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Rationale and Design of REWARD (Revving-Up Exercise for Sustained Weight Loss by Altering Neurological Reward and Drive): A Randomized Trial in Obese Endometrial Cancer Survivors

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Abstract

Background—Obesity is a leading risk factor for endometrial cancer (EC), particularly Type I forms, which are increasing in the U.S. Although death rates from most cancers have been decreasing, overall mortality in EC is increasing in the U.S. EC survivors' poor fitness combined with their surgical treatments may make weight loss particularly challenging. High intensity exercise increases neurotrophins and neurological reward via altered striatal dopamine in animals;

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and, in humans, chronic high intensity exercise enhances meal-induced satiety and may reduce hedonic eating. ‘Assisted’ exercise, a mode of exercise whereby a patient's voluntary exercise rate is augmented mechanically, may modulate brain dopamine levels in Parkinson's Disease patients but has not been previously evaluated as a treatment for obesity.

Methods—We describe the rationale and design of the REWARD trial, which has the overarching goal of randomizing 120 obese EC survivors to ‘assisted’ or voluntary rate cycling to evaluate the efficacy of ‘assisted’ exercise in enhancing and sustaining weight loss. Patients in both arms will receive 3 days/week of supervised exercise and 1 day/week of a group behavioral dietary intervention for 16 weeks and, then, will be followed for 6 months.

Outcomes—The primary outcome is weight loss. Secondary outcomes include measures for body composition, fitness, eating behavior, exercise motivation, quality of life as well as cognition and food reward and motivation as assessed by functional magnetic resonance imaging (fMRI) tasks.

Conclusions—If successful, the REWARD program could be extended to help sustain weight loss in obese cancer and non-cancer patients.

Keywords

Endometrial cancer; exercise; obesity; eating behavior; fMRI; quality of life

Introduction

Endometrial cancer (EC) is the fourth leading cancer among women in the U.S. [1] and, the sixth most common cancer worldwide [2]. Obesity is a leading risk factor for EC [3;4], particularly Type I (estrogen stimulated) forms [5;6], which are rising in the U.S. [7].

Although death rates from most cancers have decreased, overall mortality rates in EC are increasing in the U.S. [8]. Obese EC survivors have poorer overall survival than normal weight EC survivors [9] and have the highest risk of death among all obesity-associated cancers [10;11]. Many EC patient deaths have been attributed to non-cancer causes suggesting patients are dying from co-morbidities associated with their obesity [11;12][13]. Unlike other cancer survivors [14], EC survivors do not make spontaneous lifestyle changes during the ‘teachable moment’ of a cancer diagnosis [15] and, their poor fitness levels [16] and surgical treatments may make weight loss particularly challenging [17;18]. Therefore, there is a need for lifestyle programs in EC survivors; however, only three prior lifestyle interventions have focused on this population [19-21].

Obesity is clearly a neurobehavioral problem [22] and likely involves disruption to reward systems which can override homeostatic energy systems leading to overeating of high-calorie foods [23;24] with intensely rewarding properties due, in part, to dysregulated striatal dopamine [25;26;26]. In a group behavioral lifestyle intervention, which aimed to improve diet quality by increasing intake of low-calorie foods (e.g., fruits, vegetables) and decreasing intake of high-calorie foods (e.g., chips, sweets) [21], we found that obese EC survivors had decreased activation in brain regions associated with food reward and motivation in response to high-calorie images after compared to before the intervention [27].

However, we observed increased activation in frontal regions in post-intervention scans when comparing high- vs. low-calorie images post-meal [27]. Our results taken together with those from an obese non-cancer population [28] suggest that behavioral lifestyle interventions may help dampen high-calorie food response but more intensive programs, such as exercising at higher rates, may be required to fully alleviate incentive salience from food cues because high intensity exercise can enhance meal-induced satiety [29] and may suppress hedonic eating drive through enhancement of executive functions that provide ‘top-down’ inhibitory control or ‘braking’ systems [22].

We have shown in Parkinson's disease patients that ‘assisted’ exercise, which provides mechanical assistance to pedal 35% faster than voluntary rates, provides global improvements in motor function [30] and increased activity in cortical and subcortical regions, which is consistent with activation patterns after applying a dopamine agonist, suggesting ‘assisted’ exercise may be modulating dopamine levels in the brain [30;31]. However, no previous studies have evaluated the potential effects of using ‘assisted’ exercise to treat obesity.

Here, we describe the design of the REWARD trial, which is evaluating, for the first time, the efficacy of ‘assisted’ compared to voluntary rate exercise, coupled with a group dietary behavioral program, in 120 obese EC survivors. We hypothesize that patients performing ‘assisted’ exercise will have improved neurological stimulus in reward and motivation brain regions, as measured by fMRI, leading to enhanced and sustained weight loss.

Materials and Methods

Design Overview

Our design employs a single-blinded, randomized trial to evaluate the effects of ‘assisted’ compared to voluntary rate cycling in 120 obese EC survivors. Patients in both exercise groups will also be asked to participate in a group dietary behavioral program (Lifestyle, Exercise, Attitudes, Relationships, Nutrition (LEARN) [32;33]. The supervised intervention period will be conducted for 16 weeks and patients will be followed for 24 weeks after the treatment is completed (EOT+24) as illustrated in Figure 1. Patients will be recruited from University Hospitals Case Medical Center (UHCMC) and the Cleveland Clinic (CC) and the intervention will be conducted at both UHCMC and CC sites. The Institutional Review Boards (IRB) at UH and CC have approved this study and all patients in the trial will provide informed written consent.

Patient Population

We plan to enroll 120 obese (BMI ≥ 30.0 kg/m²) Stage I EC patients from UHCMC and the CC. UHCMC and the CC treat, on average, over 160-180 obese, Stage I EC patients per year. Thus, enrolling about 30 patients per year is feasible given recruitment rates of about 20% previously observed in lifestyle intervention trials in this patient population [20;21;27]. Potentially eligible patients will be identified through hospital registries and tumor boards and initially contacted using mailed letters and flyers as well as through distribution of these in the clinics by treating physicians. Demographic data in this EC patient population indicate

that about 80% are Caucasian, 20% are African-American and less than 1% have self-reported Hispanic ethnicity, which is generally consistent with the U.S. population of EC survivors where approximately 85-90% are Caucasian, 8-10% African-American [34;35] and about 1% are Hispanic [36]. Based upon previous studies in this population [27] and preliminary data, the patients have an average age of approximately 61 (s.d.=7) years and an average BMI at enrollment of approximately 41.6 (s.d.=6.6) kg/m².

Primary inclusion criteria include: 1) Adult women (>18 years old) of all races with histologically confirmed Stage I endometrial adenocarcinoma, grade 1 or 2. Patients will be eligible to participate 8 weeks after completion of treatment [37] but must have completed their treatment within the past 4 years; 2) obese with a BMI ≥ 30.0 kg/m²; 3) approved to be contacted by the patient's treating gynecologic oncologist; 4) meets screening criteria (see Screening and Fitness testing below). Primary exclusion criteria include: 1) any patient unable to read and provide informed consent; 2) women currently participating in a structured weight loss or exercise program within the past 6 months [38]; 3) any patient who will not be available for the follow-up assessments; and, 4) any pre-existing medical condition that would be a barrier for participation in exercise (see Screening and Fitness testing below).

Randomization

Patients meeting the screening criteria (discussed below) and completing the baseline testing (discussed below) will be randomly assigned to receive either the 'assisted' (n=60) or voluntary (n=60) rate exercise program. Randomization will be stratified by BMI (≥ 30 to <40 kg/m²; ≥ 40 kg/m²), time since the end of clinical treatment (2 months to 2 years; 2 to 4 years) and hospital site (UHCMC; CC) with permuted blocks of random sizes within strata and, will be centralized using the randomization feature in the database software to ensure allocation concealment.

Screening and Fitness Testing

All potential study subjects will be pre-screened with the American Heart Association (AHA)/American College of Sports Medicine (ACSM) exercise pre-participation questionnaire [39]. Prior to randomization, all potentially eligible subjects will be requested to undergo a cardiopulmonary (CPX) stress test utilizing a semi-recumbent cycle ergometer, similar to the cycle being used for training, and a MedGraphics Cardio2/CP system with Breeze software. We use a continuous incremental protocol starting at 25 Watts (W) and increasing in 10 W stages every two minutes. Subjects are encouraged to continue to exercise to the point of volitional fatigue and the test is terminated per ACSM Guidelines [39]. If the initial CPX test is terminated secondary to hemodynamic instability, arrhythmias or ischemic signs, the patient will not be eligible. VO₂ peak is determined as the highest 30 second average of VO₂ during the exercise test. Respiratory exchange ratio (RER) is determined at the highest 30 second average for VO₂. RER's >1.1 are suggestive of a peak physiological effort. If a patient terminates the test prior to an RER >1.1 , this will be documented and pre-to-post RER's will be compared to identify any significant variation that may occur. This test will also be conducted at the end of treatment (EOT), EOT+12 weeks and EOT+24 weeks to evaluate changes in fitness.

Intervention

Exercise Intervention—All exercise training will be performed under the supervision of a qualified exercise specialist (ES) certified in Advanced Cardiac Life Support at CC and UH facilities, which are equipped with a crash cart and defibrillator. Patients in ‘assisted’ and voluntary exercise groups will exercise starting from 45 minutes to 1 hour per day, three days a week for 16 weeks. Every effort will be made to have exercise sessions separated by at least one day. Intensity will be determined on an individual patient basis based on the results of the initial exercise (CPX) test. The target training heart rate (THR) zone for each subject will be determined using the Karvonen formula at the 60-80% range. The THR will be calculated as follows: $THR = ((HR_{max} - HR_{rest}) \times \% \text{ Intensity}) + HR_{rest}$. Resting heart rate (HR_{rest}) will be obtained at the cardiovascular pre-screening appointment after a 5 minute seated rest. Maximum heart rate (HR_{max}) will be determined as the peak heart rate achieved during the baseline fitness test and will be adjusted based upon the fitness test at the mid-point of the intervention. Each patient will exercise within 60-80% of the THR during the 40-45 minute main exercise set. Subjects may be deconditioned upon entry into the study; if so, the 40-45 minute main exercise set will include ‘on the bike’ rest breaks of 2 minutes every 10 minutes; and, progress to two 20 minute sessions with a 2 minute break after 4 weeks of exercise. The rate of perceived exertion (RPE) will be recorded every 10 minutes. If a patient exhibits signs of cardiac distress or hemodynamic compromise, exercise will be stopped immediately. The total and % time in the THR zone will be recorded and should be similar in both groups. The cadence (rpm) and work performed by the patient and the motor in the ‘assisted’ group will be recorded. Work by the patient should be similar but cadence will be higher in the ‘assisted’ group.

Motor Driven Cycle—Subjects in the exercise groups will perform all exercise sessions on a recumbent cycle. The ‘assisted’ cycle is a semi-recumbent stationary exercise bike with a larger seat, which is more comfortable and may provide greater cardiovascular benefits than an upright cycle [40]. Subjects will be fitted on the cycle using standard criteria [41]. Briefly, the cycle is driven by a DC motor that is controlled by a regenerative drive system. Instantaneous power (W) generated by the patient becomes $(Torque_{Measured} - Torque_{Baseline}) \times \text{cadence}$. An additional feature allows a “torque limit” to be set. The torque limit refers to how much torque the motor is allowed to exert to maintain its command velocity. If the torque limit is exceeded, the motor can be overdriven; and, once overdriven, the motor will apply a constant torque of the torque limit setting.

Experimental Groups

Voluntary Exercise: The exercise cycle will be operated in its standard mode in which the motor does not provide any assistance to pedaling. Subjects will be instructed to maintain heart rate within their individualized THR zone. No instructions will be given regarding the maintenance of a particular cadence. Cadence and resistance level will be voluntarily selected by the patient. The exercise trainer will ensure the subject maintains heart rate within THR during the exercise.

‘Assisted’ Exercise: Training pedaling rate will be set at approximately 35% greater than the subject's voluntary preferred pedaling rate determined from the baseline testing. Subjects

will be instructed to maintain their heart rate within their THR zone through active pedaling of the cycle. Subjects will adjust their contribution to the pedaling action in order to maintain their heart rate within THR. The algorithm controlling the motor is responsive to pedaling rate, patient work and heart rate; these data are used to determine the level of assistance or resistance provided by the motor.

Dietary Behavioral Intervention—Patients in both the ‘assisted’ and voluntary exercise groups will participate in a dietary group behavioral intervention. We will utilize the highly successful Lifestyle, Exercise, Attitudes, Relationships, Nutrition (LEARN) weight loss program developed by Dr. Kelly Brownell [32;33], which is a structured progressive approach for teaching weight loss and maintenance strategies primarily through dietary behavior modification in weekly group sessions. Prior studies have demonstrated that the LEARN program leads to a 6-8 kg weight loss in obese individuals [42-44], which is consistent with the 5-10% and 0.5 kg/week weight loss goals needed for clinical relevance [45-47]. The LEARN program has been successfully executed using weekly group sessions led by registered dietitians (RDs) in clinical trials [42-44] and community wellness programs. An RD interventionist will lead the LEARN program in small groups of about 8 to 12 patients each over 16, 1-1½ hour weekly sessions. Session topics will include optimal food choices for weight loss, portion control, dining out, healthy cooking skills, reading labels and healthy snacks. Behavior modification strategies such as goal setting (e.g., SuPeR SMART goal setting [48]), record keeping, cue elimination and overcoming non-hunger related eating will be integrated into each session. The LEARN program will be supplemented to include updated tools (e.g., MyPlate, American Heart Association updated guidelines). The LEARN program will be modified to address any potential special needs of EC survivors including stressing the importance of plant-based diets [49], decreasing sugar sweetened beverages [50] and, generally, to decrease intake of processed foods and increase the intake of vegetables. The LEARN program will be modified where needed to be culturally appropriate (e.g., for African-American patients, we will include soul food in food guides and provide recipes for reduced fat and sodium in popular African-American dishes). All patients will be provided with the LEARN Weight Management Program workbook and a study binder. Patients will be asked to keep daily food records and clearly defined homework assignments will be submitted weekly for feedback and used in group sessions to share successes and challenges with weight loss and engage in problem solving activities.

Intervention Adherence—Barriers to adhering to the intervention protocol will be assessed using an elicitation procedure similar to that suggested in the theory of planned behavior whereby an open-ended question is used to solicit the barrier without any preconceived notion of what the barrier might be [51;52]. If an intervention session is missed, the patient will receive a phone call later that day or evening asking for the reason. Responses will be recorded exactly as stated and we will probe further if a response is vague. We will report the number of participants providing the reason and the number of times the reason was reported and, group barriers into major themes (e.g., treatment-related; life-related; motivation-related). Reducing barriers when an exercise and/or diet program is initiated and during the early maintenance period helps to sustain behavior change [53;54].

Follow-Up/Maintenance Period

We will use the personal phone contact approach which was shown to be superior to other self-directed approaches for weight loss maintenance [55] during the follow-up period (EOT to EOT+24 weeks). This approach, which is based on motivational interviewing [56], incorporates key theoretical constructs of weight maintenance (motivation, support, problem solving, relapse prevention) with a focus on problem solving and motivational enhancement. The RD Interventionist will contact patients on a monthly basis or more frequently as needed. In addition, the RD Interventionist and ES will meet patients for an in-person visit at EOT+12 weeks. The counseling strategies will include self-monitoring and feedback, maintaining social support for desired behaviors and sustaining motivation for maintaining long term behavior change. For self-monitoring, patients will be encouraged to weigh themselves on a weekly basis, keep track of daily minutes and intensity of physical activity and dietary intake with logs provided. Patients will also be provided with accelerometers equipped with Polar® heart rate monitors. In terms of exercise goals, patients will be encouraged to maintain at least 3 hours/week of moderate to high intensity exercise similar to the supervised period. In terms of diet goals, the individualized caloric ranges provided during the LEARN program will be used and updated for any changes in weight. For problem solving, the RD Interventionist will use the 5-stage approach: orientation, problem definition, generation of alternative solutions, making a decision, and implementing and evaluating the solution. Mechanisms discussed during the LEARN program to overcome barriers to fit exercise into their daily lives and maintain healthy eating practices will be emphasized. A telephone contact form will be used to guide, structure and document each contact and will include the patients' diet and activity efforts in the prior month and any barriers or difficulties encountered.

Outcome Measures

After the screening procedures are completed and patients are deemed fully eligible for inclusion in the trial, patients will be asked to complete a battery of questionnaires (self-administered) evaluating eating behavior, exercise behavior, quality of life (QoL) and depression. Patients will also be asked to complete body composition testing and undergo a blood draw for biomarker testing. In addition, patients will be asked to participate in a functional MRI study involving a visual food task and stop signaling task (SST). Standardized cognitive tests will be administered outside the scanner by a trained study evaluator who will be blinded to group randomization. All of these tests and questionnaires will be conducted at baseline and repeated at EOT, EOT+12 weeks and EOT+24 weeks (Table 1).

The primary outcome is change in weight from baseline to EOT+24 weeks and, secondarily, at EOT. Secondary outcome variables include fitness, body fat, exercise motivation, eating and appetitive behavior measures, QoL, cognitive measures and food reward and motivation using measures as detailed below and as summarized in Table 1.

Body Composition Measures—Height will be measured to the nearest 0.1 cm using a stadiometer and weight to the nearest 0.1 kg. Waist and hip circumference will be measured to the nearest 1 cm. Whole body dual-energy X-ray absorptiometry (DXA) scans (Lunar

iDXA™, GE Healthcare, Madison, WI) will be used to measure body fat as well as bone and lean mass.

Eating Behavior Measures—We will measure eating behavior using the Three-Factor Eating Questionnaire (TFEQ) [57]. The TFEQ includes 51 items and measures dietary restraint, disinhibition and hunger with good reliability and validity [58-60]. We will measure dietary intake using 24-hour dietary recalls and the USDA 5 Step Multiple Pass Method [61] with Nutrition Data System for Research (NDSR) software. This method has been shown to assess intake within 10% [62]. Self-efficacy has been shown to be a predictor of weight loss in EC survivors [63]; thus, we will measure self-efficacy using the Weight Efficacy Lifestyle questionnaire, which specifically evaluates eating behavior self-efficacy under negative emotions, food availability, social pressure, physical discomfort and positive activities [64;65].

Exercise Motivation and Activity Measures—We will evaluate motivation to exercise using the Exercise Motivations Inventory (EMI-2) [66] and the Intrinsic Motivational Inventory (IMI) modified for exercise [67]. The EMI-2 has been found to discriminate between individuals at different points in the stages of change for exercise and to predict change in stage across a 3-month period in ways consistent with self-determination theory [68;69]. Extrinsic motivation has been shown to positively predict self-reported exercise behavior, physical self-worth and psychological well-being and intrinsic motivation has been shown to predict objective moderate-to-vigorous activity levels [69;70]. We will measure self-reported physical activity using the Godin Leisure Time Exercise (LSI) questionnaire [71].

Quality of Life Measures—We will use the Functional Assessment of Cancer Therapy - General (FACT-G) to measure physical, functional, family-social, and emotional well-being domains of quality of life (QoL) [72;73] and the FACT-En, which is a subscale specific for EC, and will use FACIT to assess fatigue. The FACT-G has exhibited good reliability and validity [74].

Executive Function Measures—We will use the Trails A and B [75], Symbol Digits Modalities (SDMT) [76;77] and Food Stroop [78] tests for executive function. The Trails A & B tests asks patients to draw a line connecting numbers and draw a line alternating between numbers and letters, respectively. The SDMT asks patients to identify 9 different symbols corresponding to numbers 0 through 9 and fill in the blank space under each symbol with the corresponding number. The Food Stroop evaluates reaction time to naming high-calorie and low-calorie foods.

Neuroimaging Measures

Stimulation Design Visual Food Task: Similar to our prior protocols [79;80], patients will be asked to complete a fasting state and a fed state scan. Patients will perform the fasted scan after an overnight fast, eat a standardized meal and then perform the fed state scan. We will use a block fMRI design with two runs performed during fasting and two runs performed in the fed state. A visual activation task will be presented during each session

which will be duplicated across Sessions 1 and 2 but post-meal images will be new. The Same/Different Object Task is a perceptual discrimination task whereby two color images of high-calorie, low-calorie and non-food items are presented side-by-side and, the patient determines if the objects are the same or different. This ensures patients are attending to the stimuli and perceptual systems are engaged for food and nonfood discrimination in hunger and satiety states. The task has eight blocks with each block consisting of six image pairs presented for 2250 milliseconds (ms) (inter-stimulus interval: 1250 ms). Data will be acquired over 2 runs per session and counterbalanced by condition.

Stop Signaling Task: We will use a stop signaling task (SST) [81], which will comprise 96 GO (75%) and 32 STOP (25%) trials distributed over 2 imaging runs. On all trials, the patient will be presented with a 500 ms warning stimulus consisting of a central fixation cross followed by a left or right arrow. For the GO trials, the patient responds as fast as possible with a left or right key press. For the STOP trials, a pure tone (900 Hz; duration, 500 ms) is presented subsequent to the GO (arrow) stimulus and, the patient is instructed to attempt to stop her response at the appearance of the tone. The time between the GO (arrows) and STOP (tone) stimuli is referred to as the stop signal duration (SSD). The SSD on STOP trials changes depending on the patient's behavior. If a patient inhibits successfully on a STOP trial, then inhibition is made more difficult on a subsequent STOP trial by increasing the SSD by 50 ms. If a patient does not inhibit successfully, then inhibition will be made easier by decreasing the SSD by 50 ms. Four staircases (starting with SSD values of 100, 150, 200, and 250 ms, respectively) will be used to ensure that the probability of correct inhibition will be approximately 50% on all trials at the end of the experiment. Average SSD will be computed for each subject from the four staircase values after she converges on 50% correct inhibitions. Values for the last 12 moves of each staircase will be averaged for a stable SSD estimate. The stop signal reaction time (SSRT) is calculated by subtracting the final SSD from the mean of median RT on GO trials. Higher SSRT values are indicative of poorer inhibition and, a higher SSD indicates greater inhibitory abilities.

Image Acquisition: Imaging data will be acquired on a Siemens Verio or Skrya Wide-Bore 3T MRI scanner. The scanners have 32 receiver channels and, a 12-channel head coil will be used for all brain imaging scans. The scanners are equipped with an MRI-compatible audio/visual system (Avotec Inc.) and an integrated four button response device developed to deliver the paradigms. All stimulus presentation and timing is controlled by a separate computer that is synchronized to the 3.0T scanner, which is equipped with Eprime (PST, Inc.) and Presentation (Neurobehavioral Systems, Inc.) software.

Visual Food Task: Images will be acquired using a gradient-echo single-shot echo-planar sequence over 36 axial slices aligned parallel to the AC-PC plane with in-plane resolution of $3.4 \times 3.4 \times 3$ mm, no gap (TR=1950, TE=22 ms, flip angle (FA)=90). Same/different task stimulus images will be back-projected onto a translucent screen placed at the end of the scanner and viewed through a mirror on the head coil. T1-weighted structural images (TR=300, TE=2.47ms, FOV=256, matrix=256x256, FA=90, NEX = 2), 3 mm thick in the same location as the echo-planar data for in-plane registration and high-resolution 3D structural images (3D MPRAGE; contiguous; sagittal acquisition; 176 images w/1 mm

isotropic voxels; TR=2500; TE=3.52ms; TI=1100; FOV=256; matrix=256x256; FA=12°; NEX=1) will be collected during Session 1 with two functional sequences and, Session 2 will have two functional sequences. *SST*: Whole-brain fMRI will be acquired with a gradient-echo, echoplanar pulse sequence [31, 4-mm thick contiguous axial slices, TE=29 ms; TR=2800 ms; flip angle=80°; FOV=256 × 256 mm; matrix=128 × 128; in-plane resolution=2 × 2 mm] over two imaging runs each lasting a total of 560 secs (200 volumes/run).

Biomarker Measures—We plan to explore changes in circulating biomarkers implicated in obesity-related carcinogenesis (e.g., leptin, adiponectin, insulin, CRP, IL-6, TNF- α , IGF-1, IGFBP-3), oxidative stress (F2-isoprostanes [82]) and neurotrophic factors (e.g., BDNF) using serum or plasma (20-200 μ l), as applicable, with standard assay kits or tandem mass spectrometry as applicable. Patients will have their blood drawn after an overnight fast (~8-12 hours). Blood will be drawn into vials (2 standard purple top K2-EDTA 4.5 ml vial for buffy coat and plasma; 2 standard red top 4.5 ml vials for serum; 1 Paxgene® DNA tube) and samples will be processed immediately for serum, plasma, and DNA extraction. Samples will be aliquoted into 0.5 mL and placed into cryovials pre-labeled with the unique study identifier and kept frozen at -70 °C until all samples are collected.

Costs—To help evaluate the potential for dissemination of the REWARD program, the costs for delivering the intervention (e.g., staff time to supervise exercise sessions, conduct group dietary behavioral sessions, conduct follow-up phone calls, etc.) will be tracked and differences in equipment costs between the two arms ('assisted' vs. voluntary) compared.

Sample Size and Power

In terms of power, we assume there will be 5% and 10% missing due to dropout at EOT and EOT+24 weeks, respectively, resulting in 57 patients per group at EOT and 55 patients per group at EOT+24 weeks. Since this is the first study to compare 'assisted' to voluntary rate exercise for weight loss, we use results from Andersen et al. [43] that compared obese women randomized to perform supervised exercise (aerobic) + LEARN or unsupervised (lifestyle) exercise + LEARN to help inform our power analysis. Assuming a standard deviation of 5 kg at the end of the follow-up period and 4 kg at the end of supervised treatment [43], differences of 2.2 kg at EOT and 2.7 kg at EOT+24 weeks between groups can be detected with 80% power (significance level of 0.05, 2-sided test). We will have 99% power to detect differences in weight when comparing the most active patient tertile to the least active tertile (-1.98 ± 4.3 kg vs. 4.88 ± 2.5 kg) [43] and 97% power when comparing the middle to the least active tertile (0.26 ± 5.5 kg vs. 4.88 ± 2.5 kg) [43] at EOT+24 weeks. For secondary outcomes, there is 80% power to detect effect sizes (standardized mean differences) of 0.53 and 0.54 at EOT and EOT+24 weeks, respectively, which are moderate [83] and attainable. For example, for fitness, we expect a change of 2.2 ml/kg/min at EOT [84] and assuming a standard deviation of 4.1 ml/kg/min [43], results in an effect size of 0.54, which is detectable with 80% power.

The primary outcome is change in weight from baseline to EOT + 24 weeks and, secondarily, at EOT. Other secondary outcome variables include fitness, body fat, exercise

motivation, eating and appetitive behavior measures, QoL and depression. Baseline characteristics (e.g., age, ethnicity, socioeconomic status variables) will be evaluated to ensure balanced randomization. Changes in absolute weight will be analyzed using mixed effects models and percent changes will be evaluated in secondary analyses. We will adjust the model for randomization stratification factors (BMI, time since treatment, hospital site) and any unbalanced factors. The null hypotheses that the groups do not differ in terms of changes at EOT+24 weeks and EOT will be tested using appropriate contrasts from the mixed model. Analyses will be done according to intention-to-treat principles in that all available outcome data from all randomized patients will be included, with the exception of patients having only baseline values. For analysis involving changes in scores, baseline scores will be included as covariates.

For the neuroimaging data, preprocessing will be conducted and motion-corrected images will be spatially smoothed using a Gaussian filter. Data from pre- and post-meal sessions for each individual will be aligned with high-resolution 2D and 3D anatomical images for display and localization.

Visual Food Task

For group analysis, anatomical 3D and individual fMRI data sets will undergo piecewise linear transformation into a proportional three-dimensional grid [85] through identification of anatomical landmarks, co-registered with the normalized high-resolution 3D data set and re-sampled to 1mm³ voxels. Regressors representing experimental conditions (e.g., [EOT: pre-meal high-calorie food - pre-meal non-food] vs. [Baseline: pre-meal high-calorie food - pre-meal non-food]) will be modeled with hemodynamic response filter and evaluated using a mixed linear model. Contrasts between conditions will be assessed with t-statistics. Within-group analyses in response to high- and low-calorie vs. non-food images will be conducted separately within each session prior to between-group interaction analyses of group (e.g., 'assisted' vs. voluntary exercise) by condition (high-calorie, low-calorie, non-food). We will employ a family-wise error correction approach at $p < 0.05$ using a minimum contiguous cluster correction applied to each contrast map for whole brain analyses. The mean signal intensity within a specific region of interest (ROI) will be used to explore correlations with weight loss and biomarkers. *SST*: A gamma variate HRF model will be used with regressors for four trial types: GO correct (GO), GO incorrect, correct inhibition (CI), and incorrect inhibition (II). Individual subject t-maps for GO, CI and II trial types will be converted to z-maps and transformed to Talairach stereotaxic space [86]. Three t-test subtraction maps (CI - GO, II - GO, and II - CI) will be generated for each group.

In terms of handling missing data, we will use the likelihood-based linear mixed modeling approach with baseline values included in the model because it has been shown to be more valid way to deal with dropout in clinical trials as compared to simple imputation procedures such as last observation carried forward [87]. It is also a valid approach when data are missing at random (e.g., as would be the case when missingness probabilities depend on observed data such as baseline values but not unobserved data). We will perform a secondary sensitivity analysis to examine possible biases between groups caused by attrition and hypotheses will be tested using multiple imputation of outcomes using an inclusive

strategy of including more baseline variables in the imputation model than are used in the analysis model [88]. If there is evidence for non-random dropout, particularly between EOT and EOT+24 weeks, shared parameter models [89] will be fit as a further sensitivity analysis.

Discussion

In the REWARD trial, we are evaluating, for the first time, the efficacy of ‘assisted’ compared to voluntary rate exercise, coupled with a group dietary behavioral program (LEARN), on weight loss at the end of treatment (16 weeks) and at the end of the follow-up period (6 months, EOT+24 weeks) in 120 obese EC patients. Secondary outcomes include fitness, body fat, exercise motivation, eating behavior, quality of life, and cognitive and food reward and motivation measures.

Overall mortality rates in EC are increasing in the U.S. [8] and, many of these deaths may be preventable since most have been attributed to co-morbidities associated with obesity and not to the cancer or its treatments [11-13]. We have previously shown that a 16-session group behavioral lifestyle intervention, which encouraged walking and healthy eating in obese EC survivors, decreased activation in brain regions associated with food reward and motivation in response to high-calorie images shown after eating a standardized meal; however, we [27] and others, who evaluated an obese non-cancer population [28], found increased activation in frontal regions after behavioral lifestyle interventions, which suggests that behavioral lifestyle interventions may help dampen high-calorie food response but, more intensive programs may be required to fully alleviate incentive salience from visual food cues. One such modification could be to incorporate higher intensity exercise because high intensity exercise can enhance meal-induced satiety [29] and may suppress hedonic eating drive through enhancement of executive functions that provide ‘top-down’ inhibitory control or ‘braking’ systems [22]. However, the very poor fitness levels of EC patients [16], coupled with their central governor [90] and other comorbidities (e.g., arthritis, hypertension, diabetes), may prohibit them from being able to voluntarily and safely initiate an exercise program at high levels.

‘Assisted’ cycling, which provides mechanical assistance to pedal approximately 35% faster than voluntary rates, has been shown in Parkinson's Disease patients to provide global improvements in motor function [30] and increased neural activity in cortical and subcortical regions, which is consistent with activation patterns after applying a dopamine agonist, and, hence, may be modulating dopamine levels in the brain [30;31]. Thus, we hypothesize that patients performing ‘assisted’ exercise will have improved neurological stimulus, extending to reward and motivation regions of the brain, which may lead to enhanced weight loss.

It is well known that most obese individuals regain the weight they lost within 1-2 years [91] and, most diet and exercise programs, alone or in combination, have not been very effective in *sustaining* weight loss [92]. This may be due, at least in part, to a failure to fully exploit the connection between exercise and eating behavior [22]. Behavioral studies suggest intrinsic motivation to exercise plays a more significant role than dietary behaviors in

predicting long-term weight loss success [67]. Interestingly, obese individuals have a lower inhibitory control as measured using a fMRI stop signaling task (similar to the one in the REWARD trial), which suggests that individuals who are successful in controlling their weight may be able to resist temptations toward palatable food by exerting greater inhibitory control [93;94]. In the REWARD trial, we aim to exploit the connection between exercise and eating behavior through the use of ‘assisted’ exercise, which we hypothesize will help to *sustain* weight loss via increased intrinsic motivation to exercise and better ‘top-down’ inhibitory control.

A strength of our study is the use of both questionnaires and neuroimaging to evaluate changes in eating behavior and cognition, and, specifically, executive function. Only a few studies have utilized visual food fMRI tasks to evaluate changes in appetitive behavior [27;28] and, to our knowledge, no studies have used the stop signaling task to evaluate changes in executive function in response to a behavioral lifestyle intervention. An additional strength of the REWARD trial is the use of the highly effective LEARN dietary behavioral program [42-44] as the basis of our group dietary behavioral intervention. The LEARN program is already being offered at many medical centers and community programs across the U.S. including the Comprehensive Weight Management Program at the Ohio State Wexner Medical Center [95], which enhances the potential generalizability of the REWARD trial. However, we recognize that it may take a few years before the ‘assisted’ cycles become commercially available to enable wide dissemination of the full REWARD program. Another limitation of our study is the inability to fully evaluate the effects of weight loss on EC recurrence and survival due to the relatively short duration of our study (5 years).

Conclusions

Results from the REWARD trial will provide the first insights into the efficacy of using ‘assisted’ exercise compared to voluntary rate exercise, coupled with a dietary behavioral intervention, to enhance and maintain weight loss in obese patients with endometrial cancer. If successful, this intervention could be easily adapted for utilization in other obese individuals with and without cancer to improve sustained weight loss, quality of life and overall survival.

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Reference List

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. *CA Cancer J Clin.* 2014; 64(1):9–29. [PubMed: 24399786]
2. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity and the Prevention of Endometrial Cancer; 2013.
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008; 371(9612):569–578. [PubMed: 18280327]

4. Schmandt RE, Iglesias DA, Co NN, Lu KH. Understanding obesity and endometrial cancer risk: opportunities for prevention. *Am J Obstet Gynecol.* 2011; 205(6):518–525. [PubMed: 21802066]
5. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer.* 2004; 4(8):579–591. [PubMed: 15286738]
6. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev.* 2002; 11(12):1531–1543. [PubMed: 12496040]
7. Duong LM, Wilson RJ, Ajani UA, Singh SD, Ehemann CR. Trends in endometrial cancer incidence rates in the United States, 1999–2006. *J Womens Health (Larchmt).* 2011; 20(8):1157–1163. [PubMed: 21682550]
8. Ehemann C, Henley SJ, Ballard-Barbash R, Jacobs EJ, Schymura MJ, Noone AM, et al. Annual Report to the Nation on the status of cancer, 1975–2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer.* 2012; 118(9):2338–2366. [PubMed: 22460733]
9. Arem H, Irwin ML. Obesity and endometrial cancer survival: a systematic review. *Int J Obes (Lond).* 2012
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003; 348(17):1625–1638. [PubMed: 12711737]
11. von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma : a Gynecologic Oncology Group study. *Cancer.* 2006; 107(12):2786–2791. [PubMed: 17096437]
12. Everett E, Tamini H, Geer B, Swisher E, Paley P, Mandel L, et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. *Gynecol Oncol.* 2003; 90:150–157. [PubMed: 12821356]
13. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol.* 2012; 126(2):176–179. [PubMed: 22507532]
14. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol.* 2005; 23(24):5814–5830. [PubMed: 16043830]
15. von Gruenigen VE, Waggoner SE, Frasure HE, Kavanagh MB, Janata JW, Rose PG, et al. Lifestyle challenges in endometrial cancer survivorship. *Obstet Gynecol.* 2011; 117(1):93–100. [PubMed: 21173649]
16. Modesitt SC, Geffel DL, Via J, Weltman L. Morbidly obese women with and without endometrial cancer: are there differences in measured physical fitness, body composition, or hormones? *Gynecol Oncol.* 2012; 124(3):431–436. [PubMed: 22101155]
17. Kirchengast S, Gruber D, Sator M, Huber J. Hysterectomy is associated with postmenopausal body composition characteristics. *J Biosoc Sci.* 2000; 32(1):37–46. [PubMed: 10676058]
18. McCarthy AM, Menke A, Ouyang P, Visvanathan K. Bilateral Oophorectomy, Body Mass Index, and Mortality in U.S. Women Aged 40 Years and Older. *Cancer Prev Res (Phila).* 2012
19. Donnelly CM, Blaney JM, Lowe-Strong A, Rankin JP, Campbell A, McCrum-Gardner E, et al. A randomised controlled trial testing the feasibility and efficacy of a physical activity behavioural change intervention in managing fatigue with gynaecological cancer survivors. *Gynecol Oncol.* 2011; 122(3):618–624. [PubMed: 21689848]
20. von Gruenigen V, Courneya KS, Gibbons HE, Kavanagh MB, Waggoner SE, Lerner E. Feasibility and effectiveness of a lifestyle intervention program in obese endometrial cancer patients: a randomized trial. *Gynecol Oncol.* 2008; 109(1):19–26. [PubMed: 18243282]
21. von Gruenigen V, Frasure H, Kavanagh MB, Janata J, Waggoner S, Rose P, et al. Survivors of uterine cancer empowered by exercise and healthy diet (SUCCEED): A randomized controlled trial. *Gynecol Oncol.* 2012; 125(3):699–704. [PubMed: 22465522]
22. Joseph RJ, Alonso-Alonso M, Bond DS, Pascual-Leone A, Blackburn GL. The neurocognitive connection between physical activity and eating behaviour. *Obes Rev.* 2011; 12(10):800–812. [PubMed: 21676151]

23. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr.* 2009; 139(3):629–632. [PubMed: 19176746]
24. Trayhurn P, Bing C. Appetite and energy balance signals from adipocytes. *Philos Trans R Soc Lond B Biol Sci.* 2006; 361(1471):1237–1249. [PubMed: 16815801]
25. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS One.* 2007; 2(1):e698. [PubMed: 17668074]
26. Volkow ND, Wise RA. How can drug addiction help us understand obesity? *Nat Neurosci.* 2005; 8(5):555–560. [PubMed: 15856062]
27. Nock NL, Dimitropoulos A, Tkach J, Frasure H, Vongruenigen V. Reduction in neural activation to high-calorie food cues in obese endometrial cancer survivors after a behavioral lifestyle intervention: a pilot study. *BMC Neurosci.* 2012; 13:74. [PubMed: 22731395]
28. Murdaugh DL, Cox JE, Cook EW, Weller RE. fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage.* 2012; 59:2709–2712. [PubMed: 22332246]
29. King NA, Caudwell PP, Hopkins M, Stubbs JR, Naslund E, Blundell JE. Dual-process action of exercise on appetite control: increase in orexigenic drive but improvement in meal-induced satiety. *Am J Clin Nutr.* 2009; 90(4):921–927. [PubMed: 19675105]
30. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair.* 2009; 23(6):600–608. [PubMed: 19131578]
31. Alberts JL, Linder SM, Penko AL, Lowe MJ, Phillips M. It is not about the bike, it is about the pedaling: forced exercise and Parkinson's disease. *Exerc Sport Sci Rev.* 2011; 39(4):177–186. [PubMed: 21799425]
32. Brownell KD. Diet, exercise and behavioural intervention: the nonpharmacological approach. *Eur J Clin Invest.* 1998; 28(Suppl 2):19–21. [PubMed: 9777323]
33. Brownell, KD. The LEARN Program for Weight Management. 10th ed.. American Health Publishing; Dallas, TX: 2004.
34. Sonoda Y, Barakat RR. Screening and the prevention of gynecologic cancer: endometrial cancer. *Best Pract Res Clin Obstet Gynaecol.* 2006; 20(2):363–377. [PubMed: 16364689]
35. Olson SH, Atoria CL, Cote ML, Cook LS, Rastogi R, Soslow RA, et al. The impact of race and comorbidity on survival in endometrial cancer. *Cancer Epidemiol Biomarkers Prev.* 2012; 21(5):753–760. [PubMed: 22426148]
36. Siegel R, Naishadham D, Jemal A. Cancer statistics for Hispanics/Latinos, 2012. *CA Cancer J Clin.* 2012; 62(5):283–298. [PubMed: 22987332]
37. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* 2010; 42(7):1409–1426. [PubMed: 20559064]
38. Milne HM, Wallman KE, Gordon S, Courneya KS. Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized control trial. *Breast Cancer Res Treat.* 2008; 108(2):279–288. [PubMed: 17530428]
39. American College of Sports Medicine. ACSM resource manual for guidelines for exercise testing and prescription. 5th Edition. Baltimore, MD: 2005.
40. Egana M, O'Riordan D, Warmington SA. Exercise performance and VO2 kinetics during upright and recumbent high-intensity cycling exercise. *Eur J Appl Physiol.* 2010; 110(1):39–47. [PubMed: 20386919]
41. Reiser RF 2, Peterson ML, Broker JP. Understanding recumbent cycling: Instrumentation design and biomechanical analysis. *Biomed Sci Instrum.* 2002; 38:209–214. [PubMed: 12085603]
42. Aggarwal S, Arena R, Cuda L, Hauer T, Martin BJ, Austford L, et al. The independent effect of traditional cardiac rehabilitation and the LEARN program on weight loss: a comparative analysis. *J Cardiopulm Rehabil Prev.* 2012; 32(1):48–52. [PubMed: 22207088]
43. Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC. Effects of a lifestyle activity versus structured aerobic exercise in obese women: a randomized trial. *JAMA.* 1999; 281:335–340. [PubMed: 9929086]

44. Jean-Baptiste M, Tek C, Liskov E, Chakunta UR, Nicholls S, Hassan AQ, et al. A pilot study of a weight management program with food provision in schizophrenia. *Schizophr Res.* 2007; 96(1-3): 198–205. [PubMed: 17628437]
45. Van Gaal LF, Mertens IL, Ballaux D. What is the relationship between risk factor reduction and degree of weight loss? *European Heart Journal Supplements.* 2005; 7(Suppl L):L21–L26.
46. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care.* 2011; 34(7):1481–1486. [PubMed: 21593294]
47. National Institute for Health and Clinical Excellence. Obesity: The Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children. 2006; 43
48. Gavin, J.; McBrearty, M. Building Enduring Futures.. In: Gavin, James; Mcbrearty, Madeleine, editors. *Lifestyle Wellness Coaching.* Second ed.. Human Kinetics; Champaign, IL: 2013. p. 198–200.
49. Biel RK, Friedenreich CM, Csizmadia I, Robson PJ, McLaren L, Faris P, et al. Case-control study of dietary patterns and endometrial cancer risk. *Nutr Cancer.* 2011; 63(5):673–686. [PubMed: 21614724]
50. Inoue-Choi M, Robien K, Mariani A, Cerhan JR, Anderson KE. Sugar-sweetened beverage intake and the risk of type I and type II endometrial cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2013; 22(12):2384–2394. [PubMed: 24273064]
51. Ajzen I. Theory of planned behavior. *Org Behav Human Decis Process.* 1991; 50:179–211.
52. Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Jones LW. Exercise motivation and adherence in cancer survivors after participation in a randomized controlled trial: an attribution theory perspective. *Int J Behav Med.* 2004; 11(1):8–17. [PubMed: 15194515]
53. Rogers LQ, Courneya KS, Shah P, Dunnington G, Hopkins-Price P. Exercise stage of change, barriers, expectations, values and preferences among breast cancer patients during treatment: a pilot study. *Eur J Cancer Care (Engl).* 2007; 16(1):55–66. [PubMed: 17227354]
54. Rogers LQ, Markwell S, Hopkins-Price P, Vicari S, Courneya KS, Hoelzer K, et al. Reduced barriers mediated physical activity maintenance among breast cancer survivors. *J Sport Exerc Psychol.* 2011; 33(2):235–254. [PubMed: 21558582]
55. Svetkey LP, Stevens VJ, Brantley PJ, Appel LJ, Hollis JF, Loria CM, et al. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. *JAMA.* 2008; 299(10):1139–1148. [PubMed: 18334689]
56. Miller, WR.; Rollnick, S. *Motivational Interviewing: Preparing People to Change Addictive Behavior.* The Guilford Press; New York, NY: 1991.
57. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res.* 1985; 29(1):71–83. [PubMed: 3981480]
58. Foster GD, Wadden TA, Swain RM, Stunkard AJ, Platte P, Vogt RA. The Eating Inventory in obese women: clinical correlates and relationship to weight loss. *Int J Obes Relat Metab Disord.* 1998; 22(8):778–785. [PubMed: 9725638]
59. Laessle RG, Tuschl RJ, Kotthaus BC, Pirke KM. A comparison of the validity of three scales for the assessment of dietary restraint. *J Abnorm Psychol.* 1989; 98(4):504–507. [PubMed: 2592686]
60. Wadden TA, Foster GD, Letizia KA. Response of obese binge eaters to treatment by behavior therapy combined with very low calorie diet. *J Consult Clin Psychol.* 1992; 60(5):808–811. [PubMed: 1401399]
61. Moshfegh AJ, Raper N, Ingwersen LA, et al. An improved approach to 24 hour diet recall methodology. *Metab.* 2001; 45:156.
62. Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. *Am J Clin Nutr.* 2003; 77(5):1171–1178. [PubMed: 12716668]
63. von Gruenigen VE, Gibbons HE, Kavanagh MB, Janata JW, Lerner E, Courneya KS. A randomized trial of a lifestyle intervention in obese endometrial cancer survivors: quality of life outcomes and mediators of behavior change. *Health Qual Life Outcomes.* 2009; 7:17. [PubMed: 19243603]

64. Clark MM, Abrams DB, Niaura RS, Eaton CA, Rossi JS. Self-efficacy in weight management. *J Consult Clin Psychol.* 1991; 59(5):739–744. [PubMed: 1955608]
65. Clark MM, Forsyth LH, Lloyd-Richardson EE, King TK. Eating self-efficacy and binge eating disorder in obese women. *J Appl Biobehav Res.* 2000; 5:154–161.
66. Markland D, Hardy L. On the factorial and construct validity of the Intrinsic Motivation Inventory: conceptual and operational concerns. *Res Q Exerc Sport.* 1997; 68(1):20–32. [PubMed: 9094760]
67. Teixeira PJ, Going SB, Houtkooper LB. Exercise motivation, eating, and body image variables as predictors of weight control. *Med Sci Sports Exerc.* 2006; 38(1):179–188. [PubMed: 16394972]
68. Ingledew DK, Markland D, Medley AR. Exercise motives and stages of change. *J Health Psychol.* 1998; 3(4):477–489. [PubMed: 22021408]
69. Sebire SJ, Standage M, Vansteenkiste M. Predicting objectively assessed physical activity from the content and regulation of exercise goals: evidence for a mediational model. *J Sport Exerc Psychol.* 2011; 33(2):175–197. [PubMed: 21558579]
70. Sebire SJ, Standage M, Vansteenkiste M. Examining intrinsic versus extrinsic exercise goals: cognitive, affective, and behavioral outcomes. *J Sport Exerc Psychol.* 2009; 31(2):189–210. [PubMed: 19454771]
71. Godin G, Jobin J, Bouillon J. Assessment of leisure time exercise behavior by self-report: a concurrent validity study. *Can J Public Health.* 1986; 77(5):359–362. [PubMed: 3791117]
72. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993; 11(3):570–579. [PubMed: 8445433]
73. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage.* 1997; 13(2):63–74. [PubMed: 9095563]
74. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes.* 2003; 1:79. [PubMed: 14678568]
75. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills.* 1958; 8:271–276.
76. Sheridan LK, Fitzgerald HE, Adams KM, Nigg JT, Martel MM, Puttler LI, et al. Normative Symbol Digit Modalities Test performance in a community-based sample. *Arch Clin Neuropsychol.* 2006; 21(1):23–28. [PubMed: 16139470]
77. Smith, A. Symbol Digits Modalities Test. Western Psychological Services; Los Angeles, CA: 1992.
78. Phelan S, Hassenstab J, McCaffery JM, Sweet L, Raynor HA, Cohen RA, et al. Cognitive interference from food cues in weight loss maintainers, normal weight, and obese individuals. *Obesity (Silver Spring).* 2011; 19(1):69–73. [PubMed: 20539296]
79. Dimitropoulos A, Schultz RT. Food-related neural circuitry in Prader-Willi syndrome: response to high-versus low-calorie foods. *J Autism Dev Disord.* 2008; 38(9):1642–1653. [PubMed: 18311513]
80. Dimitropoulos A, Tkach J, Ho A, Kennedy J. Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. *Appetite.* 2011; 58(1):303–312. [PubMed: 22063094]
81. Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci.* 2006; 26(9):2424–2433. [PubMed: 16510720]
82. Bai HY, Lin SL, Chung YT, Liu TY, Chan SA, Fuh MR. Quantitative determination of 8-isoprostaglandin F(2alpha) in human urine using microfluidic chip-based nano-liquid chromatography with on-chip sample enrichment and tandem mass spectrometry. *J Chromatogr A.* 2011; 1218(15):2085–2090. [PubMed: 21081240]
83. Cohen, J. Statistical Power Analysis in the Behavioral Sciences. 2nd ed.. Lawrence Erlbaum; Hillsdale NJ: 1992.
84. Fong DY, Ho JW, Hui BP, Lee AM, Macfarlane DJ, Leung SS, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ.* 2012; 344:e70. [PubMed: 22294757]

85. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods*. 2002; 118(2):115–128. [PubMed: 12204303]
86. Talairach, J.; Tournoux, P. Co-planar Steriotaxic Atlas of the Human Brain. Thieme; New York: 1988.
87. Mallinkrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed effects models. *Journal of Biopharmaceutical Statistics*. 2001; 11:9–31. [PubMed: 11459446]
88. Collins LM, Schafer JL, Cam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychol Methods*. 2001; 6(4):330–351. [PubMed: 11778676]
89. Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. *Stat Med*. 2006; 25(1):143–163. [PubMed: 16025541]
90. Lambert EV, St.Clair Gibson A, Noakes TD. Complex systems model of fatigue: integrative homeostatic control of peripheral physiological systems during exercise in humans. *Br J Sports Med*. 2005; 39(1):52–59. [PubMed: 15618343]
91. Jeffery RW, Drewnowski A, Epstein LH, Stunkard AJ, Wilson GT, Wing RR, et al. Long-term maintenance of weight loss: current status. *Health Psychol*. 2000; 19(1 Suppl):5–16. [PubMed: 10709944]
92. Lien LF, Haqq AM, Arlotto M, Slentz CA, Muehlbauer MJ, McMahon RL, et al. The STEDMAN project: biophysical, biochemical and metabolic effects of a behavioral weight loss intervention during weight loss, maintenance, and regain. *OMICS*. 2009; 13(1):21–35. [PubMed: 19290809]
93. Hendrick OM, Luo X, Zhang S, Li CS. Saliency processing and obesity: a preliminary imaging study of the stop signal task. *Obesity (Silver Spring)*. 2012; 20(9):1796–1802. [PubMed: 21720427]
94. Houben K, Nederkoorn C, Jansen A. Too tempting to resist? Past success at weight control rather than dietary restraint determines exposure-induced disinhibited eating. *Appetite*. 2012; 59(2):550–555. [PubMed: 22796949]
95. The Ohio State University; Wexner Medical Center: 2013. 11-11-2013

Cleveland Clinic; LEARN: Lifestyles, Exercise, Attitudes, Relationships and Nutrition.

Figure 1. REWARD Trial Schema

UHMC: University Hospitals Case Medical Center; CC: Cleveland Clinic; LEARN: Lifestyles, Exercise, Attitudes, Relationships and Nutrition.

Table 1REWARD Intervention Measures and Timeline^a.

REWARD Measures	Baseline	Intervention Period (16 weeks)	End of Intervention (EOT)	12 Weeks after EOT (EOT+12)	24 Weeks after EOT (EOT+24)
1. Exercise Screening	X				
2. Fitness (VO ₂ peak) Testing	X		X	X	X
3. Body Composition:					
- Weight	X	X	X	X	X
- % Body Fat	X	X	X	X	X
4. Supervised Exercise Sessions (3 days/week)		X			
5. Group Dietary Behavioral Program (LEARN) (1 day/week)		X			
6. Maintenance Period/Follow-Up Phone Calls (1/month for 6 months)			X	X	
7. Brain Imaging (fMRI):					
- Visual Food Task	X		X	X	X
- Stop Signaling Task (SST)	X		X	X	X
8. Blood Draw for Biomarkers	X		X	X	X
9. Eating Behavior:					
- 24 hour recall	X		X	X	X
- TFEQ	X		X	X	X
- WEL	X		X	X	X
10. Exercise Motivation:					
- EMI-2	X		X	X	X
- IMI	X		X	X	X
11. Physical Activity:					
- LSI	X		X	X	X
- Accelerometer/HR Monitor				X	X
12. Quality of Life:					
- FACT-G	X		X	X	X
- FACT-En	X		X	X	X
13. Cognition/Executive Function:					
- Trails A & B	X		X	X	X
- SDMT	X		X	X	X
- Food Stroop	X		X	X	X

^a Abbreviations: TFEQ: Three Factor Eating Questionnaire; WEL: Weight Efficacy Lifestyle Questionnaire; EMI: Exercise Motivations Inventory; IMI: Intrinsic Motivational Inventory; LSI: Godin Leisure Time Questionnaire; HR: Heart Rate; FACT-G and FACT-En: Functional Assessment of Cancer Therapy-General and, -Endometrial Cancer, respectively; SDMT: Symbol Digits Modality Test