Title of Study: Exercise Training and Increasing Non-Exercise Physical Activity (I-CAN study)
Clinical Trials ID: NCT02010060
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Specific Aims

The 2008 Federal Physical Activity Guidelines recommend that adults obtain at least 150 minutes of moderate physical activity per week to maintain and improve health. Based on these guidelines, sedentary individuals may adopt a structured aerobic exercise program (e.g. 30 minutes of treadmill exercise 5 days per week) to meet these recommendations. While this approach is beneficial, the potential exists for aerobic training programs to be optimized by also **addressing the low levels of physical activity outside of structured exercise training sessions (Non-Ex PA)**. Three large randomized controlled trials performed in our laboratory suggest that previously sedentary adults participating in aerobic exercise training still exhibit low levels of Non-Ex PA (e.g. 4,500 to 6,000 steps/day). In addition, our group has published data suggesting that obese postmenopausal women participating in aerobic exercise training with high levels of Non-Ex PA had greater reductions in waist circumference and body weight compared to those with low levels of Non-Ex PA. Our results are supported by several epidemiological studies demonstrating that the amount physical activity below the threshold of moderate to vigorous intensity has clinical benefits (lower body weight, waist circumference, and 2-hour fasting glucose) independent of the amount of moderate to vigorous physical activity performed. **Therefore, a physical activity program composed of 1) aerobic training and 2) increasing the amount of Non-Ex PA may represent a more complete and clinically effective physical activity intervention compared to a program focused on aerobic training only**. However, to date, a prospective study examining the effectiveness of an intervention of this nature has not been performed.

The Intervention Composed of Aerobic Training and Non-Exercise Physical Activity (I-CAN) study will investigate the effects of aerobic exercise training and increasing Non-EX PA on waist circumference, weight, and other cardiovascular disease risk factors in a prospective pilot trial. We will randomize sedentary (<6,500 steps per day) obese adults (N= 45) with at least one additional cardiovascular risk factor to a: (1) structured aerobic exercise program with no intervention on Non-Ex PA (AERO group, N=15); (2) structured aerobic exercise program with the additional goal of increasing Non-EX PA (AERO-PA group, N=15), or (3) a control group (CON, N=15) for 6 months. Exercise groups will participate in the same aerobic training program (50 to 75% VO_2 max), designed to be consistent with public health recommendations of 150 minutes per week of moderate physical activity. Non-Ex PA in the AERO group will be tracked throughout the entire 6 month intervention with pedometers capable of counting steps, but not displaying them to the participant (blind mode capable). The AERO-PA group will progressively increase Non-Ex PA (1,000 to 3,000 steps per day above baseline levels) throughout intervention using pedometers. The AERO-PA group will also participate in lifestyle counseling grounded in the principles of the social learning and behavioral change theories to determine/reinforce strategies to increase Non-Ex PA. The primary outcome measure will be change in waist circumference following the intervention. The study results will be used to determine the efficacy/feasibility of the intervention, and power a larger trial as an R01 application.

Specific Aims:

To test the hypothesis that:

- Aerobic exercise training and increasing Non-EX PA will reduce waist circumference to a greater extent compared to the aerobic exercise training alone and the control group.
- Aerobic exercise training and increasing Non-EX PA will reduce weight and fat-mass to a greater extent than aerobic exercise training alone and the control group.

Additional Aims: We will also evaluate the effect of the intervention on fitness and insulin sensitivity

1. Background and Significance

Definitions for physical activity terminology used in the present proposal:
Non-Exercise Physical Activity (Non-Ex PA): Free-living physical activity **not** performed during an aerobic exercise training program (pedometer-determined) or below the threshold of moderate to vigorous physical activity (accelerometer-determined).
Dose of exercise training: Amount of kilocalories expended during an aerobic exercise training intervention relative to body weight. Used to standardize training for caloric expenditure across participants. Expressed as kilocalories per kg per week (KKW).

The 2008 Federal Physical Activity Guidelines [1] recommended that adults participate in at least 150 minutes/week of moderate physical activity. Substantial evidence exists that physical activity programs consistent with these recommendation have profound health benefits for sedentary adults [2-6], and a structured aerobic exercise training program (e.g. 30 minutes, 5 times a week) represents an effective strategy to meet these recommendations [1, 6]. However, there is potential for aerobic exercise programs to be optimized. The results of several published studies indicate that the amount of physical activity performed outside training (Non-Ex PA) remains low (similar to pre-training levels) in previously sedentary adults participating in aerobic exercise training [4, 5, 7]. **Therefore, this low amount of Non-Ex PA may represent an additional intervention target to use along with aerobic exercise**. Hamilton et al. [8] has described (in reference to sitting, Figure 1.) that ample opportunities exist for sedentary behavior even individuals who are presumed to be "physically active." For example, a training session of 45 minutes represents less than 3% of waking hours leaving the remaining 95% at risk for potential sedentary behaviors.

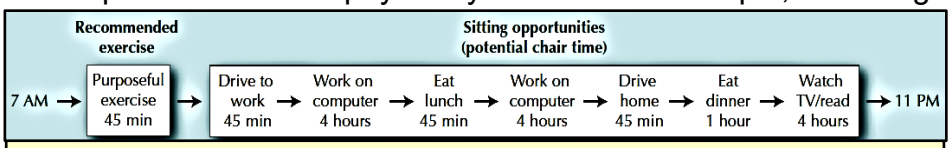

Figure 1. Hamilton et al. *Current Cardiovascular Risk Reports* 2008. Opportunities for sitting during the day for an individual who exercises 45 minutes

This relationship, along with the declining levels of occupational, [9-13] transportation-related [10], and physical activity in the home [10] has led some researchers to question the extent to which a bolus of exercise training (i.e. 30-45 minutes of aerobic exercise) mitigates the risk associated with low levels of physical activity or prolonged periods of inactivity throughout the day [8, 14, 15]. Thus, a physical activity program composed of aerobic training only, while beneficial, could be optimized by also increasing the amount of Non-Ex PA outside of training sessions. However, to date, no prospective studies exist combining aerobic exercise training and increasing Non-Ex PA. If clinically effective, this intervention could represent a more complete approach in treating obese sedentary adults compared to aerobic training alone, which may have a greater overall effect in reducing central adiposity, weight, and subsequently other cardiovascular disease risk factors. The core concepts of this intervention (aerobic exercise training and high Non-Ex PA) are transferable and feasible in clinical, public health, and exercise training settings. This may have important clinical implications as the majority of adults in the United States (58%) do not obtain the recommended amount of physical activity, which is especially prevalent in obese (64%) individuals [16].

1.1 Non-Ex PA in Aerobic Exercise Training Studies: Adults participating in aerobic training still exhibit low levels of Non-Ex PA (4,500-6,000 steps/day). Our research team has monitored Non-Ex PA in three large randomized controlled exercise training trials [4, 5, 7] . Pedometers were used to quantify the amount of Non Ex-PA over the course of the entire training intervention. **Importantly, pedometers were not worn during exercise training sessions**. In the DREW (postmenopausal women, N=464) [5], INFLAME (adults with elevated C-reactive protein, N=162) [7], and HART-D (adults with type 2 diabetes, N=262)[4] studies, we observed no significant change in pedometer determined Non Ex-PA compared to the control group (Figure 2). This finding was consistent across studies despite differences in the duration of the

intervention (4 to 9 months), exercise training intensity (50%-85% VO_2 max), and aerobic training energy expenditure (4 to 16 kilocalories per kg per week [KKW]). In the DREW trial, Non-Ex PA was not significantly different compared to control even at an exercise dose as high as 150% public health recommendations. Our findings are supported by other large randomized controlled trials such as the STRIDDE (duration: 8 months) [17] and the STRIDDE AT/RT (duration: 4 months) [18] studies, which report no significant change in accelerometer determined Non-Ex PA in overweight and obese middle aged adults.

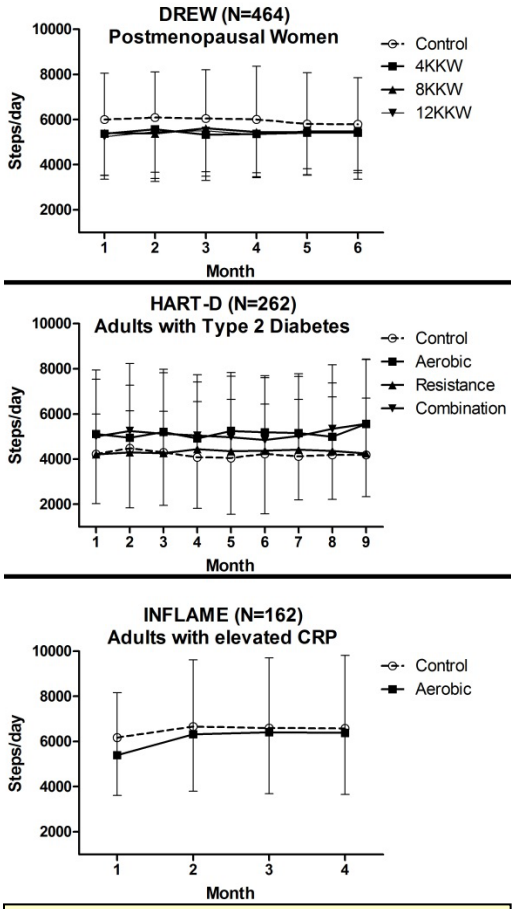

Figure 2. Non-Ex PA defined as steps/day in the DREW, INFLAME, and HART-D trials. **Step counters were not worn during exercise sessions**. KKW: kilocalories per kg per week. Data are expressed as (mean± SD)

1.2 Non-EX PA independent of MVPA (moderate to vigorous physical activity) on CVD risk factors: Non-Ex PA is likely performed for the most part below a moderate to vigorous intensity, but contributes to total energy expenditure. Epidemiological and retrospective analyses from prospective training studies suggest that high Non-Ex PA has clinical value in promoting lower weight, waist circumference and other CVD risk factors.

1.3 Epidemiological evidence: Several epidemiological studies have demonstrated that physical activity below the threshold of MVPA can have a beneficial effect on CVD risk factors independent of the amount of MVPA. Specifically, Camhi et al. [19] using NHANES data observed that accelerometer determined lifestyle physical activity (760-2,019 counts/ minute) decreased the odds of low HDL, high triglycerides, elevated blood pressure, high fasting glucose, waist circumference, and the presence of the metabolic syndrome or type 2 diabetes independent of MVPA (>2,020 counts/minute). Healy et al. [20] found that higher amounts of accelerometer determined "light intensity physical activity" (100-1,952 counts) was associated with lower 2-hour plasma glucose levels independent of MVPA (≥ 1,952 counts). Similarly, Healey et al. [21], in a different study, found that even in adults meeting physical activity recommendations, significant dose-response associations were observed for higher waist circumference, 2- hour plasma glucose and systolic blood pressure with higher television viewing time. The authors hypothesized that the cardiometabolic consequences of high television viewing time could be due to the displacement of light intensity physical activity [21].

2. Preliminary studies:

Non-Ex PA and Exercise Training: Little data exist evaluating the effect of different amounts of Non-Ex PA on anthropometric or CVD risk factors in adults participating in aerobic training. Di Blasio et al. [22] found that postmenopausal women who decreased Non-Ex PA outside of training did not have beneficial improvements in plasma low density lipoprotein and triglyceride levels compared to those that maintained or increased Non-Ex PA. Our laboratory conducted the Dose Response to Exercise in Women (DREW) study, which investigated the effects of 6 months of aerobic training at levels consistent with public health recommendations, and 50% below or 50% above those recommendations on cardiorespiratory fitness in postmenopausal women. The DREW study used pedometers to quantify the amount of Non-Ex PA outside of

exercise training [23]. Postmenopausal women with the highest amount of Non-Ex PA, while also participating in aerobic training had greater reductions in waist circumference compared to those in the lowest tertile of Non-Ex PA at all three doses of exercise training (4, 8 and 12 KKW) (Figure 3). Aerobic training with high Non-Ex PA was also associated with modest weight loss (when all exercise groups were combined and statistical models were adjusted for exercise training dose) [24]. Higher Non-Ex PA with exercise training did not provide additional beneficial effects for the change in fitness, systolic or diastolic blood pressure. Although, we investigated women who **self-selected** to levels of Non-Ex PA outside of training sessions, our data does suggest that an intervention composed of aerobic training and increasing levels of Non-Ex PA may accelerate the improvements in waist circumference. This may have greater effects on adiposity and other CVD risk factors when Non-Ex PA is **increased** along with aerobic training.

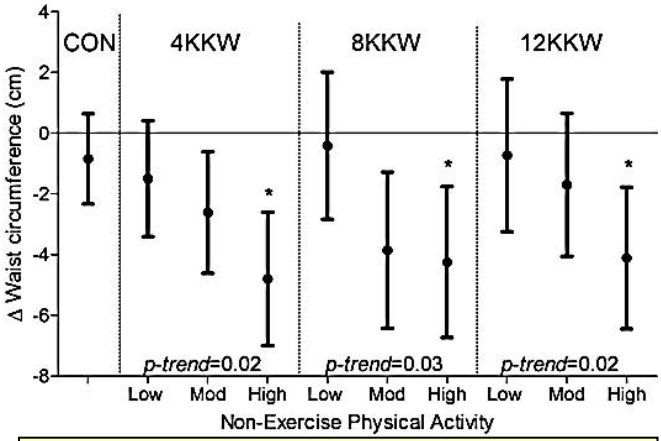

Figure 3. Swift et al. *American Journal of Preventive Medicine.* 2012. Change in waist circumference in the DREW study stratified by amount of Non-Ex PA in the 4, 8 and 12KKW

3. Research Design and Methods

3.1 Innovation:

The Intervention Composed of Aerobic Training and Non-Exercise Physical Activity study (I-CAN) study will evaluate for the first time a physical activity intervention composed of **structured aerobic exercise training along with a strong emphasis on increasing the amount of physical activity outside of training on waist circumference, weight and other cardiovascular risk factors training against the standard prescription of aerobic training alone.** To date, exercise training studies primarily focus on adherence to aerobic exercise and instruct participants not to alter Non-Ex PA. While studies following this model have established effectiveness in promoting favorable changes in CVD risk factors, the I-CAN study will attempt to optimize these benefits by also increasing the amount Non-Ex PA (defined as steps/day outside of training) through the use of pedometers along with structured aerobic training. The design of I-CAN is composed of several innovative features including: strict monitoring of Non-Ex PA throughout the entire 6 month intervention, behavioral support (both web-based and in-person), goals for progressively increasing Non-Ex PA with aerobic exercise training, and an equivalent dose of aerobic exercise training (designed to be consistent with public health recommendations) in the exercise groups. This could represent a practical and clinically effective approach for clinicians and trainers to further increase total energy expenditure in the treatment of obese patients. However, pilot data supporting the efficacy and feasibility of this intervention is necessary prior to implementation in a large randomized trial.

3.2 Approach:

The target study population of the **I-CAN** study will be sedentary obese men and women (BMI: 30-40 kg/m^2, age 40-65 yrs). We will randomize participants to aerobic training (AERO, N=15), aerobic training and increasing Non-Ex PA (AERO-PA, N=15) group or a non-exercise control group (CON, N=15) for 6 months (24 weeks). Participants in the AERO or AERO PA groups will participate in the same structured aerobic training program 3 times per week in a laboratory setting, and wear pedometers during the entire 6 month intervention (except during structured aerobic training sessions). The AERO-PA group, in addition to aerobic training, will increase Non-Ex PA progressively from 1,000 to 3,000 steps/day above baseline from week 6

to week 24 of the intervention. The CON group will continue their current physical activity habits during the intervention. **The primary outcome measure of I-CAN is the change in waist circumference following the intervention.** Secondary measures include change in fitness, body weight, body composition (fat and lean mass), pedometer determined steps/day of Non-Ex PA during the intervention, accelerometer-determined physical activity, fasting glucose, fasting insulin and homeostatic model of insulin resistance (HOMA-IR).

3.3 Inclusion/Exclusion Criteria: The inclusion/exclusion criteria are summarized in Table 1. The goal of the I-CAN study is to recruit adults with moderate to high CVD risk that can safely perform the supervised aerobic training in our facility. In addition, all participants must have sufficient health to increase Non-Ex PA in their daily lives, as this will not be directly supervised by study staff. Therefore, we will recruit sedentary obese men and women (age: 40-65) with elevated waist circumference (women: ≥88 cm, men: ≥102 cm), and at least one additional CVD risk factor. Individuals with type 2 diabetes and known cardiovascular disease will be excluded due to the pilot nature of this trial, and the necessity to establish the efficacy of this intervention prior its utilization in a higher risk study population.

Table 1. Summary of the Inclusion/Exclusion Criteria

Inclusion Criteria for Study Participation	
Age	40-65 years of age
Sex	Men and women
Non-exercisers and sedentary/low active lifestyle	Not currently participating in aerobic or resistance exercise ≥ 20 minutes on ≥3 days per week for the last 6 months. Pedometer determined objective measurement of physical activity ≤ 6,500 step/day
One or more of the following CVD risk factors	Triglycerides (TG) ≥ 150 mg/dL [25], HDL-C< 50 mg/dL, Blood pressure: systolic ≥130 mmHG and diastolic ≥ 85 mmHg or the use of BP medication, Fasting glucose: 100-125 mg/dL (type 2 diabetes is exclusionary), LDL-C≥130 mg/dL, or currently taking cholesterol lowering medications
Abdominal obesity/BMI	Waist circumference ≥ 88 cm (women), ≥ 102 cm (men) [25]; BMI: 30-40 kg/m^2
Informed Consent	The capability and willingness to give written informed consent, to understand the exclusion criteria
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 with intermittent claudication, acute, chronic or recurrent thrombophlebitis or myocardial infarction
Diabetes	Diagnosis or taking medication for type 1 or 2 diabetes and/or fasting glucose>125 mg/dL
Resting blood pressure	Systolic blood pressure >180 and diastolic blood pressure >100 [26]. Participants currently taking blood pressure medication (except for diuretics) can enroll in the present study
Blood lipids	Total cholesterol ≥ 240 mg/dL, LDL-C ≥ 160 mg/dl or TG levels ≥300 mg/dl. Cholesterol medications are permitted.
Other significant medical conditions	Including but not limited to chronic or recurrent respiratory, gastrointestinal, neuromuscular, neurological, HIV or psychiatric conditions. Hospitalization for mental illness within the past 5 years or Musculoskeletal problems interfering with exercise. Autoimmune or

	collagen vascular diseases. Other medical conditions which is life-threatening or can be aggravated by exercise training
Other exclusions	Plan to be away from Pitt County area more than 2 weeks in the next 3 months. Currently or plans to become pregnant. Currently or plans to engage in dieting or a weight loss program. No home access to internet. Previous bariatric or gastric banding surgery, or weight loss medications. Non-compliance during screening in wearing pedometers or failure to document physical activity levels in the study online database.

3.4 Primary Outcome- Waist Circumference: We have selected waist circumference as the primary outcome measure of the I-CAN study for the following reasons:1) Elevated waist circumference is associated with CVD risk factors [27], represents one of the components of the metabolic syndrome [25], and has incremental value in predicting CVD, diabetes and mortality risk over and above BMI. [28] 2) Waist circumference can be feasibly evaluated in the clinical setting, which has relevance to clinicians (e.g. physicians, personal trainers, nutritionists) working with obese adults. We considered visceral fat mass by MRI as the primary measure, however, the increased burden to participants, high costs, and the fact that it is not measured in the clinical setting lead us to the decision that it was not appropriate for this pilot trial, especially since we will obtain measurements of trunk fat mass through DEXA; 3) Our retrospective published data [24, 29] demonstrating that high Non-Ex PA with aerobic training resulted in greater reductions in waist circumference compared to low Non-Ex PA.

Measurement of waist circumference: We will utilize standard operating procedures (SOPs) for assessment measures including waist circumference. Staff are tested and certified annually on the correct measurement technique. Participants will stand in a straight, upright position with the feet together with arms at thier side. Waist circumference will be measured at the natural waist (midway between the inferior border of the rib cage and the superior aspect of the iliac crest) with a Gulick tape measure. Both landmarks (the inferior border of the ribcage and the superior aspect of the iliac crest) will be marked and the distance will be measured to determine the appropriate measurement site. Staff will confirm that: 1) the measurement tape remains horizontal; 2) the tape touches the entire circumference of the participant; 3) abdominal tissue is not compressed; 3) the tape measure is not within abdominal folds; 4) the measurement is taken at the end of normal respiration. The measurement will be repeated an additional time, and the reported value will be the average of these measurements. Both measurements must be within 0.5 cm to be considered acceptable for data purposes. A third measurement is required if values are > 0.5 cm. Waist circumference will be evaluated at baseline, mid-intervention, and at follow-up.

3.5 Secondary measures: Secondary measures include: change in fitness, body weight, body composition, pedometer determined Non-Ex PA during the intervention, accelerometer determined physical activity levels, fasting glucose, fasting insulin and HOMA-IR.

Anthropometric & Dual Energy X-ray Absorptiometry (DXA): Height will be measured at screening. Body weight will be evaluated using a calibrated scale (recorded to the nearest 1/10 of a kg), with the participant fasted and wearing only a hospital gown. DXA will be used to measure body composition (fat and lean mass).

Accelerometry: At each major assessment point, participants will wear the GT3X+ accelerometer (ActiGraph, LLC, Pensacola, Florida, USA) at their waist for seven consecutive days, 24-hrs/day. We have successfully used this 24-hour protocol in adults and find that it maximizes wear time. This accelerometer has been validated [30, 31] and is one of the most widely used accelerometers in research and has the capability of detecting minute-by-minute

steps (steps/min, which can be totaled to obtain steps/day) and physical activity intensity using previously validated activity count cut points [31]. More recently, it has been used to estimate time in sedentary behaviors as time spent at < 100 activity counts/min [32].

Maximal Exercise test: Testing will be performed on a treadmill (Trackmaster 425, Carefusion, Newton Kansas) using a modified Balke protocol to determine maximal oxygen consumption (VO_2 max), and the correct heart rate range for aerobic exercise training (50% to 75% of VO_2 max). Participants will walk at an initial speed of 2.0 mph with 0% grade for the first 3 minutes after which the treadmill speed will increase to 3.0 mph for the next 2 minutes. The treadmill grade will be increased by 2.5% every 2 minutes 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).

Pedometer: Pedometers will be used to determine sedentary status during screening (over the course of 7 days), and to measure Non-Ex PA during the intervention. We have selected the Lifecorder PLUS (New-Lifestyles, Lees Summit, Mo), which has a feature that does not allow the participant to see the amount of steps walked on the pedometer's display (blind display mode). This feature is ideal for the determination of sedentary status during screening, and monitoring Non Ex-PA in the CON and AERO groups. Non-Ex PA data will be downloaded directly from pedometers for data purposes. We elected to use pedometers for monitoring Non-Ex PA because accelerometers are rarely used in clinical practice. In addition, pedometers allow direct feed-back (i.e. steps/day) to participants about Non-Ex PA levels.

Tracking dietary changes: We will utilize the Food Frequency Questionnaire (FFQ) originally developed by Drs. Gladys Block and Linda Harlan, often referred to as the "Block FFQ" [33]. This questionnaire collects information about eating habits over a 12-month period. The FFQ contains approximately 105 items grouped by categories and is completed for both frequency of consumption as well as portion size selections by the individual. The questionnaire, upon completion, provides estimated daily intake values for selected nutrients (kilocalories, macronutrients, and micronutrients) and provides information on food group servings. **All participants will be instructed and reminded regularly not to alter dietary habits or engage in purposeful dieting during the intervention.**

Blood sample collection: Trained personnel will obtain fasting venous blood samples from the antecubital site with participants in a seated position. Either 21 or 23 gauge needles will be used, depending on vascular access. Standard OSHA guidelines will be followed at all times. At baseline and follow-up, a total of 20 mL of blood will be drawn. Of this, 10 mL will be immediately sent to the Clinical Laboratory for lipid assessment, insulin and blood chemistries. Lipids and other biochemical measures will be made using standard analytic techniques. The remaining 10 mL sample will be centrifuged under refrigerated conditions, and the supernatant will be extracted, and divided into 1 mL portions. Vials of plasma (3-4), serum (2-3), and red blood cells (2-3) will be stored at -80°C for future analysis.

3.6 Recruitment and Pre-Screening: Study personnel will screen interested individuals over the phone based on the inclusion/exclusion criteria. Eligible individuals will be invited to attend an **orientation session**, during which study personnel will provide a presentation with detailed information about the study (structure of the study, study-related procedures, risks, benefits, etc.). Individuals interested in I-CAN following this orientation session will be consented at this time, and scheduled for run-in visits.

Run-in visits: The run-in period will last for two weeks in order to: 1) verify sedentary status (pedometry) and screen for other inclusion/exclusion criteria (e.g. BMI, waist circumference, blood pressure); and 2) ensure participants are able to make the time commitment to come to

to training sessions. In our past training studies, this run-in period has helped to obtain excellent training adherence by allowing potential participants to thoroughly evaluate their ability to commit to the time demands of a study. To simulate participation in the actual I-CAN intervention, run-ins will be scheduled 3 sessions per week over the course of two weeks, and duration will be similar to that of training sessions (~1 hour). During run-ins, participants will wear pedometers for 7 days, and enter information about self-monitoring into the study website (using RED Cap, described in detail below). Participants will confirm they wore the pedometer at the beginning of the day, and notate the extent of non-wear time (Figure 4). Pedometers will be worn in "blind display mode", so the amount of steps accumulated throughout the day will not be seen by the participant. We will ask participants to employ methods to remember to wear the pedometer at the beginning of the day (placing reminders on calendars or smart phones, placing pedometer on clothes to wear). On the last run-in session, participants will meet with a trained interviewer who will use a semi-structured barriers interview, to evaluate for any major barriers to study participation or completion.

Run-in:

Information collected:

- Did you wear the pedometer today (yes/No)
- Were there any periods of time where pedometer was not worn (Yes/No)
- If so, please provide an estimate of the approximate time:_____
- Further comments:_____

Figure 4. Web-based questions to determine pedometers compliance.

Pedometer compliance tracking: We will utilize RED Cap ™, a secure online research database to: 1) track and monitor participant compliance wearing pedometers; and 2) record Non-Ex PA at run-in and during the intervention. Participants will be provided a unique name/password to log on to the study website. The use of RED Cap ™ will allow our staff to monitor participant compliance throughout the trial in real-time. Our research team is successfully using RED Cap ™ in two on-going prospective physical activity trials.

3.7 Clinical Visits (baseline, mid-intervention, and follow-up): We will obtain primary (waist circumference) and secondary outcome measures (DEXA, fitness, blood measures) at both baseline and follow-up (summarized in Figure 5). Pre-menopausal women will be asked to take a pregnancy test. A physician or a physician's assistant will obtain a medical history and perform a brief medical exam. **All clinic staff measuring outcome measures will blinded to participant randomization.** At mid-intervention (week 12), we will measure waist circumference, weight, FFQ, and accelerometry. The CON group will be scheduled for mid-intervention and follow-up visits, and will be instructed not to alter physical activity habits during the intervention. All groups will be instructed not to alter dietary habits during the study.

Phone-screen	Orientation and Run-in	Clinic Evaluation (baseline, mid-intervention and follow-up)

Screen for inclusion/exclusion criteria:
• Age (40-65 yrs)
• BMI (30-40)
• Diabetes (No)
• Heart disease (No)
• Stroke (No)
• Currently exercising (No)
• Height/weight
• Other information:
  • Ethnic identification
  • Contact information
  • Medication list
	Orientation:
	• Information session about study
	• Obtain informed consent for screening and run-in visits
	Run-in:
	• 6 run sessions over 2 weeks to test participants ability to come to PBRC 3 times per week
	• Informed consent for baseline evaluation
	• Verify inclusion criteria (ie: baseline physical activity, waist circumference, blood pressure).
	• Log compliance wearing pedometers using the RED CAP ™ systemBlood draw:
	• Lipids, CBC, chemistry panel, insulin
	• Intervention interview
		• **Clinic Evaluation**
		• Physical/review of medical history
		• Blood pressure
		• Anthropometry
		• DEXA
		• Treadmill exercise test
		• FFQ
		At baseline: Informed consent for randomization
		Randomize to the CON, AERO, or AERO-PA group
		Mid-intervention: FFQ, weight and waist circumference, accelerometry
		At follow-up: Exit interview

Figure 5. Study Flow

3.8 Exercise Training Intervention: Participants will participate in structured aerobic training 3 times a week at a heart rate associated with 50-

75% of VO_2peak. All exercise training will occur on a treadmill (or a stationary bicycle only when necessary). Participants will wear heart rate monitors during exercise sessions. The speed and grade of the treadmill will be adjusted in order to keep participants within their heart rate range. Using standard ACSM equations [34], and adjust the length of each exercise session to meet the daily caloric goal based on the speed, grade of the treadmill, and participants' weight [35]. The caloric goal of each session will be calculated by dividing the weekly caloric expenditure goal by the participant's exercise frequency (i.e. 3 times per week). **Study staff will confirm that pedometers measuring Non-Ex PA are removed prior to beginning aerobic training sessions**. Since individuals in both groups will participate in aerobic exercise training in the same room, they will be reminded frequently not to discuss group assignment with each other.

Exercise training dose and progression: Exercise dose (expressed in KKW: kilocalories per kg per week) during aerobic training will be the same in both the AERO and AERO-PA groups. During the first month of the study, both groups will participate solely in structured aerobic training with no intervention on Non-Ex PA (to allow acclimation to aerobic training). Participants in both exercise groups (AERO, AERO-PA) will expend 8KKW in week 1, 10KKW in week 2 and 12 KKW in week 3. We have selected 12 KKW as the selected energy expenditure for aerobic training because, based on our calculations, it most closely represents the current recommendations of 150 minutes per week of moderate physical activity [1]. We have utilized the 12KKW dose successfully in two completed exercise training trials [4, 5]. Thus, the amount of exercise training should be reasonable for participants to perform. For example, at a speed of 3.2 MPH and 2.5% grade, the estimated session time would be approximately 50 minutes for a participant exercising 3 days per week.

3.9 Non EX-PA: Our research team has monitored Non-Ex PA successfully in several previous exercise studies[4, 5, 7]. For the AERO-PA group, we will average the amount of Non-Ex PA from week 4 to week 6 (when participants are at the full prescription for exercise training [12KKW]) to determine **the baseline level of Non-Ex PA with exercise training (Figure 6)**. At week 6 of intervention, the AERO-PA group will begin to incrementally increase their Non-Ex PA by an average of 1,000 steps/day above baseline for the first two weeks. Participants will continue to increase Non-Ex PA by at least an average of 500 steps/day every 2 weeks until they reach an average of 3,000 steps/day above baseline (week 14) for the remainder of the intervention. We have selected 3,000 steps as the maximum goal for Non-Ex PA based on data evaluating the increase in steps from pedometry-based interventions with similar study populations/design. These studies suggest that an increase of 2,000-4,000 steps/day is feasible [36-38]. We elected to utilize a progressive increase in Non-Ex PA to allow participants adequate time to determine behavioral strategies to reach Non-Ex PA goals, and to become acclimated to the higher amounts of total physical activity. The investigative team will not impose any restrictions on how this increase in Non-Ex PA is achieved, with the exception that it is not performed specifically as additional aerobic

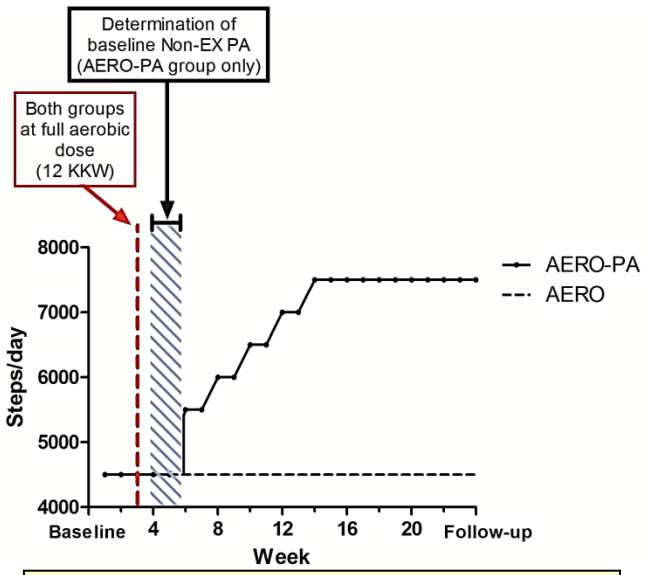

Figure 6. Non-Ex PA in the AERO and AERO-PA group in a participant walking 4,500 steps/day at baseline

exercise training (i.e. treadmill for 30 minutes). Moderate physical activity consistent with daily living (i.e. leisurely walking in the evening, walking the dog etc.) will be permitted. Participants will be instructed to take a "recuperation day" once every week, where Non-Ex PA will be tracked, but not intervened on for the purposes of the study. We believe that a weekly recuperation day will lessen the total participant burden, and allow adequate recovery time.

Lifestyle counseling to increase Non-Ex PA in AERO-PA group: The AERO-PA group will receive lifestyle counseling to help them obtain the required amount of Non-Ex PA. Participants will meet with study staff (~15 mins) once a week (from week 6-10), and every two weeks thereafter. Specific strategies to increases Non-Ex PA will be tailored to each participant (occupational strategies, home strategies, etc.). Lifestyle counseling for the AERO-PA group will occur before or after exercise training sessions, and all sessions will be conducted in a private room to avoid potential contamination with the AERO group. Examples of strategies to increase Non-Ex PA include walking around the house during commercial breaks while watching television, talking on a cell phone while walking instead of sitting, parking car farther away from workplace. The intervention is grounded in the principles of social learning and behavior change theories. Counselors will utilize motivational interviewing and enhancement for participants whose motivation decreases during the study. Behavioral strategies to foster adherence to Non-Ex PA goals include stimulus control, behavioral contracting, problem solving training, and selective reinforcement of target behaviors.

Plan for Tracking and Monitoring Non Ex-PA: Similar to run-in visits, during the intervention, we will utilize the study website (RED Cap ™ database) to monitor compliance. The AERO group will monitor Non-Ex PA in the same manner as during the run-in period throughout the intervention. In the AERO-PA group only, we will obtain self-reported steps data as a cognitive behavioral tool as well to monitor Non-Ex PA in real-time by study staff. From week 6 to the end of intervention, the AERO-PA group will input the amount of steps completed at the conclusion of the day (or within at least 72 hours of completion), whether they wore their pedometer as instructed, whether this day was a recuperation day, and any comments about Non-Ex PA (Figure 7). Non-Ex PA compliance will be defined as the amount of total days wearing the pedometer versus total amount of days in the study intervention. Adherence will be defined as total amount of steps obtained versus total amount of steps prescribed. **Non-Ex PA values will also be downloaded directly from pedometers in order to obtain objective measures of steps/day in all participants.**

Intervention (week 6-week 24)

AERO Group:

Information collected:

- Did you wear the pedometer today (yes/No)
- Were there any periods of time where pedometer was not worn (Yes/No)
- If so, please provide an estimate of the approximate time:_____
- Further comments:_____

AERO-PA Group:

Information collected:

- Total amount of steps
- Recuperation day (Yes/No)
- Did you wear the pedometer today (yes/No)
- Were there any periods of time where pedometer was not worn (Yes/No)
- If so, please provide an estimate of the approximate time:_____
- Further comments:____
- Require assistance from I-CAN staff (Yes/No)

Displayed info for participant: Number of steps left, current steps per week, recuperation days left

Figure 7. Web-based pedometer compliance questions in the AERO and AERO-PA groups

Control (CON) Group: As stated earlier, participants randomized to the CON group will be instructed not to change their physical activity habits during the study, but will participate in all assessment visits (i.e. mid-intervention, following-up testing). Non-Ex PA will also be measured in the CON group as participants will wear pedometers during the 6 month invention in "blind mode" and enter information into the RED Cap ™ database online (in the same manner as screening). In addition, participants will come in once a month to Pennington to confirm no changes in sedentary status, download pedometer data (Lifecorder Plus has a 60 day memory), and address any issues with participant compliance.

Adherence plan: We will actively monitor adherence and compliance of exercise training using EDIN (exercise training data base) and Non-Ex PA using RED Cap™. We will review these data regularly during the intervention, and I-CAN staff meetings (bi-weekly). We will also employ several strategies to promote adherence to the study such as certificates for excellent adherence, raffles for incentive items (e.g. mug, tee-shirt), and regular adherence reports to help motivate participants. In the case of non-adherence, every ethical research-based strategy will be used to prevent participant drop-out, and continued non-adherence to the protocol. We have identified signs of poor adherence from previous training studies (i.e. lack of attendance without rescheduling, not meeting protocol goals), and have developed standardized responses by study staff. In the case of a non-adherence, a "case manager" will develop an adherence plan, and work with the participant on a one-on-one basis.

3.10 Justification of study groups: Similar to pharmalogical trials, in order for the physical activity intervention used in I-CAN (AERO-PA group) to be incorporated in common practice, it must be more clinically effective compared to the current standard treatment. The current standard (or recommendation) for aerobic exercise is obtaining at least 150 minutes of moderate physical activity. Thus, the I-CAN study will determine the extent of the additional clinical benefits of increasing Non-Ex PA with aerobic exercise training.

3.11 Statistical Considerations: The results of the present pilot trial will be used to inform the design (effect size/statistical power) of a larger prospective intervention (to be developed into a future R01 application). Baseline participant characteristics (e.g., age sex, race, weight, BMI, waist circumference, % body fat, fat mass, lean mass, cholesterol, triglycerides, blood pressures) will be summarized by group (CON, AERO, and AERO-PA) as counts and percentages for categorical variables, and means and 95% confidence intervals or medians and IQRs for continuous variables. Adherence to protocol assessments (e.g., daily steps, minutes spent in very low activity, aerobic sessions/week, percent of peak VO_2, MET levels) will be summarized similarly by week for each intervention. On study change in peak VO_2, estimated METs, weight, waist circumference, cholesterol, triglycerides, and blood pressures will be summarized in an intention-to-treat analysis of (1) all participants and (2) the subset of participants who achieve a high level of adherence to protocol. Linear models will provide the primary framework for significance testing. Statistical significance of differential longitudinal changes in response to interventions will be assessed employing repeated measures mixed effects models with maximum likelihood estimation and Kenward-Rogers adjustment to the degrees of freedom in an intention-to-treat analysis of (1) and (2) for each outcome using all available data. The two interventions, measurement times (e.g., baseline, mid-intervention, study exit), race, sex and interactions will be taken as fixed effects; participants within groups will be considered as having random effects. Other covariates such as age and baseline assessments will be included in preliminary models and retained in final analytical models if warranted. The model covariance structure (e.g.: unstructured, compound symmetric, auto-regressive) across time will be investigated to enhance efficiency of statistical tests. Results for each outcome will be summarized as least squares means and 95% confidence intervals for each intervention across the assessment times (repeated measures). Model residuals will be tested to see if they have distributions that are approximately Gaussian and data transformations will be performed if needed. Group differences in baseline characteristics will be tested and corrective steps taken, such as post-stratification and adding model covariates as necessary. Linear contrasts on least squares means will be used to test differential mean changes in each outcome from baseline to subsequent assessment times between the two intervention groups. Null hypotheses will be tested against two-directional alternatives at the

nominal 0.05 significance level using Bonferroni adjusted p-values when appropriate. All statistical analyses will be performed using statistical software in SAS version 9.3.

3.12 Limitations and Strengths: A limitation of the project is the small sample size. However, we feel this is appropriate due to the pilot nature of the trial. In addition, the results of I-CAN will be used to determine the effect size and to power a larger randomized trial (as an R01 application) with more cardiovascular/diabetes-related outcomes. Another limitation is that we are not measuring total energy expenditure through doubly labeled water (DLW). Due to the high cost of DLW (each participant: $750, total study costs [baseline and follow-up] = $67,500), it is not feasible for this pilot project. However, we will incorporate DLW measurements when this study is developed into a larger randomized trial. The strengths of I-CAN are that it is a practical physical activity intervention, the core principles of which (i.e. aerobic training and attainment of high Non-Ex PA) are feasible in clinical, exercise training and public health settings. We have designed our aerobic training intervention to be consistent with public health recommendations. I-CAN will be the first training study to our knowledge with such a strong focus on the measurement of Non-Ex PA (adherence and tracking plan, pedometers [blind mode capable], and the use of internet databases to monitoring Non-Ex PA and support behavior modification) throughout the entire exercise intervention. Results of this pilot project, and the subsequent large randomized controlled trial could have implications for future public health recommendations, and other populations with co-morbid low physical activity and obesity (e.g. adults with cardiovascular disease or type 2 diabetes).

4. Ethical aspects of the proposed research: Ethical research practices will be strictly adhered to during the implementation of the present study, inclusive of the safety of human participants and safeguarding protected health information. The aspects of this study that carry the greatest safety risks are the exercise training and exercise testing components. All members of the investigative team are required to complete Collaborative Institutional Training Initiative (CITI), and all staff monitoring the exercise intervention and performing the exercise testing will be CPR/AED certified. The PI will oversee all aspects of this trial, and will ensure that I-CAN is implemented in an ethical manner.

Timeline of the I-CAN study	**Year 1**				**Year 2**				**Year 3**				**Year 4**			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
IRB approval, MOP development, training																
Recruitment and screening																
Baseline testing																
Follow-up testing																
Data cleaning & management																
Data analysis																

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