will describe the study and perform a brief screen for general eligibility. They will be asked about their age, weight, height, current physical activity habits, body weight in the past year, medical history, current medications, and

eligibility to participate. All participants must conform to the study's inclusion/exclusion criteria (see table below).

Participant Inclusion/Exclusion criteria			
Criteria	**Inclusion**	**Exclusion**	**Assessment**
Age	65-85 years		Self-report
Obesity status	BMI=30-45 kg/m^2		Measured on scale
Functional status		Dependent on cane or walker	Self-report
Weight stability	Weight stable—no loss or gain (±5%) in past 6 months	Reported unintentional or intentional weight loss or gain of >5% in past 6 months	Self-report
Physical activity status	Sedentary	Participation in regular resistance training and/or > 20 mins/day of aerobic exercise in past 6 months	Self-report
Cognitive status		Cognitive impairment (MoCA score <22)	Questionnaire
Orthopedic status	No contraindication for safe and optimal participation in exercise training	Osteoporosis (t-score < -2.3 on hip or spine scan); Severe arthritis, or other musculoskeletal disorder; Joint replacement or other orthopedic surgery in past 6 mos; joint replacement or other orthopedic surgery planned in next 2 years	DXA scan (at V2) Self-report on Medical History form, or medication use (Self-reported medications will be cross-referenced to have a medical condition listed on the Medical History form)
Comorbidity/ health status	Approved for participation by Medical Director	--Uncontrolled resting hypertension (>160/90 mmHg); --Current or recent past (within 1 year) severe symptomatic heart disease, uncontrolled angina, stroke, chronic respiratory disease other than asthma or COPD, any disease requiring oxygen use, neurological or hematological disease; cancer requiring treatment in past year, except non-melanoma skin cancers	BP measurement Self-report on Medical History form

		--Serious conduction disorder, new Q waves or ST-segment depression (>3 mm), or uncontrolled arrhythmia	Resting ECG
		--Room air SpO_2 (oxygen saturation) at rest or with exercise qualifying for supplementary oxygen ($SpO_2 \leq 88\%$)	Self-report
		--Abnormal kidney or liver function (2x upper limit of normal);	
		--eGFR <45 mL/min/1.73m^2	Metabolic panel/CB
		--Anemia (Hb<13 g/dL in men/ <12 g/dL in women);	screening blood test
		-- Uncontrolled diabetes (fasting glucose >140 mg/dl);	
		--Deficient levels of vitamin D (25 hydroxyvitamin D level < 20 ng/mL) in those not taking a vitamin D supplement;	Self-report
		--Smoker (No nicotine in past yr)	
		--No heavy alcohol use (>14 drinks/week)	CES-D
		--Unstable severe depression	
Medication use		Regular use of: growth hormones, oral steroids, weight loss medications* or prescription osteoporosis medications*	Self-report and medicatio inventory
Research participation	Willing to provide informed consent; Agree to all study procedures and assessments; Able to provide own transportation to study visits and intervention	Current participation in other research study	Self-report

*Orlistat (Xenical), Belviq, Contrave, Saxenda, Phentermine (Adipex/Suprenza), Qsymia

**Fosamax (Alendronate), Miacalcin (Calcitonin), Boniva (Ibandronate Sodium), Evista (Raloxifene), Actonel (Atelvia/Risedronate), Forteo (Teriparatide), Reclast (Zoledronic Acid) (Zometa), Prolia (Denosumab/Xgeva, Protelos (Strontium Ranelate)

Those who pass phone screening will be scheduled for an in-clinic screening visit which is conducted in the early morning following an overnight (at least 8 hrs) fast which includes

refraining from food, beverages (with the exception of water), alcohol and caffeine. Before any data collection, participants provide written informed consent and complete a HIPAA authorization form in accordance with our IRB policy. At this visit, weight and height will be measured to calculate BMI. Individuals who meet the BMI criteria will undergo a medical history and a cognitive test (MoCA). The medical history (including blood pressure, review of medications, and a fasting blood draw for metabolic panel, vitamin D level, and blood cell count) will exclude those with recent history of coronary heart disease, cancer, liver or renal disease, severe pulmonary disease, gross physical impairment, uncontrolled hypertension, or any contraindications to exercise. The fasting blood profile will exclude those with uncontrolled diabetes,[69] anemia, or liver, renal, or hematological dysfunction. Individuals with abnormal results at screening will be referred to their physicians. Prior to randomization, eligible participants will be asked if they would like to participate in an MRI ancillary study. This is visit 2.1 listed in the table on page 7. Refusal to participate in the ancillary study will not exclude them from the main (parent) study. See Appendix A for details of the MRI ancillary study. Eligible participants will be randomized to treatment using a web-based randomization scheme developed by the biostatistician, stratified by sex with random block sizes.

Study Interventions

Weight Loss intervention: 9-mo WL phase—All participants will undergo a dietary WL intervention designed to elicit behavioral changes leading to decreased caloric intake sufficient to yield a ~10% loss of initial body mass. The WL intervention includes nutrition education, state-of-the-art behavioral methods for promoting WL, and strategies that optimize self-regulation.[8, 70, 71] During the intensive phase of WL (months 1-6), participants will meet in weekly group sessions delivered by either the RD or staff trained on specific elements of the intervention with individual sessions possible on an as needed basis. These group meetings will transition to bimonthly group meetings during months 7-9 and to monthly follow-up phone/email contact during the follow-up phase (months 10-18).

Individual goals for caloric intake will be prescribed to achieve an energy deficit of ~400 kcal/d from weight maintenance energy requirements (resting energy expenditure x activity factor of 1.3). The macronutrient goal will target an intake range of 25-30% from protein, 20-35% fat, and 45-55% carbohydrates. The education and counseling component of the intervention will emphasize instruction in making healthy, lower-calorie food choices while teaching changes in eating habits to lower caloric intake. Specific emphasis will be placed on the acquisition and use of self-management skills, particularly self-monitoring of diet and weight.

Throughout the 9-month WL phase, participants will be asked to track their food and beverage intake daily (via a paper diary or an internet-based diary)) for at least the first 3 months and then on a reduced schedule as warranted. These will be reviewed weekly by the RD. In addition, body weight is measured and recorded at all group sessions. If it is evident, either through review of diet records or inadequate WL that participants are struggling to meet their WL goals or nutrient needs then they will be asked to meet with the RD for additional assessment and intervention. During the final month of the WL treatment, emphasis will be placed on transitioning to self-managed weight maintenance. Particular emphasis is placed on regular self-monitoring of body weight and discussion of how to deal with relapse.

9-mo Follow-up phase—During this phase, participants will receive a monthly phone call or email contact, for the purpose of emphasizing study adherence and continuity of self-regulatory skills for monitoring diet and body weight.

SitLess intervention: 9-mo WL phase—Participants assigned to the WL+SitLess and WL+EX+SitLess groups will be encouraged and taught to reduce sedentary behavior (SB) during waking hours. The SitLess treatment targets increases in postural shifts and light, spontaneous physical activity (SPA) (MET level <3).[41, 72] The intervention is individually tailored due to varied physical/social environments along with the heterogeneity inherent in the daily lives and capacities of older adults. The primary goal is to increase the number of postural shifts across the day by 25% and to increase light activity to a minimum of 3000 steps each day with specific goals being collaborative, progressive, and based, in part, on baselines levels of light activity to optimize motivation and to accomodate individual differences. As a general rule, we discourage bouts of SB that are >30 minutes at any one time; however, we also realize that this may not always be possible. To faciltiate achieving their goals, participants receive 6 vibrating alerts across the course of the day from a Fitbit watch. We ask participants to use these cued reminders as a means of monitoring their progress for light activity goals by checking steps accumulated on their Fitbit watch, viewing their daily postural shifts on the study website, and to reflect as to whether they are increasing postural shifts as planned. The alerts also become a cue to increase postural shifts and SPA if they are falling short of their goals.

The Fitbit is connected via bluetooth to a mobile device and data are uploaded automatically to a central website that can be viewed by individual participants and the interventionist. Each participant only sees his/her own data, while the interventionist has access to data on all participants and can encourage them via phone or email if goals are not being met or the device is malfunctioning. The study website is used: 1) to track self-monitoring, 2) to assist in motivating participants via graphic feedback on their short- and long-term progress, and 3) as a vehicle for reinforcing and modifying participants' goals. The website also provides an additional means of communication between participants and intervention staff.

The Fitbit and website are used to induce behavior change over the course of the intervention; participants begin wearing the Fitbit daily for the first 9 months and then wear time is tailored to each individual for the remainder of the study, however, we ask that all participants use the devices at least 2 days each week as described above.

The SitLess intervention counseling sessions occur in conjunction with the WL sessions and follow the same contact schedule to achieve treatment goals. Participants meet weekly during the first 6 months and bimonthly during months 7-9. These sessions will focus on: (1) reviewing data from the activity monitors, (2) reinforcement for observed changes in behavior, and (3) motivational interviewing and problem solving to increase commitment to change and assist with overcoming barriers.[73] The goal is to build commitment to the use of the devices and to link the feedback to improvements in personally-valued outcomes in their daily lives.

9-mo Follow-up phase—During this phase, participants will receive a monthly phone call or email contact for the purpose of emphasizing adherence to the SitLess goals and the Fitbit activity tracking and associated website.

Aerobic exercise intervention: 9-mo WL phase—Participants in the WL+EX and WL+EX+SitLess treatment arms will be asked to perform structured aerobic exercise (mostly treadmill walking) of moderate-intensity for 4-5 days/week, progressing to a duration of 200

min/week. Participants will attend center-based sessions for at least 3 days/week during the first intensive 6-month phase and at least one day/week during the second 3-month transition phase (months 7-9), with recording of home-based exercise for the other 2-4 days/week. The rationale for, background education on exercise training, and monitoring of study progress occurs in conjunction with the WL sessions in a manner consistent with the SitLess intervention. The level of exercise is based on current public health recommendations from the American Heart Association and American College of Sports Medicine (ACSM) for optimizing cardiovascular fitness in older adults,[74] and the ACSM recommendation for appropriate physical activity strategies for WL.[75]

The supervised exercise sessions will take place in our research facility on motorized treadmills under the direction of an exercise interventionist. Participants will keep a log of their treadmill speed, grade, exercise duration, and the amount of energy expended for each exercise session which is used for feedback and reinforcement. All participants will be instructed to wear proper footwear, will be familiarized with the treadmills prior to use and will be instructed in fall prevention safety. Participants will warm-up by walking for 3-5 min at a slow pace and will then walk at an intensity of 65-70% of heart rate reserve (HRR, assessed during the VO_2peak test). In general, the duration of supervised walking exercise will progress from 15-20 min at 50% HRR the 1st week to 40-50 min at 65-70% HRR by the end of the 6th week and thereafter. Each walking session will end with a 3-5 min cool-down followed by 5 min of large muscle flexibility exercise. At least two HR readings (by HR monitors) will be taken during each supervised walking session to monitor compliance to the prescribed intensity. Speed and grade will be adjusted individually to insure that participants exercise at their prescribed exercise intensity.
The exercise prescription for the home-based sessions will allow the participant to perform over ground walking, or treadmill walking, elliptical or stationary bike if available. They will be counseled to exercise at a moderate-intensity as determined by a rating of 13-15 using Borg's Rating of Perceived Exertion.[76]
Throughout the 18 month intervention period, those in the EX treatment arms will also wear a Fitbit device that will be integrated with the study website. Here, participants will view receive daily feedback relative to sustained bouts of physical activity (i.e., greater than 10 consecutive minutes of movement). As in the SitLess intervention, participants begin wearing the Fitbit daily for the first 9 months and then wear time is tailored to each individual for the remainder of the study, however, we ask that participants use the devices at least 2 days each week.

9-mo Follow-up phase—During this phase, participants will receive a monthly phone call or email contact for the purpose of emphasizing adherence to their moderate-intensity exercise goal of 5-6 days/week to maintain a volume of 200 min/week.

Participants in all three groups will receive a Fitbit activity monitor, prior to the start of intervention, to assist with self-monitoring of their prescribed activity (e.g., aerobic exercise and/or decreased daily SB). As stated above, they will be encouraged to wear the Fitbit daily during the 9-month WL phase, and to wear it at least twice/week during the 9-month follow-up phase. If the monitor is lost, stolen or damaged they will be provided with a replacement. If a participant withdraws from the study, they will be asked to return the Fitbit. After completion of the last study visit, participants will be allowed to keep the Fitbit.

In addition, the study interventions require the use of a smartphone to upload data from the Fitbit and to access the study website to receive encouragement and motivation. If a participant does not own a smartphone or their smartphone is not compatible with our applications, the study will provide them with a smartphone and a phone/data plan for the length of their participation in the

study. Participants will be expected to keep the phone with them daily and to take care not to lose or damage it. Participants will be instructed that the phone is for study use only. If the phone is lost, stolen or damaged they will be provided with a replacement. If a participant withdraws from the study, they will be asked to return the smartphone and it will be deactivated immediately. After completion of the last study visit (V8), participants will return the smartphones and they will be deactivated.

Schedule of assessment visits

Assessments at baseline, after the intensive WL phase (6-months), after the entire 9-month WL intervention (9-months) and at study end (18-months) include: the primary outcome of body weight, as well as physical activity energy expenditure, light, moderate and vigorous activity minutes, and sedentary behavior minutes and breaks. The other secondary outcome assessments (RMR, physical function and measures of cardiometabolic risk) will be performed at baseline, after the intensive WL phase (6-months), and at study end (18-months) (See Table). At follow up, Visit 7 and 8 may be combined to help with participant burden and some questionnaires will be administered over the phone to limit the time in the clinic.

The nature, purpose, and risks of all tests will be explained to participants prior to obtaining their written consent and prior to each test. All examiners will be blinded to participant treatment assignment and are trained in the standardized conduct of all tests. Standardized written instructions will be provided.

EMPOWER Measurements	PSV	V1	V2	V3	Inter.	V4	V5	Trans	V6	Maint	V7	V8	Other
		fast		fast		fast					fast		
Weeks		(-12)- (-8)	(-8) - (-2)	(-4) - 0	1-24	25-28	25-28	26-37	37-40	37-76	74-77	74-77	
Questionnaires													
Phone Screener	x												
Informed consent/I &E		x											
Demographics		x											
Medical history		x											
Medications		x	x	x		x	x		x		x	x	
MOCA		x											
Adverse Events			x	x		x	x		x		x	x	
CES-D		x											
FACIT questionnaire				x		x					x		
PROMIS				x		x					x		
Pittsburgh Fatigability				x		x					x		
SF-36				x		x					x		
DSST		x											
Walking Self-Efficacy			x				x					x	
Sat with Physical Function			x				x					x	
Self-Efficacy for Managing Eating			x	x		x	x				x	x	
Experiences in Close Relationships			x				x					x	
MAAS- Mindfulness			x				x					x	
Power of Food			x				x					x	
Perceived Stress			x				x					x	
Food Cravings				x		x					x		
Technology Survey									x			x	
Intervention Survey									x			x	
Physical Exams and Physical Performance Measures													
Vital signs		x											
Anthropometric Measures			x				x					x	
eSPPB				x		x					x		
Treadmill Fatigue				x		x							
VO2 Peak			x				x						
Hand Grip Test				x		x					x		
RMR				x		x					x		
Activity Monitor			x			x			x		x		
EMA			x			x							
Weight			x	x		x	x		x		x	x	
400 meter Walk- Fast				x		x					x		
Walking Efficiency			x				x						
Radiology/Imaging Tests													
DXA (WB)			x				x					x	
DXA (hip)			x				x					x	
DXA (spine)			x				x					x	
Phlebotomy													
Lipid Panel		x				x					x		
CBC		x											
Metabolic Panel		x											
Insulin		x				x					x		
HbA1c		x				x					x		
Glucose						x					x		
EDTA- Plasma Storage				x		x					x		
Red- Serum Storage				x		x					x		
Blood Processing Form		x		x		x					x		
Blood Collection Form		x		x		x					x		
Other													
Medical Approval Form			x										
Randomization				x									
Participant Status Form													x

Study Measure(s)

1. Baseline demographic data will be recorded based on participant self-report. Medical information on prior and existing co-morbidities and hospitalizations will be ascertained by self-report and confirmed by direct query of the participant at the screening visit. We will also record medication use by asking participants to bring in all medications (including nutritional supplements).

2. Adverse events will be assessed by asking participants at each assessment visit, and during monthly phone or email contact with participants during the 9-month follow-up phase, to report any health changes, injuries, etc. and these will be recorded using the Adverse Event Form.

3. Body weight and composition: Body weight (the study's Primary Outcome) will be measured in our clinic on the same scale. Body composition, bone density, visceral fat will be measured by dual-energy X-ray absorptiometry (DXA; Hologic Discovery W, Bedford, MA). All scans will be performed and analyzed by our trained DXA technician who is certified by the International Society for Clinical Densitometry. Bone mineral density (BMD) will be measured using specific scans of the anterior-posterior spine (L1-L4) and proximal femur. Visceral fat area will be measured from the whole-body scan in a 5-cm wide region across the entire abdomen just above the iliac crest at a level approximate with the 4th lumbar vertebrae.[77]

4. Resting metabolic rate will be assessed to determine participant's weight-maintaining energy needs for prescribing the 400 kcal/d energy deficit for WL and will be measured again at 6- and 18-months to determine its response to the interventions. RMR will be measured in the morning after an overnight fast (8 hour minimum of no food, beverage, alcohol, caffeine or strenuous exercise) by indirect calorimetry.[41] Upon arrival, subjects are asked to lie quietly for 20-30 min before testing. Measurement of oxygen consumption and carbon dioxide production are collected continuously for at least 30 min and RMR is calculated using the Weir equation.[78]

5. Sedentary behavior, minutes of light and moderate-vigorous physical activity, and energy expenditure: We will use the ActivPAL®™ monitor to assess treatment effects on daily SB and physical activity.[79-84] Participants will be asked to wear the devices continuously (they are water resistant) for 7 consecutive days at each time point. Data will be downloaded at the end of each 7-day period and cleaned and summarized for statistical analyses.

6. Physical function measures to be conducted include: 1) Expanded Short Physical Performance Battery (SPPB), which is a measure of lower-extremity function consisting of walking speed, balance, and repeated chair stands.[85] 2) 400-meter walk, which is a measure of aerobic endurance;[86, 87] participants are instructed to complete the 400m distance (on a flat indoor surface) as quickly as possible at a maintainable pace and the time to complete the walk is recorded in seconds. 3) Perceived Fatigue/Exertion will assess perceived fatigability at a given workload. Participants walk for 5 min at 0% grade at a fixed, comfortable speed of 2.0 mph, and heart rate and perceived exertion are recorded at midpoint and end. 4)Walking efficiency, will be assessed as the number of calories used for walking at 2.0 mph using a steady state exercise test on a treadmill. This test will be performed before the assessment of VO_2 peak and serves as a warm-up to acclimate participants to the treadmill. 5) Peak aerobic capacity (VO_2peak) will be measured during a graded exercise test to exhaustion and used for prescription of exercise intensity (at baseline) and as an outcome measure of fitness.

Additionally, a baseline, room air, oxygen saturation (SpO2) will be recorded prior to the start of the graded exercise test and at peak aerobic capacity. The graded exercise test during the screening visit will also be used as screening for participants who would otherwise qualify for supplementary oxygen. We have extensive experience measuring VO_2peak in older persons.[88-90]

7. Psychosocial Assessments: Since attachment-related behavior is an important facet of group-mediated interventions and known to be associated with responsiveness to behavior change, we will assess anxiety and avoidance experienced in close relationships.[91] As social cognitive measures, we will assess self-efficacy expectations related to physical activity[92] and eating behavior,[93] and outcome expectations for physical function and appearance.[94] Perceived stress will be evaluated with a short-form of the perceived stress scale,[95] trait mindfulness with the MAAS,[96] and control in resisting food using the power of food scale.[97]

8. Craving Assessment: One tertiary goal of EMPOWER is to examine whether appetite and craving for desired foods may change over the course of the study. At baseline and follow-up visits, and following an overnight fast, we will administer a multidimensional state measure of craving.[98] The measure of craving provides subscales that assess the desire to consume highly valued foods, the positive reinforcement resulting from their consumption, the relief from negative feeling states that these foods provide, lack of control related to food consumption, and hunger.

9. Cardiometabolic risk factors: A fasting venous blood sample will be collected at baseline, 6-months and 18-months to measure lipoprotein lipids, C-reactive protein, and HbA1c, glucose and insulin (all will be measured by LabCorp). Vitamin D will only be collected at baseline. For those participants that agree to blood storage, plasma and serum will also be extracted from whole blood samples and stored at -80^{o}C for future assays. We will also assess treatment effects on seated blood pressure, which will be assessed in the right arm using an automated sphygmomanometer after resting quietly for 10-15 minutes

10. Fatigue measures: The following fatigue questionnaires will be administered: 1) PROMIS Short-form 8a; 2) FACIT Fatigue Scale; and 3) Pittsburgh Fatigability Scale.

11. Cognitive function will be assessed during screening using the Montreal Cognitive Assessment (MoCA); participants must score ≥22 to be eligible. We will also assess psychomotor speed, attention, and working memory using the Digit Symbol Substitution Test (DSST). Participants are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in 2 minutes (120 seconds).

12. Ecological Momentary Assessment: Increasingly researchers are recognizing the large degree of variability within the individual, and within the day, and the role this variability has on intervention efficacy. Therefore, ecological momentary assessment (EMA) will be used to study within-person and within-day interactions between sleep quality and duration (assessed via items from the Pittsburgh sleep quality inventory), feeling states (i.e., calmness, fatigue, relaxation, tiredness, assessed via items from the exercise-induced feelings inventory), affect (assessed via the feelings scale), level of hunger (assessed by asking current level of hunger), and craving for food (assessed by asking current craving for favorite meals or snack foods).

Prior to the start of the intervention and following the initial 9-month intervention period, participants will complete week-long daily assessments. These data will align with ActivPAL monitoring. Because data collected via the study EMA website are time-stamped, they will be time-matched to the hourly ActivPAL data. Participants will be instructed to complete assessments upon waking up in the morning and immediately prior to going to bed at night.

Additionally, each participant will receive up to five daily text message prompts with links to secure web-based questionnaires. Each assessment will take the average user less than two minutes to complete, and will contain all items with the exception of sleep items, which will be assessed only during the first assessment of the day.

13. A Technology survey and Intervention survey will be administered at 9 months and 18 months assessment visits to gain insight on the participants opinion of the technology and group dynamic used in this study.

Statistical Analyses

Sample size: The sample size chosen for this study (n=180; 60/group) provides >85% statistical power (with estimated 51 completers per group, see Table) to definitively test our Primary Hypothesis. In our pilot project, the adjusted mean group weight difference after 10 months (5 months of weight loss and 5 months of follow-up) was 3.6 kg (95% CI= 1.2-6.0 kg). Thus, with the longer 18-month time frame in the proposed study, we anticipate there could be a mean group difference between WL+EX+SitLess and WL+EX or WL+SitLess of ~4 kg; however, we will have power to detect a mean group difference as little as 2.7 kg. This corresponds to 3.0-4.4% of the baseline weight for a 90 kg person and is considered clinically meaningful. We also anticipate that the WL+SitLess group will regain less weight than WL+EX, and will have >85% power to detect a mean group difference as small as 2.3 kg (not adjusted for multiple comparisons). Based on our prior 18-month exercise and diet trials in similar populations,[8,70] we expect no more than 15% drop-out. In addition, with 51/grp, we have at least 80% power to detect effect sizes of 0.49-0.52 for our Aim 2 outcomes (physical activity energy expenditure, and minutes of SB and SPA), under ANCOVA with repeated measures (to estimate the time-averaged difference in response), assuming a compound symmetry covariance structure, and effect sizes of 0.24-0.49 for our Aim 3 outcomes under ANCOVA models as for the primary aim.

Table 5. Power to detect significant differences in mean change (α=0.05 level; 2-sided test, Bonferroni adjustment for multiple comparisons) between groups using ANCOVA, adjusting for sex; Baseline SD and pre-post correlations (adjusted for sex) were calculated using data from obese, older persons enrolled in our pilot.

Outcome	Group Comparison	Pre-Post Correlation	SD	Mean 18-mo grp difference	Effect Size (diff/SD)	Power	
							51/grp (85% retention)
Weight (kg)	WL+EX+SitLess vs. WL+EX & WL+SitLess (α=0.025)	0.87	8.2	2.7	0.33		0.87
				4	0.49		>0.99
	WL+SitLess vs. WL+EX (α=0.05)	0.87	8.2	2.3	0.28		0.81
				2.5	0.30		0.87

Database management: All data except those generated from the activity monitors will be entered into the web-based study database as collected. Our data entry system will protect confidentiality and data security and the use of text containing identifying information will be avoided. Activity monitor data will be downloaded to a server and the summary data merged with other study data. Final analysis datasets will be stored in SAS. All data will undergo range checks at the time of data entry and will be examined periodically by histograms and bivariate scatterplots to check for inconsistencies, unusual data needing further verification, and outliers. Plots of longitudinal observations will be used to inspect for unusual changes that need to be verified against source documents.

Data analyses: Initial analyses will follow the “intent-to-treat” principle in which data from all randomized participants are analyzed according to their randomized groups. We will document withdrawal and compliance in detail. We will attempt to identify baseline covariates that predict

attrition and compliance, and if such covariates can be identified, the analyses may need to incorporate stratification by these factors to decrease bias. Aim 1 hypothesis will be tested using analysis of covariance (ANCOVA) to compare group differences in 18-mo body weight, adjusted for baseline weight, gender (used to stratify randomization), and treatment arm. Differences in least-squares means and associated 95% confidence intervals will be calculated. Bonferroni adjustment will be used to account for multiple comparisons.

Secondary analyses (Aims 2 & 3)—Hypotheses of Aim 2 secondary outcomes will be tested using ANCOVA with repeated measures, where within subject correlations will be accounted for by using a compound symmetry covariance structure. Differences in least-squares means and associated 95% confidence intervals will be calculated. Group differences in breaks in SB will be tested using a generalized linear model with repeated measures, since a Poisson distribution is a better fit for such count data. Linear regression will be used to examine whether total physical activity energy expenditure and sedentary behavior at 6-months is predictive of less weight regain at 18-months, adjusted for baseline body weight and gender.

Hypotheses of our Aim 3 secondary outcomes will be tested at the 0.05 significance level using ANCOVA techniques similar to those used for the primary hypothesis. All initial models will be adjusted only for gender and baseline variable value; however, specific factors (e.g., age, race, initial body weight or composition, medication or supplement use, etc.) that may influence the measured responses to the interventions will be evaluated and possibly included in secondary analyses. We expect the treatments to similarly affect responses in men and women and between races. Nevertheless, we will assess whether there is an interaction between gender and/or race and treatment group, and will report this as part of our secondary results. We will also consider conducting analyses adjusted for intervention compliance and process measures (such as average attendance at the exercise sessions, amount of initial weight lost, social cognitive/group process measures, etc.) to examine the extent to which these factors moderate/alter the effect of the intervention on the outcomes.

Human Subjects Protection

Subject Recruitment Methods: We will recruit individuals using community-based recruitment strategies including newspaper ads and mass mailings. We will also advertise in the Aging Center's VITAL newsletter and participate in community outreach events.

Informed Consent: The informed consent process will follow the procedures of the WFSM Institutional Review Board. The potential participant is mailed the informed consent form and asked to read it before their initial screening visit. The form is written in simple easy to understand language. At first contact with the prospective participant during the initial screening visit, the study staff member will explain the purpose, methods and extent of the study. We require study staff to review all of the key aspects of the study verbally with the potential participants and to question potential participants to ascertain whether s/he has understood the information. Potential participants are encouraged to ask questions regarding the consent form and the study. Those who are illiterate or have impaired vision must have the consent read to them, followed by opportunity for questions and discussion. A copy of the signed and dated consent form will be given to participants, and the original document will be placed in their individual study file, which will be stored in a secure location. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information only after obtaining informed consent.

Potential Study Risks: There are inherent potential risks to human subjects who participate in any research study and the potential risks to study participants in this study are listed below.

Any injuries or illnesses (adverse events) during the course of a participant's enrollment in the study are monitored regularly as described in the Data Safety Monitoring Plan.

Assessment risks:

- DXA scans: There are risks with exposure to radiation from the whole body, anterior-posterior spine, and proximal femur DXA scans. The total radiation dose is 45 mRem for baseline and follow-up scans. The potential long-term risk from these radiation doses is uncertain, but these doses have never been associated with any definite adverse effects. Thus, the risk to study participants, if any, is estimated to be slight.

- Physical function tests: There is a small risk of injury during the physical function tests, such as muscle strains or pulls, falls, or joint injury. Risks will be minimized by having experienced/trained staff conducting these assessments. A warm-up and range of motion practice will be conducted before testing. If a participant reports pain, dizziness, or other medical problem, the test will be terminated.

- Blood draw: There is a risk of discomfort, bruising, and/or infection at the sight of puncture for blood drawing. To minimize these risks, blood will be drawn only by trained and experienced phlebotomists who will minimize the discomfort as much as possible and will use good clinical practice procedures to reduce risk of infection.

- Maximal exercise testing is a common procedure with risks, including fainting, dizziness, chest pain, irregular heartbeat, or heart attack, although the latter is extremely rare (<1 death in 10,000 tests) in people with no history of heart disease. The test is monitored by an exercise physiologist and will be stopped if problems occur. Blood pressure, heart rate and rhythm, and breathing will be closely monitored before, throughout, and after the test.

Intervention risks:

1) Risks of weight loss at any age include the concomitant loss of lean (muscle and bone) tissue along with fat mass loss. However, the clinical impact of this muscle and bone loss is not known. Since most adults with obesity have a higher muscle mass and bone density, this risk is mitigated by excluding individuals who are non-obese and less likely to benefit from weight loss and by excluding those with a bone density t-score less than -2.3. In addition, we will assess each participant's 25 hydroxyvitamin D blood level at baseline, 6- and 18-months; if found to be deficient (< 20 ng/mL) a participant will be referred to his/her primary care physician for follow-up assessment and supplementation before beginning the study intervention.
During the behavioral weight loss classes, we will also provide nutrition education regarding adequate intake of calcium and Vitamin D, including encouraging use of dietary supplements. Participants will be counseled to consume, either using food or dietary supplements, at least 1300 mg of calcium and 1000 IU of Vitamin D daily.

Finally, if any participant experiences a bone density decline (either at hip or spine) of ≥10%, or has a t-score of < -2.5, at the 6-month DXA assessment, she/he will be counseled to stop their caloric restriction and will be referred to his/her primary care physician.

2) The risks of the structured exercise intervention may include: 1) musculoskeletal complications and muscle soreness in the early phases of the intervention, 2) an increased fall risk, and 3) increased risk of hypoglycemia or hyperglycemia, especially in participants with type II diabetes on insulin or short-acting insulin secretagogues.

Musculoskeletal and fall risks are minimized since all center-based exercise sessions will be supervised by trained exercise staff who will instruct participants in proper treadmill walking and balance safety, proper footwear, and in selection of safe walking areas outside of the center.

Hypoglycemia/hyperglycemia risks will be mitigated by following the recommendations of the American College of Sports Medicine and American Diabetes Association for safety precautions of exercise in patients with diabetes.[99] Specifically, risks will be reduced by educating participants of this risk, by discussing signs and symptoms for them to be aware of prior to, during, and after an exercise bout, and by encouraging proper nutrition and hydration prior to exercise. For center-based sessions, we will have easily digestible snacks, glucose tablets, and juice in the exercise center and we will encourage them to have one of these carbohydrate sources accessible during their home-based sessions. Participants who use insulin or short-acting insulin secretagogues for blood glucose control will have their blood glucose checked via glucometer before and after exercise at the supervised sessions and will be encouraged to do this for their home-based exercise. If a participant's glucose is <100 mg/dl we will require them to consume a snack containing about 15 grams of carbohydrate prior to exercise; if it is >300 mg/dL they will be encouraged to hydrate and postpone exercise until their blood glucose level is below 300 ng/dL. We will also encourage participants to monitor their glucose after exercise to determine if food consumption or medication changes should be made. In some cases, we may ask a participant to consult with their physician about reducing medication dosage prior to an exercise session.

3) Risks of the SitLess intervention are minimal, but also may include an enhanced fall risk. This will be minimized by reviewing environmental factors that are known to increase fall risk.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify study participants, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The co-PIs, along with the study physician, will be responsible for the overall monitoring of the data and safety of study participants. In addition, all clinical intervention studies conducted by Aging Center investigators are monitored by the WFU Claude Pepper Older Americans Independence Center's NIH-approved Data Safety Monitoring Board (DSMB). Finally, the external NIA-appointed Data and Safety Monitoring Board (DSMB) will have overall responsibility of independently monitoring all aspects of the study, including those that require access to any un-blinded data. This committee acts in an advisory capacity to the NIA to monitor participant safety, evaluate the progress of the study, review procedures for maintaining the confidentiality of data, and the quality of data collection, management, and analyses. The

DSMB will have access to all study data, documents and progress information, and will be notified of all changes that are made to the protocol.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any major AE, i.e., any serious injury, including all SAEs, will be recorded and reported to the co-PIs immediately after completing any and all actions that are necessary to protect the subject's health and safety. Minor AEs will be recorded and reported within seven days. A description of the event, and the date and location of the event will be recorded on the AE Reporting Form. The PIs and the Medical Director will meet quarterly, or as needed, to review all reported events and these will be compiled and reported in aggregate to the DSMB at each biannual meeting of the DSMB.

Within 24 hours of notification of any SAE, the PIs will report the event to the WFSM Institutional Review Board (IRB). If the event occurred as a direct result of participation in this study, an amendment will be made to the consent form and the co-PIs will request new IRB approval. The SAE will also be reported within 24 hours to the NIA and Chair of the DSMB via a verbal phone call, or by a report submitted by fax or email.

Use of biological samples by other investigators

Biological samples may be used by investigators other than the investigators of the current study. The use will be limited to non-commercial purposes. The names and other personal identifiers of the study participants will not be sent to any recipients of the blood samples.

Storage and disposal of biological material

Blood samples will be stored at Wake Forest University Medical Center for up to twenty years after the end of the trial at which time the samples will be destroyed. Biological specimens will be stored in locked -70^{o}C alarmed freezers located in a locked room. The lab coordinator and the PIs have access to the keys of the freezers. All the specimens will have numerical study IDs with no personal identifiers of the participants. These are stored under the Pepper Center Tissue Repository (IRB#1219).

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Appendix A

Background, Rationale and Context

Although the scientific premise of the EMPOWER Sitless intervention is based on research showing that sedentary behavior in aging has adverse effects on the regulation of body weight[1,2] and functional decline[3,4], recent evidence[5,6] suggests there will be considerable within-treatment variability in weight loss during the intensive phase of treatment (the first 6-months) and in weight regain from 6- to 18-months. ***For the past six years, we have been investigating whether or not there are brain-based phenotypes among aging adults that place certain individuals at high-risk for failing to lose weight when involved in structured programs of weight loss.*** Indeed, relative to older adults with a low self-reported drive to consume highly palatable foods, their high-scoring counterparts exhibited a shift in brain networks that is typical of other addictive behaviors following exposure to a short-term food restraint.[7] Most recently, using baseline brain gray and white matter volume within a support vector machine learning model on older adults (n = 52) enrolled in an 18-month weight loss

intervention, we were able to predict classification to the lower or upper half of the weight loss distribution with an average accuracy of 72.62%; a receiver operating characteristic analysis indicated that classification performance was robust based on an area under the curve of 0.82.[11] In unpublished work, we have recently used functional network data and have increased prediction accuracy to 93%.

The ancillary study to EMPOWER will enable us to acquire baseline brain magnetic resonance imaging (MRI) scans on a random subset of n = 90 participants (EMPOWER has a total n = 160). We will test the robustness of the brain phenotypes identified in our existing work on an independent cohort, examining how well these phenotypes predict (a) weight loss during the first 6-month intensive phase and (b) weight regain from 6 months to 18 months of follow-up across all three treatment groups, and whether the predictive accuracy is similar between treatment groups. Furthermore, we are leveraging mobile technology in EMPOWER to collect ecological momentary assessment data on patterns of change in appetite, mood, and fatigue throughout the day both at baseline and again at the 6-month assessment following the intensive phase of treatment. A secondary aim of this ancillary study is to examine whether daily fluctuations in appetite, mood, or fatigue mediate the relationship between baseline brain phenotypes and weight loss at 6-months and/or weight regain from 6 to 18 months of follow-up.

Primary Aim: To evaluate the classification accuracy of brain phenotypes based on both structural brain MRI scans and functional brain networks to predict baseline-adjusted weight loss at 6 months and weight regain from 6 to 18 months both as a main effect across the three treatment groups as well as between the three treatment groups.

Secondary Aim: To examine whether the ability of both brain structure and functional brain networks to predict baseline-adjusted weight loss at 6 months and weight regain from 6 to 18 months across the three treatment groups as well as between the three treatment groups can be explained by variation in daily appetite, mood, and fatigue ratings assessed at both baseline and 6-months following the intensive phase of treatment.

Methods and Measures

Our main premise is that the structural features of gray matter and white matter in combination with functional brain networks constitute a brain phenotype for predicting the amount of weight that older adults lose following involvement in the intensive 6-month phase of a weight loss program and the amount of weight regained from 6 months until the 18-month closeout visit. We also hypothesize that the effects of this phenotype on weight loss and weight regain can be explained, in part, by self-regulatory failure due to daily fluctuations in appetite, mood, and fatigue.
A random subset of n = 90 participants (from the EMPOWER total n = 160) stratified by sex will be recruited for participation. All participants must be enrolled in the EMPOWER study and must not have contraindications for an MRI scan. All participants selected for this MRI sub-study will be asked to complete a separate informed consent.

Protocol for collecting brain images: imaging data will be collected after medical approval to participate in the EMPOWER parent study but before beginning the intervention. This baseline MRI scan will take place following an overnight fast by the participant. After completing a brief food craving and a regulation of eating questionnaire, participants will be positioned in the MRI scanner such that they can view an MR-compatible flat panel display positioned at the end of the MRI scanner. The screen is connected to the computer that will be used to present experimental stimuli. The scanning protocol involves a resting functional scan in which participants simply lie still with their attention

focused on a cross that appears on the display screen. Following the resting scan, there is both a food cue trial and a neutral cue trial that are randomly ordered. During the food cue trial, participants are presented with a series of words representing their favorite snack foods (these are collected prior to the MRI scan) and are asked to create an image of each food in their minds-eye and to focus on the taste, smell, and pleasure of consuming each food. For the neutral cue trial, neutral stimuli, such the word "chair", are presented and participants are asked to create an image of each object focusing on the shape, color, texture and overall appearance of each object visualized. Visual analogue scales are presented immediately following each scan to acquire ratings of state craving for their favorite foods, a rating on positive/negative affect and, following the visualization tasks, a rating of how vivid the images appeared in their minds-eye.

Methods of data acquisition and processing: This project utilizes MRI data acquisition and processing techniques that our laboratory has used for the last decade. In brief, all scans will be performed on a research Siemens 3T Skyra MRI scanner with a 32-channel head coil utilizing our typical imaging protocol. T1 / T2 / FLAIR structural scans, a blood-oxygen-level-dependent (BOLD)-weighted resting scan, and BOLD-weighted trials of food cues and neutral cues will be collected. Diffusion Tensor Images (DTI) and Perfusion Images may also be acquired. The high-resolution (0.98 x 0.98 x 1.0 mm) T1-weighted structural scans will be acquired in the sagittal plane using a single-shot 3D MPRAGE GRAPPA2 sequence (TR = 2.3 seconds, TE = 2.99 ms, 192 slices). Both BOLD-weighted image sequences will be acquired in the axial plane using an echo-planar imaging (EPI) sequence (resolution = 4 x 4 x 4 mm, TR = 2.0 seconds, TE = 25 ms, flip angle = 75˚, 35 slices per volume, 160 volumes).

Anatomical Image processing: the T1-weighted structural images will be first segmented into gray matter (GM) and white matter (WM) images using statistical parametric mapping toolbox version 12 (SPM12). Advanced normalization tools (ANTS) will then be used to warp the segmented images to standard space[8]. The warped images will be modulated with the Jacobian deformation field and masked using GM/WM masks provided by the International Consortium for Brain Mapping (***http://www.loni.usc.edu/atlases***). Finally, the images will be smoothed using ANTS median filter with a radius of 1.5 mm. The resulting images will serve as the inputs into a support vector classifier in order to classify subjects in the low and high weight loss groups.

BOLD-weighted Scans: The resting state and food cue and neutral cue functional images will be processed using our typical protocol of realignment, slice-time correction, co-registration to the structural image, normalization, global signal adjustment, regression of signal from the superior sagittal sinus, and motion-correction. The first 10 images of scans will be discarded to allow for signal equilibration. This will leave us with a volume of 147 time points. Functional volumes will be slice-time corrected, and then realigned to the first image. Confounding signals, including 6 rigid-body transformation parameters generated during the realignment process and 3 mean signals (whole-brain, white matter, and CSF) will be regressed out of the functional data. The inverse of the deformation field resulting from ANTS registration will be applied to transform the Yale brain atlas[9] to each subject's native brain space. Unlike commonly used brain atlases which integrate functionally different areas into one region, the Yale atlas is a functional atlas which parcellates brain into finer functional unites (268 regions versus 90 regions of automated anatomical labeling (AAL)). Finally, the resulting atlas in the individuals' brain space will be used to extract the mean time series for each region from the preprocessed functional images. Correlation matrices will then be thresholded to maintain edge density consistency across subjects. This process ensures that comparisons between networks are of equivalent density relative to the number of network nodes. This will be done using the formula $N = K^{s}$ [10], with N equal to the number of nodes and K equal to average degree (number of

edges per node in the network). Networks will be thresholded at S = 2.5 based on work showing that brain networks fragment when S > 3 [11] and that the reproducibility is highest with an S between 2 and 3[12]. Correlation values equal to or greater than the correlation coefficient solving the threshold formula are preserved and all others set to 0 to produce undirected, weighted networks. The resulting whole-brain networks from each study participant will then serve as the basis for the machine learning algorithm testing.

Data Analysis

Support Vector Machine (SVM) Learning classification: Our recently published SVM model was developed to classify weight loss success and failure in an elderly cohort.[13] We will apply our published SVM model to the warped GM and WM images from the high resolution structural scans of the participants in the 3 arms of this study, and this SVM will classify the participants into successful and unsuccessful weight loss. In addition, we will apply our more recent machine learning hypergraph model that uses functional brain networks of the resting state and task-based functional brain network data. In addition, we will combine GM and WM images with resting state and task-based fMRI networks in a single machine learning model to compare the performance of this model with the models trained using structural or functional data, alone. We expect that this combined model will enhance prediction accuracy.

Following this EMPOWER clinical trial, we will assess our machine learning models by determining the accuracy, sensitivity, and specificity in classifying the participants' weight loss success/failure. Similar to our published analyses, we will also perform receiver operator characteristic (ROC) analyses to investigate how efficiently the classifiers performed at different decision thresholds. ROC curves plot sensitivity versus '1-specificity' in a given classification decision threshold, and the area under the curve (AUC) is calculated to determine the effectiveness of the predictions and is considered as the best representative score to represent classification algorithm performance. The AUC will be determined for the structural, resting state fMRI brain network, and task-based fMRI networks by themselves, as well as for the analysis combining these datasets in a single model. A one-way repeated measure analysis of variance (ANOVA) will be performed to evaluate for significant differences for the AUC between the 3 types of classifiers.

Human Subject Protection

Subject Recruitment Methods

All study participants will be enrolled in the EMPOWER study and must not have contraindications for an MRI scan. All participants selected for this MRI sub-study will be asked to complete a separate informed consent.

Informed Consent

The participant will be seated in a quiet room with a copy of the consent form. After being given time to read the form, the PI or his designee will go through the document with them, and answer any questions they might have about the study. Participant consent will be documented.

Potential Study Risks

The risks associated with MRI scans are metal objects in or on the body and fear/anxiety associated with being in the MRI scanner. To reduce any risks associated with metal, we will screen all potential participants to exclude anyone with metallic or electronic implants. In addition, all individuals are screened prior to entering the MRI suite to ensure that they do not have any metallic objects on their person. This process is performed by the MRI technologist.

To reduce fear and anxiety, the participants will be fully informed of exactly what will happen during the scan session at the informed consent meeting. They will be reminded that they are allowed to stop participating in the study at any time without any adverse consequences. Throughout the scan, the participant will be in communication with the MRI technologist. They will also have an emergency squeeze ball that alerts the technologist that they want the scan stopped. Should the participant decide to stop the MRI scan before completion, they will be allowed withdraw from the MRI portion of the study, but remain in the rest study.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected participant identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The MRI scans will be reviewed for potential abnormalities by a board certified neuroradiologist and all findings confirmed by study coinvestigator Dr. Jonathan Burdette, MD. Although the MRI scans collected for this study will not be of diagnostic quality, they might reveal incidental findings. Participants will be notified of such findings, and their primary care physician notified if requested by the participant. In the event that the participant does not have a primary care physician, they will be referred to the appropriate clinical practitioner based on the MRI findings. Follow up clinical evaluation would be required to validate any potential findings observed in the research MRI scans. Any medical costs associated with follow-up of an incidental finding will be the responsibility of the study participant and their parents.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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