The Ohio State University Comprehensive Cancer Center
Addressing Obesity to Reduce Cancer Risk and Health Disparities in Rural Ohio:
Home-based Exercise in Rural Ohio (HERO) Study

Investigators

Brian C. Focht, PhD, FACSM, CSCS
Professor, Kinesiology
Vice Chair, Department of Human Sciences
The Ohio State University

Phone: 614-292-2165
Email: focht.10@osu.edu

Electra Paskett, Ph.D.
Professor and Chair, Division of Cancer Prevention and Control, Department of Medicine
Associate Director for Population Sciences
Comprehensive Cancer Center
The Ohio State University

Phone: 614-293-3917
Fax: 614-293-5611
Email: electra.paskett@osumc.edu

Project Staff

Xiaochen Zhang, MB, MPH, PhD (c)
Division of Population Sciences
Comprehensive Cancer Center
Phone: 614-366-4751
Fax: 614-293-5611
Email: Xiaochen.Zhang2@osumc.edu

Victoria R. DeScenza
Department of Human Sciences
The Ohio State University
Email: descenza.1@osu.edu

Jessica Bowman, MS
Department of Human Sciences
The Ohio State University
Email: bowman.1396@osu.edu

Zachary L. Chaplow, MS, CSCS, EP-C
Department of Human Sciences
The Ohio State University
Email: chaplow.1@osu.edu

Kathryn Dispennette, MS
Department of Human Sciences
The Ohio State University
Email: dispennette.2@osu.edu

Consultant

Steve Heymsfield, MD
Department of Metabolism & Body Composition
Pennington Biomedical
Email: Steven.Heymsfield@pbrc.edu

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A PROJECT OVERVIEW

A.1 Title

Addressing Obesity to Reduce Cancer Risk and Health Disparities in Rural Ohio: **H**ome-based **E**xercise in **R**ural **O**hio (HERO) Study

A.2 Overview

Home-based Exercise in Rural Ohio (HERO) is a single-blind, 2-arm randomized controlled pilot weight loss trial designed to establish the feasibility of a 15-week telephone-based weight loss intervention with tailored strategies for rural populations with a novel point-of-care approach to assess body composition, lipid profiles, and inflammatory markers. Up to 50 overweight or obese rural Ohio residents will be randomly assigned to a 15-week telephone-based weight loss (n=30) or an active control group (up to 20). We will utilize a novel, portable 3D optical imaging technology to overcome the lack of access to body composition measures through DXA. Together with lipid profiles measured by Cholestech LDX and inflammation markers measured by fasting blood draw, this study will establish a practical point-of-care approach to assess disease risk factors that could be implemented in rural community settings. Upon completion of this study, we will determine the feasibility and preliminary efficacy of a 15-week telephone-based exercise and diet intervention for weight loss and improvements in body composition and inflammation biomarkers among overweight and obese rural residents. Studying the dose-response relationship will allow us to understand the therapeutic effect of weight loss interventions and cancer risk, which has the potential to identify optimal lifestyle modifications to reduce obesity-related cancer disparities. Findings from our study would provide evidence of the efficacy and therapeutic effect of weight loss interventions in cancer prevention in rural populations.

A.3 Specific Aims

Obesity is the leading preventable cause of cancer. Obesity significantly elevates risk for cancers of the breast, colon and rectum, endometrium, liver, pancreas, and nine other sites. Residents of rural areas are considered medically underserved, with less access to quality healthcare and fewer health resources. Rural populations experience higher rates of obesity, obesity-related comorbidities and mortality, and higher cancer incidence and mortality compared to residents of urban areas. Obesity and poor health behaviors are major contributors to health disparities in rural populations. Lifestyle interventions that combine physical activity and a healthy diet for weight loss have favorable impacts on weight, body composition, and inflammatory markers. These outcomes are consistent with hypotheses from observational studies that physical activity and weight loss potentially attenuate the negative effects of obesity and reduce cancer risk. Although evidence-based weight loss programs have been implemented and showed health benefits, these programs focused on health-promoting resources available in urban areas. Generalizing such programs to rural populations is not feasible due to the limited access to recreation facilities, availability of healthy food, and the burden of travel. Additionally, rural residents differ from urban counterparts in terms of barriers, self-efficacy, and social support for health behaviors due to their unique personal (e.g., family roles, living priorities) and environmental (e.g., limited resources for self-health) factors. Therefore, the development of tailored lifestyle interventions to meet the specific needs of rural populations can facilitate the improvement of health behaviors and ultimately reduce cancer-related health disparities.

To achieve our long term goal of integrating lifestyle modifications to reduce cancer risk and related disparities for rural populations, understanding the underlying biological mechanism of weight loss, body composition, and inflammation is critical. However, empirical evidence documenting the efficacy of lifestyle weight loss interventions in rural populations is limited. Among completed or recently awarded trials (as of January 2020), none measured body composition and inflammation markers. Estimating the effect of lifestyle interventions on weight loss, body composition, and disease risk factors (inflammatory markers, lipid profiles) in rural populations is essential for the design and implementation of evidence-based approaches on a larger scale.

This study will recruit up to 50 obese rural Ohio residents and randomly assigned to a 15-week telephone-based weight loss (n=30) or an active control group (up to 20). The study objective is to determine the feasibility and preliminary efficacy of a 15-week telephone-based weight loss intervention on weight, body composition, and inflammatory markers, with tailored strategies and group messages to address barriers, self-efficacy, and social support for rural Ohio populations. We will utilize a novel and applicable point-of-care approach to assess body

composition, lipid profiles, and cancer risk factors in rural community settings. The Specific Aims for this study are:

1. To determine the feasibility and acceptability of a 15-week telephone-based weight loss intervention among obese rural residents.
   We hypothesize that 80% of obese rural residents who participate in the study will complete the assigned intervention (*feasibility*), and 80% of the participants in the intervention group will engage in at least 75% of the weekly telephone counseling session (*acceptability*). During the 15-week weight loss intervention, we anticipate the minimal occurrence of intervention-related adverse events.

2. To estimate the preliminary efficacy of the lifestyle modifications on weight loss, body composition (fat mass, fat percentage), inflammatory biomarkers (IL-6, TNF-α, and CRP), and other disease risk factors (lipid profiles).
   We hypothesize that the lifestyle intervention will result in substantial improvements in weight loss, fat mass, fat percentage, IL-6, TNF-α, CRP, and lipid profiles (with moderate effect size), compared to the active control group.

B BACKGROUND AND RATIONALE

B.1 Literature Review/Current State of Knowledge

Rural residents experience obesity-related disparities, including high rates of obesity, obesity-related comorbidities, cancer incidence, and premature mortality. Although evidence-based weight loss interventions have demonstrated health benefits in clinical settings, utilizing the same strategies may not be feasible and effective for rural populations due to their unique characteristics. This study aims to determine the feasibility and preliminary efficacy of a 15-week telephone-based lifestyle intervention combining exercise and diet for weight loss and improvement in body composition and inflammation biomarkers in overweight and obese rural populations.

This project is well-aligned with the mission of the American Institute for Cancer Research (funding agency) and its special Cancer Prevention Research Priority as it will address how lifestyle modifications (physical activity and dietary restriction) can reduce cancer risk (e.g., inflammation biomarkers) through improvements in weight and body composition in rural populations. The following sections summarize the obesity problem in rural populations, past studies examining obesity, weight loss, and cancer risks, and the novelty of utilizing a point-of-care approach to assess body composition and cancer risk factors in rural populations.

B.1.a Magnitude of the problem

Health disparities in rural populations are significant. About 97% of the U.S land is located in rural counties, and 60 million Americans live in these areas (1). Residents in rural areas are considered underserved populations with lower access and fewer resources to health care, and experience higher rates of obesity, obesity-related comorbidities and mortality, and higher cancer incidence and mortality, compared to residents in urban areas (2-5). Although many of the social determinants of health (e.g., low income/education, lack of health insurance) are linked to health disparities, obesity and poor health behaviors are the major modifiable contributors to health disparities in rural populations (6-10). Developing effective strategies to provide weight loss programs to promote healthy behaviors and reduce obesity-related cancer risk in rural populations is an important public health priority.

B.1.b Obesity and cancer

Obesity is the leading preventable cause of cancer (11). Each year more than 1,600,000 people are diagnosed with cancer and more than 600,000 people will die from cancer in the U.S (12). Approximately 40% of cancer cases and 14-20% of cancer-specific deaths are attributed to overweight and obesity (13). Obesity leads to abnormal and excessive adiposity accumulation, which negatively impacts metabolic and inflammatory processes that promote cell growth, carcinogenesis, and tumor promotion (14-18). Additionally, the dysfunctional adipose tissue promotes tumor progression and metastasis (17, 19). Due to these unfavorable physiological modifications, obesity elevates the risk of 13 cancers (17, 20-23).

Obesity-related inflammation is linked to elevated cancer risk, independent of obesity itself (24). The accumulation of adipose tissue due to obesity produces pro-inflammatory cytokines such as interleukin 6 (***IL-6***), tumor necrosis factor-alpha (***TNF-α***), and C-reactive protein (***CRP***), which subsequently affect multiple systemic processes and promotes various aspects of tumor growth, development, and metastasis (25). ***IL-6***, a cytokine that produced up to 35% by adipose tissue, is involved in the development and growth of a variety of cancers through the STAT3 pathway by promoting cancer cell proliferation, survival, migration, and angiogenesis (26-28). Elevated IL-6 is observed in several cancers (e.g., breast, colon, gastrointestinal tract, lung, ovary) and is correlated with cancer prognosis (29-35). ***TNF-α*** controls inflammatory cell proliferation and mediates many aspects of the inflammatory process, such as regulating cytokines, chemokines, adhesions, and pro-angiogenic activities (36, 37). Similar to IL-6, TNF-α stimulates proliferation, survival, migration, and angiogenesis in most cancer cells, leading to tumor promotion (38). ***CRP,*** an acute-phase protein produced in the liver and controlled by IL-6 and TNF-α, is a stable downstream marker of systemic inflammation (39-41). Circulating CRP is positively associated with risks of cancers in the breast, colon, liver, lung, bladder, kidney, endometrium, and ovary (42-47). The dysregulation of these cytokines leads to inflammation in both local (tissue) and global (circulating in serum) levels, which promotes tumor growth (48).

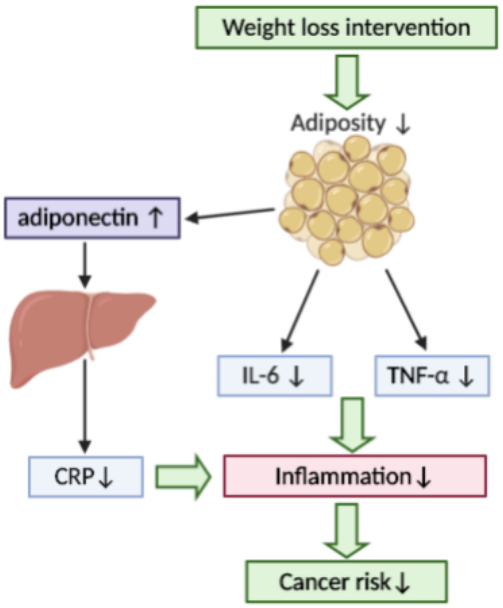

Figure 1. Mechanistic pathway describing how weight loss intervention reduce inflammation & thus reduce cancer risk. Adapted from Bianchi et al. 2018 *Clin Nutr ESPEN*

B.1.c Weight loss and cancer risk

Weight loss may reverse obesity-related metabolic imbalances and chronic inflammation (49-54). Obesity-related cancer risk could be reduced in response to weight loss as a result of improved inflammatory profile (55) (**Figure 1).** Accumulating evidence indicates that a period of weight loss improves obesity-related inflammation markers, such as IL-6, TNF-α, and CRP (56-62). While increasing physical activity level alone could lead to a substantial decrease in TNF-α, lifestyle interventions that combine physical activity and dietary modification can produce a 24-31% decrease in TNF-α, 34-44% decrease in CRP, and 33-62% in IL-6 (58-62). Lifestyle weight loss interventions provide additional metabolic benefits on insulin, lipid profiles, and improvements in body composition (63-67). These outcomes are consistent with the hypotheses that weight loss, physical activity, and healthy diet may potentially attenuate the negative effects of obesity and reduce cancer risk and premature mortality (68-70).

B.1.d Weight loss in rural populations

Evidence-based lifestyle weight loss interventions have been implemented and demonstrated favorable results in clinical settings targeting populations with various diseases (e.g., cancer, type II diabetes, hypertension) (71-82). These programs focused on and utilized resources in urban areas. To utilize the same intervention strategies from these programs may not be feasible and effective for rural populations to lose weight due to their unique personal (e.g., family roles, living priorities) and environmental (e.g., limited resources) factors (83-85). Barriers to healthy diet and the lack of recreation facilities explain variations in health behaviors in rural populations. These populations also have lower self-efficacy in healthy diet and exercise (i.e., belief of the ability to eat healthy/exercise when there are barriers), and minimal social support from family and friends to promote healthy lifestyle (83-85). Individuals with lower self-efficacy and social support are less likely to overcome barriers to achieve improvement in health behaviors (86). Self-efficacy and social support are critical in successful weight loss efforts by supporting the expectation, setting goals, establishing healthy dietary habits, increasing daily physical activity, and persistence in overcoming barriers (87, 88). However, tailored strategies to improve self-efficacy and social support for rural populations are understudied. Moreover, although remotely accessible interventions are suggested to achieve more weight loss with better cost-effectiveness than face-to-face interventions in rural areas (89, 90), web-based interventions have not provided clinically meaningful weight loss (91). Therefore, the proposed study, HERO, will include a telephone-based weight loss intervention, specifically focused on improving self-efficacy and increasing social support to help rural populations overcome barriers,

improve healthy diet and physical activity, and maintain a healthy weight, with the goal of reducing obesity-related cancer risk and health disparities.

B.1.e A Point-of-care Approach to Assess Body Composition and Cancer Risk in Rural Populations

The significance of the HERO study is enhanced by the potential to develop a more applicable point-of-care approach to assess body composition, lipid profiles, and cancer risk factors in rural populations, in addition to translating an evidence-based lifestyle program with the integration of tailored strategies. Body mass index (BMI) is limited as a measure of adiposity, as it does not truly reflect body fat and fat distribution (92). Measures of body fat are more relevant to assessing cancer risk, as adiposity deposition is associated with inflammation and carcinogenesis (93, 94). Dual-energy X-ray absorptiometry (DXA) is a standard measure of body composition that provides estimates of fat, bone, and bone-free lean mass (95). DXA-derived fat mass is positively associated with risk of breast cancer, independent of BMI and other risk factors (96-99). Rural populations may differ from the general population in the physiological response to lifestyle interventions due to variations in perceived stress, depressive symptoms, and other life stressors. However, among the handful of lifestyle weight loss interventions in rural populations, completed or recently awarded trials, none measured body composition (91, 100). This might be due to the access burden of standard measurement of body composition (e.g., DXA) in rural community settings. In order to provide body composition measures for rural populations, the HERO study will use a novel, portable 3-Dimension (3D) Body Scanner, Styku S100 (Styku LLC, Los Angeles, CA), to assess body measurements, including fat mass and fat percentage, in rural community-settings. Together with lipid profile measured by finger stick and inflammatory markers measured by fasting blood draw, the proposed study will provide preliminary data from a lifestyle weight loss intervention on weight, body composition, and inflammatory markers in rural populations. We will estimate the preliminary efficacy of lifestyle modification on weight loss, body composition, and inflammatory markers among overweight/obese rural residents. Findings from the HERO study will serve as preliminary data for a large-scale randomized controlled trial to quantify the therapeutic effect of weight loss interventions and cancer risk in rural populations, with the goal to identify optimal lifestyle modifications to reduce obesity-related cancer disparities.

B.2 Preliminary Studies

Previous weight loss interventions conducted by the P.I., Dr. Focht, have focused on disease prevention and health promotion in various populations. The current and previous NIH funded randomized controlled weight loss trials (Comprehensive Lifestyle Intervention Program for Knee Osteoarthritis Patients, R01AG050725; Feasibility of An Exercise and Dietary Intervention in Men on Prolonged Androgen Deprivation Therapy, IDEA-P trial; R03CA16296901) have demonstrated a strong interdisciplinary team with extensive experience in design/delivery of weight loss program (**Figure 2**). The Co-I of this proposed project, Dr. Electra Paskett, is a nationally recognized investigator in health disparities. Her research with underserved populations established the expertise and capability to conduct studies in disease prevention, health disparities, and improving access in underserved areas, including a faith-based weight loss program in Appalachian states (The Walk by Faith Trial; U54 CA153604) and the Rural Interventions for Screening Effectiveness (RISE; R01 CA196243). The RISE Project recruited 1039 participants from rural Ohio and Kentucky who had complete data on height and weight and agreed to be contacted about opportunities for future research. About 573 of them live in northwest rural Ohio, and 330 had a BMI≥ 25 kg/m^2. We anticipate at least 40% of these participants would be willing to participate in this study.

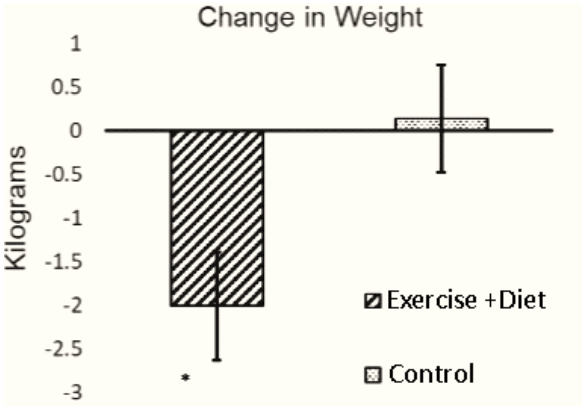

Figure 2. 12-week lifestyle intervention effect on weight loss, the IDEA-P trial (Dr. Focht)

C RESEARCH DESIGN AND METHODS

C.1 Overall strategy.

This study is a single-blind, 2-arm randomized controlled pilot study designed to determine the feasibility and preliminary efficacy of a 15-week telephone-based weight loss in obese rural populations. Up to 50 obese rural Ohio residents will be randomly assigned to a 15-week telephone-based weight loss group (n=30) or active control group (up to 20). The primary outcome of this trial is the feasibility of a 15-week telephone-based weight loss intervention. The exploratory outcomes include changes in weight, body composition, lipid profiles, and inflammatory markers (CRP, IL-6, and TNF-α). Exploring the efficacy of the telephone-based intervention on weight loss, body composition, lipid profiles, and inflammatory markers will provide preliminary effect estimates for future larger-scale randomized controlled trial in rural populations.

C.2 Research Team

C.2.a Research role and responsibilities

Overall study responsibility belongs to Drs. Focht and Paskett, Co-PIs of the study (**Table 1**). Dr. Focht and his research team will be responsible for day-to-day study oversight including obtaining regulatory approval, screening/recruiting participants, obtaining informed consent, conducting in-person assessments, deliver intervention, and data management activities. Dr. Paskett will be responsible for the refining the study materials and supervising the recruitment process. Dr. Heymsfield will serve as the team consultant to provide expertise on body composition assessment using the 3-D body scanner.

Table 1. Research Role and Responsibilities

Research Role		Responsibilities
Investigators	Dr. Focht (PI) Dr. Paskett (Co-PI)	Oversee study progress
Project manager	Xiaochen Zhang	Obtain regulatory approval, screen and recruit participants, obtain informed consent, schedule and deliver intervention, and manage data collection and analysis
Health coaches	Zachary Chaplow, Victoria DeScenza, Alyssa Dispennette, and other OSU Kinesiology students with training in exercise physiology and behavioral changes and experience in weight loss trials	Screen and recruit participants, obtain informed consent, and deliver intervention (go through the exercises, provide behavioral change techniques and strategies, and moderate group messages)
Other research staff	Jessica Bowman and other OSU Kinesiology staff/students with training in exercise physiology and experience in weight loss trials	Screen and recruit participants, obtain informed consent, conduct in-person assessments
Dietitian	OSU staff with background in nutrition	Provide dietary counselling to participants when needed
Consultant	Dr. Steve Heymsfield (from Pennington Biomedical)	Consult on body composition measures using 3D body scanner

C.2.b Research team training

Prior to the initiation of the project, all research staff will receive standardized training to ensure that the activities of the study are conducted in a uniform, safe, confidential and secure manner. All research staff will attend a one hour long training using slides and manuals developed for prior studies and will be modified for the current study. Contents covered in the training session will include: 1) overview of study objectives; 2) description of study groups and interventions; 3) protection of human subjects, HIPAA, and confidentiality issues; 4) cultural sensitivity; 5) roles and responsibilities; 6) documentation and reporting requirements; 7) data monitoring

and quality assurance procedures; 8) handling problems/questions during recruitment/data collection; 9) effective communication techniques; and 10) use of the REDCap for data entry.

The success of a weight loss intervention is dependent upon the health coaches' ability to communicate with a wide range of people and in the culturally accepted vernacular. Personal skills such as the ability to be empathetic, patient, and caring are important when it comes to helping participants understand and comply with behavioral changes. Health coaches trained by Dr. Focht in exercise physiology and behavioral change, and have experience in weight loss trials will deliver the intervention to participants. All health coaches will take a refresher training before study started. The refresher training will include information about concept and strategies of behavioral intervention, principle and goals of physical activity and dietary modification, and ways to overcome barriers to behavioral change. Health coaches will also be trained in communication, consistency, and collaboration in the rural community and cultural setting.

In addition to the one-hour training, research staff will be trained using standard protocols for assessments, including measuring weight, height through scales, body composition via 3D body scanner, and timed fitness performance. In terms of colleting blood samples, research staff will be trained to use finger stick using Cholestech LDX. Only research staff who are certified phlebotomists will conduct blood draw. Following the training session, research staff will role-play and receive feedback until they have reached 100% compliance with recruitment, assessment, and data collection integrity.

C.3 Study Population

C.3.a Rural Ohio

Within Ohio, 50 of the total 88 counties (56.8%) are considered rural according to Rural-Urban Continuum Codes (RUCC). These counties have a population of about 2.3 million, most of whom are Caucasian. Our study will target adults 20-64 years old who reside in rural Ohio counties. We will enroll up to 50 adults 20-64 years of age in the designated counties.

C.3.b Eligibility Criteria

Inclusion Criteria: 1) BMI≥ 25kg/m^2; 2) Age ≥20 years and <65 years; 3) Not currently participating in any weight loss intervention or meeting the 2018 Physical Activity Guidelines for Americans (150 min/week of moderate-intensity exercise or 75 min/week of vigorous exercise); 4) Ability to walk two city blocks (about 400 steps) comfortably; and 5) Ability to speak and read English.

Exclusion Criteria: 1) Prior cancer diagnosis (except non-melanoma skin cancer) or severe medical conditions such as unstable cardiovascular disease or digestive disorders that would preclude physical activity and dietary intervention; 2) pregnant or nursing women (if one becomes pregnant over the course of the study, she will be asked to report to research staff); and 3) unable to give informed consent.

Potential participants will be screened for eligibility by phone or online survey. To determine whether an interested individual should consult with his or her physician before beginning an exercise program, potential participants who self-reported to have pre-existing health conditions (e.g., heart problems, insulin-dependent diabetes, poorly controlled blood pressure, other severe disease) will be asked to obtain medical clearance before enrollment. For potential participants who self-reported any health condition that may preclude them from the exercise/dietary modification (e.g., poorly controlled blood pressure, insulin-dependent diabetes, any heart disease, or any other severe disease), we will ask their permission to contact to their physicians to obtain medical clearance. Their physicians must fax, email or mail a medical clearance form (see 10. Medical Clearance Form) to OSU by baseline assessment so that the individual can participate in the study. If physicians indicated the participant is not eligible for our study, we will contact the participants by phone/email to inform their ineligibility (see 1d. Not eligible from physician clearance).

Eligible participants will be grouped by their residency locations (e.g., county, geographic region) to schedule in-person assessments (baseline and 15-week). To optimize retention and maintain data fidelity, all assessments

will be obtained on-site at community locations (e.g., library, Area Health Education Center) close to participants' homes by trained study staff.

C.3.c Recruitment

We will recruit up to 50 overweight/obese rural residents through social media (i.e., Facebook), flyers, and a list of participants from a previous study (The RISE Project). We anticipate to screen 9-15 individuals per week and recruit 4-5 participants per month.

C.3.d Randomization

Participants will be randomized to either the weight loss intervention group (Telephone-based health counselling) or the active control group (Health education) using block randomization in 4-5 waves. Every 6-12 participants consented and enrolled, one wave will be formed. For each wave, participants will be assigned to either weight loss (n=30) or active control group (up to 20 participants).

C.3.e Informed consent process

After confirming eligibility for the trial, each participant will be given a unique study number. The research staff (see **table 1** for details) will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. The individual will be asked to provide written informed consent to participate in the study. If an eligible participant refuses to provide written consent, the research staff will not proceed with the baseline assessment. The research staff will follow talking points that will outline all of the requirements of the study and will cover the content of the informed consent form. The participants will be given a copy of the informed consent document for their records and afforded the opportunity to ask questions and have them answered to their satisfaction. Once the individual fully understands each element of the consent and the study, including the purpose, requirements, risks, confidentiality, right to withdraw, and contact person, then he/she will be asked to provide consent. The screening process will take approximately 5 minutes, and the informed consent process could take up to 15 minutes to complete.

The consent process will be documented in detail including any questions asked by the individuals and the responses provided by research staff. The research staff will date and sign the documentation. In addition, the time the consent process began and ended will also be documented. Prior to the beginning the baseline assessment, participants will be asked once again if they understand the requirements of the study and if they wish to continue. Any subsequent changes to the informed consent process will be submitted to the OSU IRB for approval prior to activation.

Participants assigned to the weight loss group will notify the research study staff of any pre-existing medical conditions, including injuries and recent surgeries, at baseline before they start the weight loss intervention and will inform the research study staff should they experience any medical problems, including injuries, over the course of the weight loss program. Their responses at baseline and throughout the weight loss intervention will be recorded on an Adverse Events Log.

C.4 Weight Loss Intervention

C.4.a Overview

The proposed weight loss intervention is a 15-week telephone-based, multi-component approach adapted from the Healthy Living and Eating Program (73), which was designed for cancer patients. We will modify the program from the in-person group sessions to a remotely accessible telephone-based intervention to reduce the burden of travel for rural populations and transform the program from a cancer patient's focus to one of a general population with obesity. Participants randomized

Table 2. Dietary intake and exercise goal.

Dietary budget per day		
Baseline Weight	< 250 lbs	≥250 lbs
Calorie (kcal)	1200-1500	1500-1800
Fat (g)	40-50	50-60
Protein (g)	60-75	75-90
Aerobic exercise (moderate-intensity) per week		
Goal	150-200 min	
Week 1	30-60 min	
Week 2-4	↑ 30 min till reach 150 min	
Week 5-15	>150 min/week	

to the weight loss group will receive weekly telephone sessions led by health coaches with a background in exercise physiology and behavioral weight loss interventions for 15 weeks to achieve a 7% weight loss goal. Participants will be encouraged to lose weight through a modest restriction in caloric intake (500-1000kcal/day) that gradually progresses towards a personalized, target daily caloric intake goal (1200-1800 kcal/day) and concomitant increase in energy expenditure via physical activity including aerobic exercise and resistance training (**Table 2**). Participants will be asked to self-monitor dietary intake and physical activity through a paper food log or MyFitnessPal on a daily basis. They will also receive a lifestyle modification manual (will be submitted in the first amendment) based on the Health Living and Eating Program and the Look AHEAD study to guide behavioral changes with weekly goals (73, 101).

C.4.b Dietary Component

During the weekly telephone session, participants will receive dietary recommendations tailored to their current weight and weight loss target. The specific dietary objectives will be consistent with recommendations from the American Institute of Cancer Research (AICR) (102). The AICR nutrition guidelines were selected to be implemented in the dietary portion of the intervention because: a) of their value for offsetting adverse changes in body weight, body composition, and metabolic and inflammatory markers; b) they are the most comprehensive, scientifically-based cancer prevention guidelines available; and c) the education materials available from AICR in support of their guidelines are clear, easy-to-follow and very consumer-friendly.

The dietary intervention encourages reductions in portion size and caloric and fat consumption together with a gradual transition from an animal-based diet to a more plant-rich diet while still incorporating animal foods, including milk and meat, with an emphasis on monitoring food proportion and portion size. Specifically, the dietary component includes: 1) reduction in energy intake by 500-1000 kcal per day; 2) reduction in total fats to 25-30%, saturated fats to 7%, and protein to 15% of total calories; 3) increase in fruit and vegetable consumption to 5 servings per day; 4) intake of 3 or more servings per day of whole grains and a gradual increase to at least 25 grams of dietary fiber per day, and 5) increase water intake.

The weekly intervention on dietary intake will use a motivational interviewing approach. This technique has been extensively used in substance abuse counseling and recently, has been applied to diet-related behavior change. Motivational interviewing has been demonstrated to be an effective communication method to promote behavior change in various populations (103, 104). Additionally, participants will receive tailored dietary strategies built upon many of the cognitive-behavioral self-management techniques utilized in the behavioral exercise counseling component, including self-monitoring, building self-efficacy, goal setting, and anticipating and overcoming barriers to dietary behavior change. Dietary consultations will be provided by a registered dietitian to participants, as needed.

C.4.c Physical activity component

A combination of home-based aerobic and resistance exercise will be described through a lifestyle modification manual and telephone counseling. The goal of physical activity will be to achieve 150-200 min/week moderate-intensity aerobic physical activity and 2-3 sessions/week resistance training. The aerobic physical activity consists of gradually progressing from 10-30 minutes of exercise on most, if not all days of the week, with a primary focus placed upon brisk walking as the primary accessible mode of aerobic exercise for each participant. However, participants are encouraged to engage in their preferred choice of exercise mode that they are able and willing to perform including brisk walking, running, or cycling. The home-based resistance exercise involves performing 1-3 sets of 8RM-12RM repetitions of various exercises (e.g., sit-to-stand, standing leg curl, seated leg extension, chest press, lateral raise, bent-over row, straight-arm pulldown, arm curl, triceps pushdown, and chair abdominal curls) using body weights and resistance bands (see exercise manual). All exercise prescriptions were appropriately modified for safe and effective home-based exercise.

During the telephone counseling in the first two weeks, health coaches will go through the exercises described in the lifestyle modification manual with each participant, and if needed, modifications of the exercises will be provided. Participants will be provided an exercise manual and access to online *YouTube* videos (as another option) that demonstrate safe, effective techniques for each of the prescribed exercises, provide examples for

alternative exercise options, and provide simple tips for proper exercise form. These videos have been successfully implemented to facilitate home-based exercise in prior lifestyle interventions led by the investigative team. Each week participants will gradually increase their exercise duration and intensity in increments of 10-30 min until attaining the target physical activity volume goal.

C.4.d Behavioral component

Each week, participants will receive a 30-45 minute telephone counseling session that provides behavioral change techniques tailored to rural populations using the contemporary principles of cultural-tailoring and Social Cognitive Theory (105), and focus on motivation, relapse prevention, emotional distress, time management, and overcoming barriers. Each session will include a review of the previous week's activity, planned weekly lessons, dietary and exercise goals for the subsequent week, and strategies tailored to each participant to improve self-efficacy, social support, and overcome barriers. Additionally, group messages following the weekly telephone counseling is integrated with the behavioral component to promote independent adherence to lifestyle modification.

Participants will also receive a physical activity tracker (e.g., Fitbit) and a weight scale. Participants will learn how to use the Fitbit and will wear it during the entire study period. Participants will learn how to conduct self-measurements and record body weight each week, as well as set up MyFitnessPal (or using paper log) to self-monitor dietary intake and physical activity throughout the 15-week study period.

The objective of the behavioral component is to promote increased self-efficacy and social support for lifestyle modifications and gradually facilitate participants' transition toward successful independent self-regulation of a healthy diet and physical activity. The behavioral component focuses upon the acquisition and practice of self-regulatory skills in conjunction with a continuous problem-solving model of behavior change to empower participants to exert greater control over their behavior, cognition, and environment. The behavioral component is designed to: a) increase health knowledge of the benefits of physical activity and dietary modifications; b) enhance self-efficacy and positive outcome expectancies through the promotion of a series of successful experiences in changing exercise and eating behavior; and c) improving self-regulation of exercise and eating behaviors through the use of goal-setting, self-monitoring, stimulus control, cognitive restructuring, and barrier problem-solving strategies. The efficacy of this approach for promoting adoption and maintenance of exercise and dietary behavior change has been demonstrated in prior randomized controlled trials that Dr. Focht has served as principal and co-investigator on other studies (106-109).

C.5 Active Control Group

At the beginning of the study, participants randomized to the active control arm will receive education brochures (will be submitted in the first amendment) describing the American Institute for Cancer Research physical activity and dietary guidelines. Participants will be asked to meet the 2018 Physical Activity Guidelines for Americans (150 min/week of moderate-intensity exercise or 75 min/week of vigorous exercise), and increase fruit and vegetable intake, reduce fat intake, reduce sugary drink, increase consumption of whole grain, and increase water intake. An exercise manual with access Online *YouTube* videos (as another option) will be available as examples for proper exercise form for strength training. We will also encourage them to self-monitor weight, dietary intake, and physical activity through MyFitnessPal or paper log. To achieve the retention and provide motivation and strategies for behavioral change in the active control group, participants will receive a Fitbit and the lifestyle modification manual at the end of the study.

C.6 Covid-19 Safety Protocols and Planning

In order to minimize risk of exposure in research activities conducted during the COVID-19 pandemic, we will be using multiple strategies that align with OSU Office of Research recommendations included in the Staged Reopening Plan guidance including: a) Promote healthy hygiene practices including frequent and thorough hand washing and hand sanitizer; b) Maintain recommended social distancing during all in-person research assessments; c) Limit personnel to no more than 1 person per 150 sq ft; d) Staggered scheduling of research staff and assessment visits will be enacted to maintain social distancing protocols; e) Assessment visits will be scheduled in a manner that limits the amount of time spent on campus or in the field to absolute minimum needed

to accomplish research and continue to work remotely as much as possible. In this regard, during the ongoing pandemic, in-person contacts are limited to outcome assessments which significantly reduces time spent in the labs and/or field settings by participants and personnel. Self-report measures will be completed via virtual and/or mail to reduce in-person contact time; f) PPE including masks, face shields, and gloves will be worn during contact to limit risk of virus spread; Homemade or cloth masks are accepted; g) Use of a Daily symptom log for all participants and personnel- fever of 100.4 over the past 24 hours, symptoms related to COVID, or suspect they may have been exposed within the recent 14 days should stay home and call PCP; h) Clean and disinfect using approved disinfectant cleaners for all lab/office surfaces that require contact (desk, keyboard, ipads, doors, etc) before and after each required activity in assessment visits ; i) Personnel must remove one glove when opening doors, pushing elevator buttons, etc to avoid cross contamination; j) Our designated investigative team will coordinate all scheduling and oversight of research activities in consultation with PI (Dr. Brian Focht) to reduce overlap of researchers in a given space; j) Log time of entry, time of departure, and temperature; and k) Participants will not have anyone accompany them to assessments unless they require assistance.

C.7 Assessment

Outcome assessments will be obtained at baseline and 15 weeks later at in-person visits by research staff blinded to treatment group assignment. All outcome assessments will be conducted at a community center or public location convenient to the participant. Each outcome measure will be collected through paper or online survey (through REDCap) and stored in REDCap (Research Electronic Data Capture).

C.7.a Primary Outcome: feasibility and acceptability

Completion rate and participation of the weekly telephone counseling session will be measured to evaluate the feasibility and acceptability of the 15-week telephone-based weight loss intervention.

C.7.b Secondary Outcome Assessment

Self-reported questionnaires and objective measures by research staff will be used (**Table 3**).

Table 3. Assessment Approach

Assessment	Approach	Time
Weight, height	Research staff using weight scale	2 mins
Body composition	Research staff using Styku 3D body scanner	10 mins
Hydration status	Research staff using urine specific gravity	3 mins
Lipid: Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)	Research staff (with training) using Cholestech LDX	3 mins
Inflammatory markers: C-reactive protein (CRP), Interleukin (IL)-6, TNF-α	Research staff (certified phlebotomists) conducting blood draw	5 mins
Objectively measured physical activity	Participants will wear ActivPAL for 7 days	--
IPAQ Leisure-Time Exercise Questionnaires	Self-reported via paper or online survey	5 mins
Diet diary (developed by NCI)	Self-reported via paper for 7 days	--
Healthy eating and weight SE questionnaires	Self-reported via paper or online survey	5 mins
Multi-dimensional Self-Efficacy scales	Self-reported via paper or online survey	5 mins
Social Support Inventory for Physical Activity	Self-reported via paper or online survey	5 mins
Social Support Inventory for Healthy eating	Self-reported via paper or online survey	5 mins
Physical Fitness	Research staff (with training) using standard protocols	15 mins

1. *Anthropometric assessment*

Body weight (kg) and height (cm) will be measured to calculate BMI (kg/m^2).

2. *Body composition*

Fat mass (kg), fat%, lean mass (kg), lean% will be measured using a 3-Dimension (3D) Body Scanner, Styku S100 (Styku LLC, Los Angeles, CA). The Styku S100 scanner uses an infrared camera built into a tower and a rotating platform to capture body circumference and volumes. Participants will stand on the platform with their arms positioned in the A-pose and then will be rotated clockwise. The Styku S100 scanner uses Microsoft Kinect Fusion software to recognize body landmarks, which are used to calculate and visualize various body measurements (110). The Styku S100 scanner produced reliable measures of body composition compared with dual-energy X-ray absorptiometry (**Figure 3**). Most importantly, the Styku S100 scanner is feasible to use in rural community-settings because of its portable size and ease of assembling (**Figure 4**).

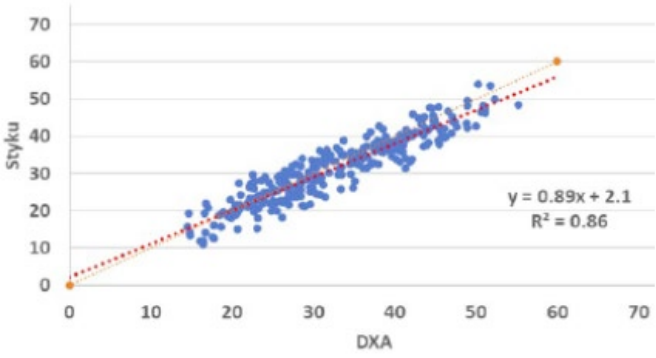

Figure 3. Styku vs. DXA measured fat % in adults

3. *Hydration*

Proper hydration is critical for collecting blood samples through finger stick and venipuncture. In addition, inflammatory markers are sensitive to hydration status. Therefore, to ensure proper hydration, participants will be asked to consume 2 cups of water the night before the assessment and another 2 cups the morning of the assessment. Urine samples will be checked for urine-specific gravity (USG) using a refractometer. A USG<1.025 indicates euhydration.

4. *Lipid profile*

Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) will be obtained by fasting capillary blood sampling from fingerstick and analyzed using Cholestech LDX (Hayward, CA). The Cholestech LDX has demonstrated the accuracy and precision to assess blood lipid (111, 112). It is a point-of-care assessment to screen abnormal blood lipid in clinical, community, and other health promotion settings (113, 114). The Cholestech LDX provides lipid profiles result within 5 minutes, which will allow research staff and participants to receive results at the same visits.

Figure 4. Portable Styku S100 Scanner

5. *Inflammatory markers*

All participants will undergo a fasting (≥6 hr) blood draw (50mL per assessment). Plasma samples will be stored at -80°C until assayed. C-reactive protein (CRP) concentration (ng/L), Interleukin (IL)-6 concentration (pg/mL), and TNF-α will be quantified with electrochemiluminescent multiplex immunoassay platform (Meso Scale Discovery, MSD).

6. *Physical activity*

Objectively-determined minutes of PA participation will be assessed and The ActivPAL captures free-living sedentary and ambulatory PA and is well-established as one of the most accurate wearable activity monitors

(115). The monitor will be set to collect PA data using the manufacturer settings and is affixed to the midline of patients' right thigh in a waterproof pouch allowing for continuous wear time. Participants will be provided verbal and written instructions on how to wear the ActivPAL and wear the monitor 24 hours per day for the 7 consecutive days following the completion of the study assessment visits. In the event of wear time problems, patients must have at least 10 hours per day of wear time on 4 days of the week (including at least 1 weekend day) for a valid assessment. Monitors will be returned to trial staff via U.S. postal service.

Participants will also complete self-reported Leisure-Time Exercise Questionnaires (116) in the 1st and 15th week.

7. Dietary intake

All participants will complete 7-day food checklist for at the 1st and 15th week. This food checklist was developed by the National Cancer Institutes that comprised of a list of foods. Over the course of a day, participant makes a check beside a food each time she or he eats it. It yields estimates of macro nutrient intake, as well as intake by specific food groups. Participants in the weight loss intervention will also be encouraged to complete daily food log using MyFitnessPal (or paper log) during the trial. The food log and weekly summary of caloric and macronutrient intake will be regularly monitored by the trial's staff and registered dietitian to track adherence.

8. Self-Efficacy and Social Support

Participants will be asked to complete self-reported Healthy Weight and Eating Self-Efficacy, Multi-dimensional Self-Efficacy scales (117-119), as well as adapted Social Support Inventory for Physical Activity (SSPA) and Eating Habits (SSEH) questionnaires (120, 121).

9. Physical fitness

Participants will be asked to complete valid and reliable timed performance-related mobility tasks, such as 400-meter walk and lift and carry task (122-125). These assessments at baseline will serve as a reference to tailor exercise counseling for each participant.

C.9. Timeline

Table 4. Study Timeline

	Year 1	Year 2
ACTIVITY	1 2 3 4 5 6 7 8 9 10 11 12	1 2 3 4 5 6 7 8 9 10 11 12
Database Development and Training	⟷	
Recruitment	⟷	⟷
Intervention & and Follow-Up Data	⟷	⟷
Analysis and Presentations		⟷

Database development and personnel training will occur in the first 2 months of Year 1 (**Table 4**). Participant recruitment, with a target accrual of 4-5 participants per month, will begin month 3 of Year 1 and continue through month 7 of year 2. The intervention data collection will begin in Month 4 of Year 1 and end in month 10 of Year 2. The remaining 3 months of Year 2 will be used for data analyses, presentations, and manuscript preparation and provide flexibility in the event of unexpected barriers encountered during data collection.

C.10. Potential problems and alternative strategies

C.10.a. Recruitment

Rural residents may experience the burden of travel, limited affordable healthy food options, and fewer exercise facilities. We opted to use a telephone-based weight loss intervention to reduce the burden of travel to a face-to-face program. Our research team has been successful in conducting studies in rural populations, which allows us to contact participants from previous research (RISE) to achieve our recruitment goal. Although RISE participants are all women, we anticipate enrolling men by other recruitment approaches, such as community events. As the primary aim of the proposed study is the feasibility, not generalizability, the representation of participants' sex is not our focus.

C.10.b. Intervention

We have access to an in-house registered dietitian who will provide participants with resources and strategies to optimize their food selections and improve dietary intake as needed. If, during the 15-week intervention, participants experience barriers to exercise facilities, we would expand exercise options, including an exercise manual with home-based alternative exercises, and access to online *YouTube* videos (as another option), to allow participants to utilize more resources to complete the moderate-intensity exercises.

C.10.c. Assessment

We considered using a standard measure of body composition using Dual-energy X-ray absorptiometry (DXA) but opted not to as this is likely to add the burden of travel to facilities equipped with DXA. However, we will assess body composition using a 3-D Styku body scanner, which is portable to rural community-settings and can provide valid and reliable data on body composition. Together with using Cholestech LDX to evaluate participants' lipid profiles, the proposed study is innovative to test new point-of-care approaches to assess disease risk factors in rural populations.

D DATA HANDLING AND ANALYSES

D.1. Outcome Analysis Plan

D.1.a Primary outcome

The feasibility of completing the study is defined as the percentage of enrolled participants who complete the study. If we observe an 80% completion rate in the weight loss intervention group (n=30), the 85%, 90%, and 95% confidence intervals (CIs) for the completion rate would be (69.5, 90.5), (68.0, 92.0), and (65.7, 94.3), respectively. If the true completion rate is 80%, we have 95% power to rule out the unacceptable 50% completion rate with 95% confidence (one-sided).

The acceptability of the weight loss intervention is the percentage of participants in the weight loss intervention group who engage at least 75% of the weekly telephone counseling session. Intervention-related adverse events, satisfactory, and other feasibility assessments, such as the percent of initial contact to enrollment, reasons for consent refusal, barriers to adherence to weekly goals, and reasons for drop-out will also be assessed.

D.1.b Secondary outcome

Significance test for the preliminary efficacy of the lifestyle intervention will quantify the difference in means using repeated measures analysis of variance (ANCOVA) statistical model to adjust baseline values and control for the effect of age. The sample size of 30 participants in the weight loss group and at least 15 in the active control group is feasible to recruit for a pilot/preliminary efficacy study that accounts for a projected attrition rate of 20% yet also still provides adequate power to detect meaningful, moderate to large effect size (0.54-0.72) on weight loss, body composition, inflammatory markers, and lipid profiles.

Analyses will be conducted using the intention to treat principle with last value carried forward approach used to account for data missing due to participant attrition. Exploratory analyses will compare outcomes including weight loss, changes in body composition, changes in physical activity and dietary intake, changes in lipid profiles and inflammatory biomarkers between the telephone-based weight loss group and the active control group. We will also examine whether social support and self-efficacy changes among participants from the weight loss group. These exploratory analyses will provide effect size estimates to inform the development of a large-scale phase II randomized controlled lifestyle weight loss intervention trial.

D.2. Data Management

As mentioned above, we will use REDCap as our data entry system. It will be used to store the baseline and follow-up questionnaires, will work directly with the OSU CCTS Research Informatics Services Core and will be

used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners (including OSU) and the NIH National Center for Research Resources, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the CCTS Research Informatics Services Core. As part of the data dictionary development process, individual fields can be denoted as "identifiers". When exporting a de-identified dataset, these variables are omitted. Additionally, the data export tool also allows shifting of dates for a limited data set export. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data and has real time validation rules (with automated data type and range checks) at the time of entry. It offers easy data manipulation with audit trails and ad hoc reporting functionality for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap is 21 CRF Part 11 capable. Currently, REDCap installations support electronic signatures by positively identifying the user through a unique username and password combination. The provisioning of accounts and user access to specific database (s) is integrated with the OSU Medical Center LDAP authentication service, and the provisioning of access and specific user rights are managed by CCTS staff.

Each participant will be assigned a unique study ID (SID) when first recruited that will follow their electronic information in REDCap, throughout the study. Each participant will have their own folder that will contain a copy of their consent documentation form, any paper format self-reported questionnaires or assessments, Medical Clearance (if any), and any letters sent to the participant. The folders will be stored in locked filing cabinets in a locked office. No information about a study participant will be given to third parties unless that subject has given written or witnessed consent to do so.
Information will be obtained and maintained on all individuals screened for this study. If available we will keep demographic data on those individual who are ineligible and eligible but refuse. The data will be used to ensure that we do not contact individuals who are ineligible for the study or who have told us they do not want to participate in the study. The data will also be used to characterize/compare this group individual to those who are eligible and agree to participate; it is important to determine if those who are ineligible and especially those who refuse to participate, are in way inherently different from the women who participate in the study.

D.3. Record Retention

All research records (including identifying information) will be maintained until data analysis and all manuscripts have been completed, or for the length of time designated by the institutional requirement and the NCI and AICR. Paper records will be maintained in a secured storage facility and electronic data will be stored in a password protected database until is appropriate to destroy the data. The IRB at OSU, the NCI, and AICR will be notified of our intent to destroy the data. If required by NCI or AICR, de-identified data may be shared with the NCI and AICR and their data repositories.

E HUMAN SUBJECTS

E.1 Anticipated Risks

There are minimal risks associated with completing the objective and self-report measures for this study. Possible psychological risks may occur in that some individuals may experience some guilt or embarrassment in objectively measured body composition and self-reporting low levels of motivation or intention to exercise. Embarrassment or discomfort could occur from certain baseline or follow-up survey questions, but participants are able to skip any questions that they do not wish to answer. Risks anticipated with receiving the intervention materials (brochures, telephone-based counseling) or encouraging participants to promote healthy lifestyle are minimal. There are minor risks associated with venipuncture (taking blood from a vein) including mild discomfort or bruising. Less commonly, a small clot, swelling of the vein, infection, or bleeding may occur at the site of puncture.

There is the possibility of muscle soreness from increased physical activity. The muscle soreness may last several days after each exercise session, but it is not likely to be severe enough to limit activities of daily living. There is

also a risk of muscle injury, which may require medical attention, may take several months to heal, and may limit activities of daily living for a period of days, weeks, or months. Participants will be informed that there is an increased risk with starting a physical activity program and be advised of all of the potential risks. Additionally, Dr. Focht and research staff with training in exercise physiology and behavioral changes will be directly involved in conducting physical fitness tests and delivering exercise components.

There is a slight risk of breach of confidentiality, but steps are in place to protect participants' personal information. Electronic data will be stored behind a firewall and accessed only by study staff through password-protected computers. Paper-based data will be stored in a locked cabinet within a locked file room.

Collectively, the participants will be assuming no more than minimal risk in completing the assessment protocol and the minimal risk inherent to completing the assessments will be mitigated via stringent pre-test medical screening and during testing supervision.

E.2 Benefits of participation

Participants may gain awareness of healthy eating and physical activity from evidence-based program. Participants in the telephone-based counseling group will receive a physical activity tracker (e.g., Fitbit) at the beginning of the study, and weekly telephone-based weight loss counselling for 15 weeks. Participants in the active control group will also receive a physical activity tracker and lifestyle modification manual at the end of the study. All participants will receive regular body weight, body composition, and blood tests for lipid profiles and inflammatory biomarkers free of charge.

E.3 Adverse events

Adverse events, including any unfavorable and unintended sign (e.g., abnormal laboratory finding or symptom) will be collected as they occur, regardless of whether it is considered related to the weight loss intervention. Musculoskeletal injuries and previously undocumented major medical events incurred during the intervention will be systematically collected on all participants during the study period using standardized forms from our prior work. Patients will have instructions to contact the PI or their primary health providers to discuss and manage any possible side effects. The PI, study coordinator should immediately be contacted in the event such a problem arises.

E.3.a Severity

1) Serious adverse event: Any adverse event that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization or prolongs hospitalization, or results in a congenital anomaly or birth defect;
2) Life-threatening event: Any adverse event in which the subject is at immediate risk of death from the reaction as it occurs; does not include a reaction that, if it occurs in a more serious form, might cause death;
3) Unexpected event: Any adverse event that is not identified in nature, severity, or frequency in the investigator brochure, study protocol, consent form, or IND application; or the event is more serious than anticipated.

E.3.b Association

1) Definitely Related: An adverse event that has a timely relationship to the administration of the study intervention and follows a known pattern of response for which no alternative cause is present;
2) Probably Related: An adverse event that has a timely relationship to the administration of the study intervention and follows a known pattern of response, but for which a potential alternative cause may be present;
3) Possibly Related: An adverse event that has a timely relationship to the administration of the study intervention, follows no known pattern of response, but a potential alternative cause does not exist;
4) Unrelated: An adverse event for which there is evidence that it is definitely related to a cause other than the study intervention; in general, no timely relationship to the administration of the drug/procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

E.3.c Documentation

The adverse event form will be used by study staff to report injuries or other adverse events reported by participants throughout the study. The patient will be observed and monitored carefully until the condition resolves, stabilizes, or its cause is identified. All adverse events, including laboratory abnormalities, will be followed up according to good medical practices. Information to be recorded includes: 1) specific type of reaction; 2) duration of reaction; 3) severity/grade of reaction according to the NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE); 4) suspected cause of the reaction (i.e. possibly or probably related to one of the following: study treatment, progression of disease, concurrent medications, concurrent illness, or other factors); 5) changes made in the administration of the study intervention and other actions taken to alleviate the clinical event; and 6) patient's response to medical interventions.

E.3.d Reporting

In accordance with IRB guidelines, serious adverse events will be reported within 10 days of the investigator's or research staff members' learning of the event to OSU IRB. OSU IRB Event Reports should be submitted through BuckIRB at: http:/orrp.osu.edu/irb/buck-IRB/. Events resulting in temporary or permanent interruption of study activities by the investigator or sponsor to avoid potential harem to subjects should be reported within 48 hours whenever possible.

All events that may represent unanticipated problems involving risks to subjects or others will be promptly reported (as described above), regardless of whether they occur during or after the study, or involve a subject who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, a protocol amendment will be submitted for IRB review.

Related events involving risk but not meeting the prompt reporting requirements will be reported to the IRB in summary form at the time of continuing review.

E.4 Confidentiality

Participants enrolled the study will be assigned to a study ID. Individuals will not be identified by name or by any other personal identifying information in reports, or publications resulting from this study. All information will remain de-identified. Thus, risk of disclosure of confidential medical information will be essentially nonexistent. Additionally, all data will be number coded and stored in a password protected files and a locked research office that can only be accessed by the research staff. These procedures have been successfully used to protect confidentiality in our prior studies.
Study patients may voluntarily withdraw at any time from the protocol. The reasons for discontinuation of the study will be documented in the patient record and data collection forms. A letter to the PI in writing

F. Ethical and Regulatory Considerations

F.1 Institutional Review Board

Prior to initiating the research project and conducting any research project activities the PI will obtain written approval to conduct the research project from the appropriate institutional regulatory bodies. Should changes to the research project protocol become necessary, the PI will submit protocol amendments in writing to the IRB for approval prior to implementation.

F.2 Informed Consent

As noted in section 3.2.3, consent will be sought and obtained via phone and verbal consent process completed prior to initiating any research project procedures. Each element of the consent will be verbally explained to the potential participant. The woman will be given an opportunity to ask questions and have the questions answered to her satisfaction. Once the individual understands each element of the verbal consent, including the purpose, requirements, benefits, risks, confidentiality, right to withdraw, and contact person, then and only then will it will

be documented that the individual consented to participate in the study.

F.3 Compliance Monitoring

In accordance with IRB guidelines, the study program will be reviewed by the IRB every 12 months or less. Deviations from the protocol must be documented in the medical record and reported immediately to the PI. Deviations that meet the criteria for Immediate Event Reporting (http://orrp.osu.edu/irb/event/index.cfm) such as those that increase risks to subjects and/or compromise scientific integrity will be reported immediately to the IRB.

F.4 Data and Safety Monitoring Plan

We have developed a Data and Safety Monitoring Plan for this study. The purpose of the data and safety monitoring plan is to ensure the safety of participants, the validity and integrity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the study cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include:

1. Monitoring the progress of the study and the safety of participants;
2. Plans for assuring compliance with requirements regarding the reporting of adverse events (AE);
3. Plans for assuring that any action resulting in a temporary or permanent suspension of the study is reported to the appropriate agencies; and
4. Plans for assuring data accuracy and protocol compliance.

Prior to the initiation of the project, all project staff will receive standardized training to ensure that the activities of the study are conducted in a uniform, safe, confidential and secure manner. A tracking system will be put in place to document data collection activities, and reports will be generated on a weekly and monthly basis to monitor the study activities (**Table 5**). Meetings will take place on a monthly basis to monitor the activities of the project and to continually reassess the progress of the project including assessments of data quality, timeliness, participant recruitment, accrual, retention and monitoring of the risk versus benefits throughout the study period.

Table 5. The frequency of data review

Data Type	Frequency of Review
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	Monthly
Adverse event rates (injuries, symptom changes requiring altered exercise prescription)	Monthly
Compliance to treatment, dropout rates	Twice per month

All AEs will be reported according to the policy outlined by the OSU Institutional Review Board (IRB). The appropriate forms will be completed and sent in accordance to the timeline set forth by the IRB. All AEs will be reported to and reviewed by the study team. The research project manager will conduct a 10% eligibility verification. If a violation is noted, the research manager will document the violation and inform the project investigators of the matter. The appropriate action will be taken to rectify the violation and to determine what or if any corrective actions need to take place. All protocol violations will be documented and reported to the IRB. Also, any privacy violations will be reported to the IRB and the institutional privacy office. All privacy violations, adverse events, and protocol violations will be reported to and reviewed by the principal investigators (Dr. Brian Focht) and the research team, who will be responsible for reporting to the appropriate regulatory bodies at OSU.

The IRB will be provided feedback more frequently if there should be any adverse events or other recommendations. The investigators are responsible for reporting to the NCI and AICR project director any action resulting in temporary or permanent suspension of the research project at OSU. These actions will be reported to the NCI and AICR program director within 72 hours of notification. All documents or correspondence that are generated in the course of correcting or appealing the suspension status must also be forwarded to the program

director within 72 hours of it being presented to the institutional body that put for the directive to temporarily or permanently suspend the research project. During this time no research project activities can occur.

The principal investigators are responsible for submitting reports; annual reports will be sent to the OSU IRB, and as required by the NCI and AICR project offices. Information included in the reports will include the number of individuals enrolled in the study, dropout rates and any protocol deviations.

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