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Prescribed exercise to Reduce Recidivism After Weight Loss-Pilot (PREVAIL-P): Design, methods and rationale

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ABSTRACT

Clinically significant weight loss is associated with health benefits for overweight and obese adults. Participation in adequate amounts of physical activity is critical for weight maintenance. However, the recommended amount of physical activity needed to promote weight maintenance is based primarily on retrospective studies that quantified physical activity levels through questionnaires which tend to overestimate physical activity levels. In addition, the present literature has provided little data on the impact of these physical activity levels on cardiovascular and diabetes risk factors, which may have equal or more clinical importance than weight changes. The Prescribed Exercise to Reduce Recidivism After Weight Loss-Pilot (PREVAIL-P) study will evaluate the effect of aerobic exercise training amount on weight maintenance following clinically significant weight loss in overweight and obese adults (BMI 25–40 kg/m^2) age 30–65 years. Participants (N = 39) will complete a 10-week OPTIFAST® weight loss program with supervised aerobic exercise training. Individuals who achieve ≥7% weight loss from baseline will be subsequently randomized to levels of aerobic training consistent with physical activity recommendations (PA-REC) or weight maintenance recommendations (WM-REC) for 18 additional weeks. The primary outcome of the PREVAIL-P study will be change in weight from the completion of OPTIFAST® program to the end of the study. Notable secondary measures include changes in clinically relevant cardiometabolic risk factors between study groups (e.g. blood lipids concentrations, oral glucose tolerance, arterial stiffness). This pilot study will be used to estimate the effect sizes needed for a randomized controlled trial on this topic.

1. Introduction

Clinically significant weight loss is associated with a reduction in cardiovascular disease (CVD) and type 2 diabetes (T2D) risk factors [1–3]. Although overweight and obese adults can often achieve clinically significant weight loss, only 20% of individuals are able to maintain the weight loss after 1 year [4]. This has clinical implications as the regression of weight back toward the pre-weight loss value is associated with regression in major CVD (e.g. blood lipid concentrations, inflammation) and T2D risk factors (e.g. blood glucose and insulin concentrations) [5,6]. Importantly, regaining weight following clinically significant weight loss may lead to unfavorable changes in body

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composition (more fat mass with less lean mass, lower resting metabolic rate), which may increase the susceptibility to future weight gain [7]. Thus, intervention strategies aimed at reducing the regression in weight after weight loss are critical for the prevention of T2D and CVD.

Low physical activity levels are an established risk factor for weight regain after weight loss [8–11]. However, as illustrated in the recent weight maintenance guidelines [10], major limitations exist in this research area which include lack of randomization to exercise levels after weight loss, the use of retrospective study designs, and physical activity questionnaires being a primary method of quantifying physical activity level. In addition, many studies focus specifically on weight maintenance without data evaluating the impact of exercise level on clinically relevant risk factors. Risk factors that have independent relationships with CVD or T2D may provide more prognostic information regarding the change in disease status than simply evaluating the change in weight alone. The limited studies that examine the impact of exercise after weight loss on metabolic risk factors suggest that aerobic exercise can attenuate the regression in risk factors with weight gain [3,12], but have evaluated only one level of aerobic exercise training. Thus, although aerobic exercise has the potential to improve weight loss maintenance, research is needed to determine the dose response relationship of physical activity level after weight loss on weight maintenance and cardiometabolic risk factors. Prospective studies on exercise amount after weight loss will also help to determine the feasibility of aerobic exercise for weight maintenance guidelines. For translation purposes to weight loss, clinical and health-related settings, further research in this area will help clinicians provide evidenced-based recommendations on how exercise can facilitate weight maintenance and improvements in risk factors after weight loss. To our knowledge, no study has evaluated aerobic exercise training level after clinically significant weight loss in a prospective supervised manner.

The Prescribed Exercise to Reduce Recidivism After Weight Loss-Pilot (PREVAIL-P) trial will evaluate the impact of aerobic exercise training level after weight loss on weight maintenance and change in CVD risk factors. This pilot study is designed to determine the feasibility the intervention and provide information to power a randomized control trial (RCT) on this topic. The purpose of this paper is to describe the design, methods and the rationale of the PREVAIL-P trial.

2. Methods

Study design: The PREVAIL-P study will recruit 39 overweight and obese adults with elevated CVD and T2D risk from the Pitt county, North Carolina area. We selected this criteria based on the 2013 AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults [13]. We will exclude individuals with diagnosed T2D or significant CVD, and/or those taking medications or have conditions that confound weight loss or regain (e.g. hypo/hyperthyroidism [both medicated or untreated], bariatric surgery). In addition, we will exclude individuals with gait or joint issues that are contraindications for exercise training. Participants will undergo an OPTIFAST® weight loss program and supervised aerobic exercise training for 10 weeks. Participants who obtain clinically significant weight loss (≥7%) will be subsequently randomized to either 18 weeks of aerobic training consistent with the minimum physical activity recommendations (PA-REC, ~550 MET minutes per week) or weight maintenance recommendations (WM-REC, ~970 MET minutes per week). We will evaluate the percentage of participants that obtain at least 7% weight loss following OPTIFAST® treatment, retention rates in the weight loss program and the study as whole, and adherence to exercise levels. We will also evaluate changes in major health risk factors due to the intervention. A flow diagram for the PREVAIL-P study is shown in Fig. 1.

Rationale for inclusion/exclusion: For the inclusion criteria, we made several key decisions in regard to BMI levels, postmenopausal women, and those with advanced CVD or T2D. We decided we will include individuals who are overweight with an indication of increased cardiometabolic risk. This was based on the 2013 AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults [13], which provided recommendations for adults who need to lose weight. As the secondary aims of the study focus on the impact of the intervention on cardiometabolic risk factors, it is necessary to recruit a population that has some elevation in these factors at baseline.

In regard to participants with established CVD or other major health conditions, the PREVAIL-P study represents a primary prevention strategy to reduce future CVD events, T2D diagnosis and other metabolic diseases. Therefore, the examination of the project objectives in higher risk populations (e.g. diabetes, secondary prevention CVD) would be better addressed in a separate study with outcome measures specific to those conditions. We will include postmenopausal women in the present study since the current weight maintenance guidelines for physical activity do not exclude them or have different exercise recommendations based on menopausal status [10]. Additionally, previous physical activity studies evaluating weight maintenance have included postmenopausal women [8,14–16]. The study has been approved by the East Carolina University (ECU) Institutional Review Board and has been registered as a clinical trial (NCT03685123).

Recruitment: Participants will be recruited in the Pitt County, North Carolina area through newspaper advertisement, targeted Facebook advertisement (based on age and location), emails to ECU employees, web-screening from a study website, targeted direct mailers, and flyers in local physician offices. Potential participants will be phone screened for major aspects of the study inclusion/exclusion criteria (summarized in Table 1). Participants will also be able to complete a short, web-based questionnaire on a study website for screening. Individuals who remain eligible following phone or web-based screen will participate in a screening visit.

Screening visit: Research staff will consent the participant (e.g. provide information about the study, structure of the study, study-related procedures, risks/benefits, answer questions about participation). If the participant is interested in screening for the study, the participant will sign the study consent form. After this, we will ask the individual to complete a mock exercise calendar where they will indicate when they can attend OPTIFAST® weight loss classes and the required amount of exercise sessions in the study protocol. Participants

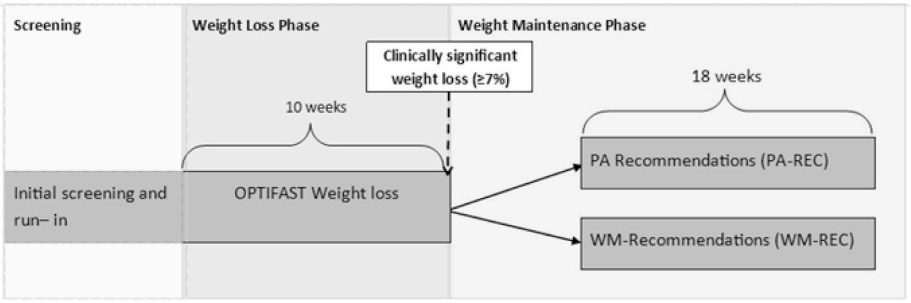

Fig. 1. Flow diagram of the PREVAIL-P trial.

Table 1
Inclusion and exclusion criteria for the PREVAIL-P study.

Age/sex	Men and women 30–65 years of age, Postmenopausal females permitted
BMI/Physical activity	25–40 kg/m^2 at enrollment, current sedentary status
Informed Consent	The capability and willingness to provide written informed consent
Exclusion Criteria	
Significant CVD or disorders	Including, but not limited to, serious arrhythmias, cardiomyopathy, congestive heart failure, stroke or transient ischemic attacks, peripheral vascular disease, acute, chronic or recurrent thrombophlebitis or myocardial infarction/stroke, postmenopausal women
Diabetes	Previous diagnosis or taking medication for type 1 or 2 diabetes, fasting blood glucose ≥126 mg/dL
Blood pressure	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg [44].
Other medical conditions	Including, but not limited to, chronic or recurrent respiratory, gastrointestinal, neuromuscular, neurological, HIV or psychiatric conditions. Hospitalization over the last 5 years or currently treatment for mental illness. Major joint issues or gait that would be contraindicated for exercise training. Conditions which are life-threatening or can be aggravated by exercise training
Other exclusions	Plans to be away from the Pitt County area more than 3 weeks in the next 3 months. Pregnant or plans to become pregnant. Currently engaging a diet or a weight loss program. Do not own smartphone for MyFitnessPal and Centrepoint Apps. Non-compliance during screening visits.

will also identify potential back-up times for exercise training sessions. In addition, research staff will interview the participant to assess for major barriers for study completion (e.g. distance from home to the facility, available time for participation, weekly time commitments, and acceptability for participation in both weight loss and exercise components of the study). Research staff will then assess height, weight and resting blood pressure. If those values meet the criteria for the study, the participant will be given an ActiGraph accelerometer (Pensacola, FL), which will be used to measure steps, moderate to vigorous physical activity, and sleep over the course of 7 consecutive days. Participants will also wear an activPAL4 accelerometer (PAL technologies, Glasgow, UK) to measure the amount of sitting time. Participants will be instructed to wear actigraph accelerometers at all times except for during bathing. ActivPal4 accelerometers were attached to the thigh using tegaderm and participants were able to wear the devices during bathing. After 7 days, the participant will return both physical activity monitors and a nurse will draw a fasting blood sample to evaluate hepatic, renal, hematological, endocrine, and metabolic function for inclusion/exclusion purposes. Premenopausal women will take a pregnancy test to confirm that they are not pregnant. Participant laboratory values will be reviewed for compliance to the study protocol and approved by the study physician. After screening measurements, the participant will undergo baseline testing for primary and secondary measurements.

Primary outcome: The primary outcome measure of the PREVAIL-P study is change in weight after obtaining clinically significant weight loss to follow-up of the intervention. Body weight will be evaluated using a level beam scale (Health O Meter Professional, McCook, IL) and recorded to the nearest tenth of kg. All weight measurements will be performed in the morning in a fasted state (12 h), with the participant wearing only a hospital gown, and after the participant has voided. Weight change will be evaluated in both absolute (kg) and relative terms (%) after completion of the weight loss phase (baseline to 10 weeks) and after the weight maintenance phase (Week 11 to Week 28).

Secondary outcomes: Secondary measures will be collected at all major assessment points (Baseline, Week 10, and Week 28). We specifically chose cardiometabolic risk factors which have been shown in the literature to improve with weight loss, exercise training (independent of weight loss) or a combination of both. The rationale for this is that even in the presence of weight regain after clinically significant weight loss, aerobic training may attenuate the deleterious effect on cardiometabolic risk factors. Thus, we will evaluate the effects of the proposed intervention on traditional (lipid concentrations, brachial systolic/diastolic blood pressure), non-traditional (cardiorespiratory fitness, lipoprotein particles size and subclass, c-reactive protein, pulse wave velocity, augmentation index, central blood pressure, heart rate variability) CVD risk and T2D risk factors (blood glucose/insulin, insulin sensitivity). We will also compare the percentage of individuals in each group that are able to maintain at least 3% of the initial weight loss [10]. In addition, we will obtain total energy expenditure, sedentary behavior, non-exercise physical activity, energy intake (macro/micronutrient information) to inform energy balance apart from exercise training. A schedule of the assessment visits in PREVAIL-P are shown in Table 2.

All outcome measures will be assessed in two separate visits at baseline, after the weight loss phase (10 weeks) and follow-up (28 weeks). On the first visit, we will assess body weight, body composition (DXA, waist circumference), resting metabolic rate, heart rate variability and fitness testing. On a separate day, we will measure pulse wave velocity, oral glucose tolerance, blood draws and administer questionnaires (psychological and food frequency questionnaires). Both assessment visits will be conducted after an overnight fast. Primary and secondary outcome measures will be performed at baseline, after weight loss (Week 10) and at follow-up (Week 28).

2.1. Outcome measures visit 1

Body composition: Body composition will be measured using whole body dual energy x-ray absorptiometry (DXA) (Hologic, Horizon A Marlborough, MA) with the participant in the supine position. From the whole-body DXA scan we will quantify total fat mass, visceral fat mass (at the level of L4), lean tissue and bone mass (APEX version 5.6.0.5). Segmental body composition analysis will be performed using standard skeletal landmarks according to the manufacturer. If the subject is too wide for the DXA scanning area, they will be positioned to capture the entire the right side of the body. Any missing segments from the left side will be estimated from the right using the mirror scan feature of the DXA software. If a subject is too tall for the DXA scanning area, they will be positioned such that the feet will extend outside the scan and not quantified in the analysis. Waist circumference will be evaluated with a Gulick tape measure at the natural waist. Three measurements will be taken, and the results will be averaged.

Resting metabolic rate: Resting metabolic rate (RMR) will be measured using indirect calorimetry (TrueOne 2400, Parvo Medics, Salt Lake City, UT) with a clear ventilated canopy and dilution pump. Participants will be fasted for at least 12 h and will refrain from caffeine for at least 12 h, light-to-moderate intensity exercise for at least 24 h, and moderate-to-heavy intensity exercise for at least 48 h. All medications taken the morning of the baseline RMR measurement will be logged and repeated for mid-intervention and follow-up measures. RMR will be collected simultaneously with HRV during the morning in a quiet, temperature-controlled room. Initially, participants will rest in the seated position for a 20-min period wearing a heart rate monitor (Zephyr Bioharness 3, Medtronic, Annapolis, MD). Participants will rest in the supine position for at least an additional 20 min with the hood covering their head and the room dimly lit. Instructions will be given to the participant to minimize body movements and to remain awake for the entire measurement. RMR will be determined from approximately 10 min of data at the end of the procedure when the $FECO_2$ dilution is maintained between 1.0 and 1.2%. RMR for this study will be considered valid if the CVs for REE, VO_2 and VCO_2 were ≤10%.

Heart rate variability: Heart rate variability (HRV) will be assessed in accordance with the Task Force for Pacing and Electrophysiology [17]. Briefly, participants will be fasted and refrain from caffeine for at least 12 h, light-to-moderate exercise for at least 24 h, and moderate-to-heavy exercise for at least 48 h. Medications and

Table 2
Assessment schedule of the PREVAL-P study.

Schedule of assessments	Baseline	Weight loss component	Attainment of CWL	Mid-Exercise Component	Follow-up
Weight, anthropometrics	X		X	X	X
Body composition, resting metabolic rate	X		X		X
Blood pressure	X		X		X
Blood lipids, lipoprotein particle size, C-reactive protein, glycoprotein acetylation	X		X		X
Oral glucose tolerance, augmentation index, heart rate variability, central blood pressure, pulse wave velocity, cardiorespiratory fitness	X		X		X
activPAL (sitting behavior and total energy expenditure)	X		X	X	X
ActiGraph accelerometers (Non-exercise physical activity)	X	X	X	X	X
Energy intake (FFQ)	X		X	X	X
Quality of Life (SF-36)	X		X		X

supplements will be documented at the baseline HRV assessment and repeated at follow-up. All HRV assessments will be conducted during morning hours in a quiet, temperature-controlled room. Participants will wear a heart rate monitor (Zephyr Bioharness 3, Medtronic, Annapolis, MD) while resting in the seated position for at least 20 min and, will subsequently rest in the supine position for 20–25 min with the lights dimmed. The final 10 min of supine rest will be timestamped for HRV recording and analysis. HRV analysis will be conducted using Kubios software version 3.2.0. (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland). HRV variables will be collected for analysis including time-domain, frequency-domain, and nonlinear measurements. Time-domain components will include the mean of R-R intervals, standard deviation of R-R intervals (SDNN), which reflects overall variation within the R-R interval series, and root mean of successive R-R interval differences (RMSSD), which estimates vagal tone. Frequency-domain components included low frequency (LF) and high frequency (HF) bands in log transformed power (LFln) (HFln), normalized units (LFnu) (HFnu), and LF/HF power ratio. LF represents both sympathetic and parasympathetic activity of the cardiac autonomic nervous system, while HF indicates parasympathetic activity only. Nonlinear methods included the Poincaré plot, approximate entropy (ApEn), sample entropy (SampEn), correlation dimension (D_2), detrended fluctuation analysis (DFA), and recurrence plot (RP) analysis.

C**ardiorespiratory Fitness:** A modified Balke treadmill (Trackmaster 425, Carefusion, Newton Kansas) protocol will be used to determine cardiorespiratory fitness, and the appropriate heart rate range for aerobic exercise training. Participants will walk at an initial speed of 2.0 mph with 0% grade for the first 2 min, after which the treadmill speed will increase to 3.0 mph for the next 2 min. Treadmill grade will be increased by 2.5% every 2 min until volitional exhaustion. Respiratory gases (VO_2, CO_2) and ventilation will be measured continuously using a True Max 2400 Metabolic Measurement Cart (Parvomedics, Salt Lake City, Utah). Fitness will be quantified in relative (ml/kg/min) and absolute terms (L/min). We will also quantify fitness in terms of estimated METs due the association with CVD disease and T2D [18]. A physician will be present to supervise exercise testing at baseline assessments. The electrocardiogram during the baseline exercise test will be evaluated and cleared by a physician prior to the start of intervention. After medical clearance, subsequent exercise tests for study timepoints will be supervised by an exercise physiologist unless there is a medical concern requiring a physician.

2.2. Outcomes measure visit 2

Blood measures: A fasting blood sample will be obtained through venipuncture for analyses of fasting blood lipid (e.g. total cholesterol, high density lipoprotein, low density lipoprotein, very low-density lipoprotein), glucose, insulin and c-reactive protein concentrations. The sample will be subsequently sent to LabCorp for analysis. In addition, we will archive a serum sample for lipoprotein size and class and GlycA. This sample will be frozen at −80 °C and stored until analysis by Liposcience (Cary, NC) after the completion of data collection.

Pulse wave velocity and aortic blood pressure parameters: Pulse wave velocity (PWV) and aortic blood pressure parameters will be measured using a SphygmoCor XCEL (Atcor Medical, Itasca, IL). Participants will refrain from large meals and caffeine for at least 2 h and alcohol, and vigorous exercise for at least 12 h. Testing will occur in a quiet temperature controlled room [19]. Blood pressure parameters (e.g. brachial blood pressure, aortic blood pressure, augmentation index) will be obtained in the seated position after a 5-min rest. After this, the participant will rest in a hospital bed supine for 15 min and a blood pressure cuff will be placed on the mid-thigh. Study staff will then measure the distance from the sternal notch to the cuff, carotid to the sternal notch and the femoral to the cuff using a tape measure. After completion of the resting period, a tonometer will be held against the carotid artery during the PWV measurement. Once adequate pulse wave forms are visible, we will measure PWV across a 10-s interval. PWV will be quantified in meters/sec. Following this a second PWV measurement will take place. If the first two measurements are $\leq$0.5 m/s of each other, we will report the average of both measurements. If the difference between both measurements is $>$ 0.5 m/s then a third measurement will be performed and the median of the 3 measurements used to quantify PWV [19].

Oral glucose tolerance test: An intravenous (IV) line will be placed in an antecubital vein for blood draw purposes and will remain there throughout the testing. After a resting fasting blood sample is drawn, participants will drink a solution consisting of 75 g of glucose. Additional blood samples will be drawn 0, 30, 60, 90, and 120 min after drinking the glucose beverage. Insulin and glucose areas under the curve (AUC) will be determined following sample analysis. Insulin sensitivity will also be estimated from fasting glucose and insulin concentrations using the Matsuda index [20]. At baseline, OGTT measurements will occur prior to exercise testing to avoid confounding these measurements with acute exercise. At follow-up, the OGTT will occur 24 h following the last exercise session and precede exercise testing. Samples will be archived at −80 °C until sample analysis. Eating habits 24 h prior to the baseline OGTT will be recorded by research staff and participants will reproduce their eating habits as closely as possible for subsequent OGTT assessments.

Questionnaires: Food frequency questionnaire (FFQ) data will be assessed using the NutritionQuest (Berkley Inc.) data-on-demand system, which will facilitate immediate scoring and estimation of caloric and macronutrient intake. Quality of life will be measured by the short form health survey (SF-36) [21]. The SF-36 will be administered using a laptop at a clinical visit and all SF-36 sub-scales will be calculated (Optum, PRO Analytics, Eden Prarie, MN).

Total physical activity: An activPAL4 accelerometer (Scotland, UK) will be worn for 7 days prior to each timepoint to assess time spent sitting, standing and total energy expenditure.

3. Intervention

After all baseline measurements are obtained, all participants will begin the weight loss phase of the trial. The weight loss phase will consist of an OPTIFAST® weight loss program (Vidant Wellness Center, Greenville, NC) and supervised aerobic exercise training at ECU. Participants who achieve ≥7% weight loss during the program will proceed to the weight maintenance phase of the study. After the completion of assessment measures after the weight loss phase, participants will be randomized to levels of aerobic exercise associated with general public health guidelines (PA-REC) or the weight maintenance guidelines (WM-REC) (Fig. 1). The weight maintenance phase will consist of 18 weeks of aerobic exercise training according to group randomization.

Rationale for the selection of clinically significant weight Loss (CWL) of ≥7%: The range for clinically significant weight loss is generally considered to be 5–10% [10]. We decided not to select the minimum levels of CWL (5%) as this would likely reduce the magnitude of change in cardiometabolic risk factors that are hypothesized to be responsive to weight loss (e.g. blood glucose, insulin, cholesterol concentrations). The goal of 7% has been used as the weight loss criteria in major multi-site trials (e.g. LookAhead [22], DPP [23]) and other weight loss studies [24–29].

OPTIFAST® weight loss program (initial weight loss): OPTIFAST® is a comprehensive medically supervised weight loss program that combines lifestyle education and medical monitoring with portion-controlled, nutritionally balanced meal replacement products (e.g. shakes, bars and soups). The major goal of the OPTIFAST® program is to provide clinically significant weight loss in PREVAIL participants equal to or exceeding 7% of weight loss. While involved in the OPTIFAST® program, participants will also perform supervised exercise training at ECU.

Participants will receive a nutrition assessment with by a registered licensed dietitian/nutritionist. The active weight loss phase of the program consists of 10 weeks with the first 2 weeks consuming full meal replacement. Each OPTIFAST® product provides 160–170 kilocalories, 14 g protein (whey, casein, and/or soy), 3 g total fat, 0 *trans*-fat, ~20 g carbohydrate, 220 mg sodium, 470 mg potassium, <1 g lactose, and 10–30% of the RDI for vitamins and minerals. Participant nutrient goals are based on BMI. Participants will consume approximately 5 OPTIFAST® products per (800–820 kilocalories per day, protein 70 g). At week 8, participants have the option of eliminating 2 products per day and introducing 350 kilocalories of food from a Healthy Food Exchange list. During this time, caloric intake usually reaches 1300–1500 kilocalories per day. By week 8, participants will be transitioned, at an individual pace, to all self-prepared food except for 1 or 2 products daily if desired.

VIDANT Wellness Clinic has over 10 years of experience delivering this intervention and the dietitians implementing the program are certified by Nestle. The cost of the weight loss program and the OPTIFAST® products will be provided by the study's resources to help recruit a generalizable sample and include participants from socioeconomic groups who would otherwise could not afford the program.

The classes that will be utilized in the PREVAIL-P study are shown in Table 3. The overall goal of the classes is to assist participants in meeting the weight loss goal and increasing compliance to the dietary aspects of the weight loss program (e.g. eating cues, motivation to change, mindful eating). Classes will be delivered in a rolling fashion (e.g. participants can enter the classes at any week and go through the full 10-week progression), which will allow the assessment schedule to be feasible when participants complete the weight loss component. The expected class size is typically about 20–25 participants (and will only contain research participants) and will occur once per week. At each class, participants will weigh in, fill out a questionnaire from Nestle (regarding the number of products consumed, fluid intake, and any physical changes) and receive a didactic topic relevant to weight loss. About 15 min before the end of the class is left open for participants to ask individual questions.

Table 3
Weight loss class schedule of participants during the weight loss phase.

Identifying Eating Cues, Triggers, and Eating Style
Where are the calories? Reading Food Labels
Strategies for Portion Control
Motivation to Change
Relaxation Techniques
Effects of Stress on Body Weight
Exercise Update
Mindful Eating and Emotional Eating
Eating Out, Special Occasions
Cooking Quick and Light

My Fitness Pal: Participants will enter data through a mobile App called MyFitnessPal (MFP). The App allows subjects to track the nutritional values of their diets, by either scanning in the barcode or searching an extensive database for their chosen food and/or drink. The App incorporates elements of social cognitive theory, including self-monitoring, goal setting, and feedback. Total daily intake can be viewed in the form of caloric, nutrient or macronutrient values as graphs and pie charts, with warnings when preset calorie or nutrient limits are being approached. MFP data will be used to assist participants in tracking dietary intake.

Exercise training during weight loss component: Participants will come to ECU 2–3 times per week for supervised aerobic training on a treadmill during the weight loss component. Exercise facilitates a greater magnitude of initial weight loss when combined with caloric restriction [13] and should therefore increase the likelihood of achieving clinically significant weight loss. Additionally, the exercise will allow all participants to have adequate fitness to exercise at the required levels in the weight maintenance phase. The initial exercise level will be 300 MET minutes per week and increased by 50 MET minutes per week until the participant reaches the full amount of exercise during the initial weight loss component of 700 MET minutes (week 9–10) (Table 4). Similar exercise volumes have been used during the initial weight loss phase [9,16]. See "Exercise training procedures" for further details on exercise sessions.

Randomization after attainment of CWL: Participants who achieve 7% weight loss at the end of the weight loss phase will be randomized to exercise levels consistent with physical activity recommendations (PA-REC) or weight maintenance recommendations (WM-REC) for an additional 18 weeks. We will utilize adaptive randomization to balance the study groups by baseline BMI and the magnitude of weight loss in the weight maintenance phase [30].

Rationale for the selected exercise amounts during exercise component: The rationale for the PA-REC group is this is the minimum amount of

Table 4
Exercise levels in the weight loss and maintenance phases of PREVAIL-P.

Weight Loss Phase (Weeks 1–10)			**Exercise amount**
		Week 1	300 MET min.
		Week 2	350 MET min.
		Week 3	400 MET min
		Week 4	450 MET min.
		Week 5	500 MET min.
		Week 6	550 MET min.
		Week 7	600 MET min.
		Week 8	650 MET min.
		Week 9–10	700 MET min.
Randomization to study groups		PA-REC	WM-REC
Weight Maintenance Phase (Weeks 11–28)	**Week 11**	550 MET min.	750 MET min.
	Week 12	550 MET min.	800 MET min.
	Week 13	550 MET min.	850 MET min.
	Week 14	550 MET min.	900 MET min.
	Week 15	550 MET min.	950 MET min.
	Week 16–28	550 MET min.	970 MET min.

recommended exercise (150 min of moderate physical activity per week) based on current guidelines to improve cardiometabolic risk factors [31,32]. Based on previous data, this should support improvements in cardiometabolic risk factors, but insufficent for weight maintenance [10]. For the WM-REC group, we decided to target an exercise volume (MET minutes) consistent with 250 min per week, which is consistent with WM guidelines (200–300 min per week) [10]. We believe dosage is feasible in a supervised format of 4–5 exercise sessions per week. To inform this decision, we reviewed data from two aerobic training studies performed in our laboratory. Based on expected speed/grade of treadmill exercise at week 12 (similar to week 12 of the present proposal), we estimated that the average participant would exercise at a speed of 2.6 mph and 3.0% grade. Based on the proposed exercise level of the WM-REC group, this participant would exercise about 60 min, 4 times per week or 50 min, 5 times per week. We estimated that our least fit participants would exercise at 2.4 mph and 2.0%, which would amount to 56 min, 5 times per week.

Since weight maintenance recommendations (200–300 min/wk at moderate intensity) are based solely [10] on moderate intensity physical activity, we had to translate this for a program composed of aerobic exercise training which can be performed at moderate and vigorous intensities. Therefore, we decided to prescribe the exercise levels using MET minutes. The derivation of the exercise requirements in each study group are summarized in Table 5. Based on our laboratory data in obese adults, we estimated that the average VO_2 max of participants in PREVAIL-P would be 23.7 ml/kg/min. We further estimated that 50% of VO_2 max (deemed moderate intensity) [33,34] would correspond to a VO_2 during exercise of 11.5 ml/kg/min or 3.3 MET minutes. Based on this, it would require 494 MET minutes per week at moderate exercise intensity to correspond with the current minimum physical activity recommendations of 150 min per week of moderate intensity exercise. Similarly, we estimated that moderate exercise at 825 MET minutes per week would correspond to approximately 250 min/week of moderate intensity exercise for the WM-REC group. Next, we needed to factor in the expected adherence rates for each group. Based on our laboratory's data in obese adults, we expect at least 92% adherence to MET minute goals in the PA-REC group. Due to the additional exercise requirements of the WM-REC group, we expect at least 85% adherence to MET minute goals. Therefore, we set the exercise level of the PA-REC group at 550 MET minutes per week and the WM-REC group at 970 MET minutes per week (Table 5).

Exercise training procedures: The weekly MET minute requirements will be divided into 3–5 sessions per week on a treadmill depending on group requirements/participant preferences. Exercise sessions will be directly supervised by research staff. After the weight loss component, all participants should be accustomed to exercise at 550 MET minutes (since there was supervised exercise training during the weight loss component). Therefore, participants in the PA-REC group will exercise immediately at the required levels. The WM-REC group will start exercise at 700 MET minutes per week and increase 50 MET minutes per week until they reach the required exercise levels of 970 MET minutes per week (Table 4). Every week, staff will weigh participants using a calibrated scale. Following a 5-min warm-up, participants will exercise at the heart rate range associated with 50%–75% of VO_2 max (determined from the baseline exercise test). Continuous heart rate (second by second) will be recorded during exercise using Zephyr BioModule heart rate monitors (Medtronic Annapolis, MD). After each exercise session, average heart rate for the entire session will be exported into the OmniSense 5.0 (Medtronics, Annapolis MD) software program, where study staff will calculate the average heart rate during each exercise session (elimination of warm-up and cool-down heart rate during the session and averaging exercise session time). Training data (e.g. mean heart rate, total energy expenditure, rating of perceived exertion, MET minutes exercised and total exercise time) will be entered into the study database after each session.

Exercise adherence will be quantified by dividing the total amount of MET minutes exercised by the amount required. Exercise compliance will be quantified the as the sessions of exercise attended divided by the required amount of sessions. Aerobic exercise intensity (%VO_2) for the weight loss phase will be estimated using the heart rate/VO_2 relationship [35], established from the baseline exercise test. After completion of the weight loss phase, this relationship will be updated (using exercise testing data after the weight loss phase) for the maintenance phase.

To enhance the accuracy of the calculation of exercise-related energy expenditure, we will perform periodic submaximal exercise tests to directly measure the energy expenditure rate during steady state exercise at the same intensity as the training sessions. A correction factor will be obtained (actual energy expenditure/predicted energy expenditure) to account for individual variability in prediction equations for energy expenditure. Indirect calorimetry has been used in previous NIH trials evaluating the effects of exercise training on weight to improve the accuracy of energy expenditure from aerobic exercise training [36–38].

Exercise training data quality: We will actively monitor exercise adherence/compliance and other indicators of intervention fidelity (e.g. target heart rate compliance, wear rate accelerometers, participant morale, progression rate of speed/grade) on a weekly basis. Our database will be designed to compute intervention fidelity measures in real time using a SAS script that queries the REDCap© database and produces customized intervention fidelity reports. Proactive monitoring of intervention fidelity measures has helped us to obtain excellent training adherence in the past (>90%) by allowing our research team to quickly respond to participants demonstrating major risk factors for low adherence or protocol non-compliance.

Nutrition management during the weight maintenance phase: By the end of the weight loss component, participants will be transitioned to self-prepared foods. Participants will be provided dietary information to support weight maintenance based on the resting metabolic rate (assessed by indirect calorimetry) obtained after the weight loss component. In consideration of the activity level of each group, the weight maintenance recommendations will be calculated by multiplying resting energy expenditure by 1.2 (for the lower end of the recommended kilocalorie range) and 1.4 (for the upper end of the recommended kilocalorie range). Based on this calculated range of total kilocalorie intake, we will also provide a range of recommended daily caloric and gram intake of fat, for diets consisting of 25% or 30% fat. Additionally, participants will be encouraged to follow the 2010–2015 Dietary Guidelines for Americans [39], which includes consuming less than 10% of calories per day from added sugars, 10% of calories per day from saturated fats, and less than 2,300 mg per day of sodium.

Behavioral management of participants in exercise groups: Several strategies will be utilized to promote high exercise adherence. Extensive pre-screening will be performed inclusive of run-in visits (evaluation of available time to exercise, exercise calendars, assessment

Table 5
Derivation of required exercise levels in the PA-REC and WM-REC groups during the weight maintenance phase. Required levels for the minimum physical activity and the weight maintenance guidelines were converted to MET minutes (as aerobic exercise can take place at moderate to vigorous intensity). The expected adherence level for each group was also used to establish the required amount of exercise in PA-REC and the WM-REC groups (See methods section for a detailed discussion on the derivation of exercise levels).

Study Group	Physical Activity Guideline	Equivalent MET mins.	Expected adherence	Exercise levels	Expected time commitment
PA-REC	150 min/wk mod. intensity	494	92%	550 MET mins	36 min, 3 sess. per wk.
WM-REC	200–300 min/wk mod. intensity	825	85%	970 MET mins	40 min, 5 sess. per wk.

of time commitments) to screen-out participants with high drop-out risk. Participants will have two face-to-face and two telephone sessions with a doctoral student in clinical health psychology. The face-to-face sessions will occur at the beginning of the weight loss phase and the weight maintenance phase. These sessions will employ motivational enhancement techniques to enhance motivation for weight loss and weight loss maintenance, respectively. The two telephone sessions will occur at the approximate midpoint of the weight loss and weight maintenance phases and will focus on brief problems-solving of issues related to eating and exercise nonadherence. Other strategies for reducing attrition/poor adherence will be modeled after the retention recommendations provided by the NIH [40].

We will monitor adherence weekly in study meetings. Participants with adherence levels <75% or that display major warning signs for low adherence (e.g. frequent rescheduling, missed sessions, low morale) will meet with the research coordinator to problem-solve the causes of poor adherence and to create a plan to improve adherence. If adherence levels remain <75% or issues related to the low adherence remain unresolved, the participant will be referred for motivational enhancement therapy (i.e. motivational interviewing) to increase intrinsic motivation for exercise which will be performed at the same time of the training sessions to not increase participant burden. Motivational enhancement therapy [41] will be provided by a doctoral student in clinical health psychology trained in the administration of motivational interviewing. Numerous reviews and meta-analyses support that motivational interviewing is effective at promoting and maintaining health behavior change including exercise [42]. Should adherence remain low or deteriorate further, booster motivational interviewing sessions will be employed. If the previous methods are not effective or drop-out risk is determined to be especially high, the participant will be referred to the lead behaviorist of the trial.

Non-exercise physical activity: Non-exercise physical activity will be tracked using a GT9X Link accelerometer (ActiGraph, Pensacola, FL). Devices will be blinded using the ActiGraph software, so participants will not be able to see their data. During exercise training sessions, accelerometers will be removed to avoid mixing exercise and non-exercise physical activity data. Recharging of the device (14-day battery life) will be performed during the exercise session by study staff while participants are exercising. Study staff will use the database program for ActiGraph (Centrepoint, Pensacola, FL) to monitor and download non-exercise physical activity data (e.g. steps, moderate to vigorous physical activity, sleep, wear/non-wear rates). The Centrepoint program will provide updates in our database by using an app in the participants' mobile device or can be uploaded manually at our facility.

Data management: Study data will be stored in a REDCap© database [43]. The database will be designed to develop recruitment reports (e.g. total contacts, reasons for exclusion during screening, screen to randomization ratio for recruiting projections), weight loss program data (% weight loss, class attendance), exercise training data (e.g. exercise adherence, heart rate compliance) and outcome data. Recruiting, weight loss program and exercise training data reports will be reviewed weekly to monitor the intervention fidelity.

4. Statistical design

Initial analysis will check for baseline differences between the groups to help determine possible covariates that need to be taken into account. Intent to treat analysis will be conducted first, followed by those that had high adherence to the exercise group (>75%). The analysis for the primary aim (weight change) will be a mixed effect linear model with an autoregressive covariance matrix. In brief summary, this model will use the baseline, weight loss midpoint, and the follow-up weights all while accounting for the baseline covariates as well as the weekly weight changes. Results will use least square means with *t*-test determining differences both between and within groups. Heterogeneity of variance will be tested to ensure these subgroups, like sex and age groups, are correctly modeled. The second aim will use a mixed effect logistic model to model the probability of achieving weight maintenance, with results presented as adjusted odds ratios. The third aim will be analyzed similarly as the first aim, but the outcomes will be the CVD risk factors.

5. Conclusion

The PREVAIL-P study will provide valuable data to inform the design of subsequent studies on the impact of exercise level on weight loss and cardiometabolic risk factors after clinically significant weight loss. This pilot study will also demonstrate the ability of the study team to implement the weight loss intervention and demonstrate adherence to exercise training after clinically significant weight loss. The PREVAIL-P study will address limitations in this research area identified by a recent position stand [1] and an NIH sponsored working group [104] on weight maintenance by randomizing individuals to groups following a clinically significant weight loss, prospectively measuring exercise training amount (supervised exercise), non-exercise physical activity (objective physical activity monitors) throughout the entire intervention. The results of the PREVAIL-P study will have high clinical implications given the high rates of regain following weight loss treatment and further inform future physical activity guidelines on weight loss maintenance.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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References

[1] R.R. Wing, et al., Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes, Diabetes Care 34 (7) (2011) 1481–1486.
[2] E.P. Weiss, et al., Effects of matched weight loss from calorie restriction, exercise, or both on cardiovascular disease risk factors: a randomized intervention trial, Am. J. Clin. Nutr. 104 (3) (2016) 576–586.
[3] G. Fisher, G.R. Hunter, B.A. Gower, Aerobic exercise training conserves insulin sensitivity for 1 yr following weight loss in overweight women, J. Appl. Physiol. 112 (4) (2012) 688–693.
[4] R.R. Wing, S. Phelan, Long-term weight loss maintenance, Am. J. Clin. Nutr. 82 (1) (2005) 222S–225S.
[5] T. Soleymani, S. Daniel, W.T. Garvey, Weight maintenance: challenges, tools and strategies for primary care physicians, Obes. Rev. 17 (1) (2016) 81–93.
[6] C.M. Kroeger, K.K. Hoddy, K.A. Varady, Impact of weight regain on metabolic disease risk: a review of human trials, Journal of Obesity 2014 (2014) 8.
[7] K.M. Beavers, et al., Is lost lean mass from intentional weight loss recovered during weight regain in postmenopausal women?1–3, Am. J. Clin. Nutr. 94 (3) (2011) 767–774.
[8] J.M. Jakicic, et al., Effect of exercise on 24-month weight loss maintenance in overweight women, Arch. Intern. Med. 168 (14) (2008) 1550–1559. ; discussion 1559-60.

[9] J.M. Jakicic, et al., The effect of physical activity on 18-month weight change in overweight adults, Obesity 19 (1) (2011) 100–109.
[10] J.E. Donnelly, et al., Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults, Med. Sci. Sports Exerc. 41 (2) (2009) 459–471.
[11] R.E. Andersen, et al., Effects of lifestyle activity vs structured aerobic exercise in obese women, J. Am. Med. Assoc.: JAMA, J. Am. Med. Assoc. 281 (4) (1999) 335–340.
[12] T.R. Thomas, et al., Exercise and the metabolic syndrome with weight regain, J. Appl. Physiol. 109 (1) (2010) 3–10.
[13] M.D. Jensen, et al., AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and, The Obesity Society, 2013, 2013.
[14] C.I. Voils, et al., Maintenance of weight loss after initiation of nutrition training: a randomized trial, Ann. Intern. Med. 166 (7) (2017) 463–471.
[15] L.P. Svetkey, et al., Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial, J. Am. Med. Assoc. 299 (10) (2008) 1139–1148.
[16] J.M. Jakicic, et al., Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial, J. Am. Med. Assoc. 290 (10) (2003) 1323–1330.
[17] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Circulation 93 (5) (1996) 1043–1065.
[18] D.L. Swift, et al., Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention, Circ. J. 77 (2) (2013) 281–292.
[19] R.R. Townsend, et al., Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement from the American Heart Association. Hypertension, 2015.
[20] M. Matsuda, R.A. DeFronzo, Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp, Diabetes Care 22 (9) (1999) 1462–1470.
[21] J.E. Ware Jr., C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection, Med. Care 30 (6) (1992) 473–483.
[22] A.R.G. Look, et al., The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it, Obesity 14 (5) (2006) 737–752.
[23] G. The Diabetes Prevention Program Research, The diabetes prevention program (DPP): description of lifestyle intervention, Diabetes Care 25 (12) (2002) 2165–2171.
[24] R.H. Coker, et al., Whey protein and essential amino acids promote the reduction of adipose tissue and increased muscle protein synthesis during caloric restriction-induced weight loss in elderly, obese individuals, Nutr. J. 11 (1) (2012) 105.
[25] D.S. West, et al., Lay health educators translate a weight-loss intervention in senior centers: a randomized controlled trial, Am. J. Prev. Med. 41 (4) (2011) 385–391.
[26] S.L. Pagoto, et al., Translating the diabetes prevention program into a hospital-based weight loss program, Health Psychol. 27 (1) (2008) S91–S98. Suppl.
[27] C.A. Pellegrini, et al., A smartphone-supported weight loss program: design of the ENGAGED randomized controlled trial, BMC Publ. Health 12 (1) (2012) 1041.
[28] K.L. Campbell, et al., Feasibility of a lifestyle intervention on body weight and serum biomarkers in breast cancer survivors with overweight and obesity, J. Acad. Nutr. Diet. 112 (4) (2012) 559–567.
[29] C.A. Slentz, et al., Effects of exercise training alone vs a combined exercise and nutritional lifestyle intervention on glucose homeostasis in prediabetic individuals: a randomised controlled trial, Diabetologia 59 (10) (2016) 2088–2098.
[30] J.M. Lachin, J.P. Matts, L.J. Wei, Randomization in clinical trials: conclusions and recommendations, Contr. Clin. Trials 9 (4) (1988) 365–374.
[31] W.L. Haskell, et al., Physical activity and public health: updated recommendation for adults from the American college of sports medicine and the American heart association, Med. Sci. Sports Exerc. 39 (8) (2007) 1423–1434.
[32] U.S. Department of Health and Human Services, Physical Activity Guidelines for Americans, 2008, pp. 1–3, 2008.
[33] G.M. Morss, et al., Dose-response to exercise in women aged 45-75 yr (DREW): design and rationale, Med. Sci. Sports Exerc. 36 (2) (2004) 336–344.
[34] W.E. Kraus, et al., Studies of a targeted risk reduction intervention through defined exercise (STRRIDE), Med. Sci. Sports Exerc. 33 (10) (2001) 1774–1784.
[35] J.S. Skinner, et al., Heart rate versus %VO2max: age, sex, race, initial fitness, and training response–HERITAGE, Med. Sci. Sports Exerc. 35 (11) (2003) 1908–1913.
[36] C.A. Myers, et al., Examination of mechanisms (E-MECHANIC) of exercise-induced weight compensation: study protocol for a randomized controlled trial, Trials 15 (2014) 212.
[37] J.E. Donnelly, et al., Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the midwest exercise trial, Arch. Intern. Med. 163 (11) (2003) 1343–1350.
[38] J.E. Donnelly, et al., Aerobic exercise alone results in clinically significant weight loss for men and women: midwest exercise trial 2, Obesity 21 (3) (2013) E219–E228.
[39] U.S.D.o. Agriculture, Dietary Guidelines for Americans, eighth ed., 2015.
[40] M. Coday, et al., Strategies for retaining study participants in behavioral intervention trials: retention experiences of the NIH Behavior Change Consortium, Ann. Behav. Med. 29 (Suppl) (2005) 55–65.
[41] W.R. Miller, S. Rollnick, Motivational Interviewing: Helping People Change, Guilford press, 2012.
[42] R.K. Martins, D.W. McNeil, Review of Motivational Interviewing in promoting health behaviors, Clin. Psychol. Rev. 29 (4) (2009) 283–293.
[43] P.A. Harris, et al., Research Electronic Data Capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inf. 42 (2) (2009) 377–381.
[44] National Institutes of Health, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2004.