Exercise Time of Day for Cardiometabolic Health in Prediabetes and Type 2 Diabetes

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CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Exercise time of day for cardiometabolic health in prediabetes and type 2 diabetes

Principal Investigator: Steven K. Malin, PhD

Study Summary: This consent form is part of an informed consent process for a research study, and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not. Overall, the purpose of this study is to test exercise time of day effects in adults with either prediabetes and/or type 2 diabetes on weight regulation and glycemic control for cardiovascular health. While some work suggests people who exercise in the afternoon may see greater improvements in cardiometabolic health, other research suggests morning exercise improves body weight regulation. Additional work is needed to understand the influence of exercise time of day on health to improve medical care. People will be asked to visit Rutgers University about 17 times. Nearly 12 of these visits are for supervised exercise training. Before and after the intervention, metabolic and vascular health will be assessed primarily in the Clinical Research Center (CRC) at Robert Wood Jonson Medical School. Visits will range from approximately 1 to 6 hours to perform a 1) screening, 2) test of aerobic fitness and body composition, and 3) glucose tolerance test with blood flow to see how the body handles delivery and clearing glucose from the blood. Tests performed before the intervention will be repeated afterwards. People will be randomized to these treatments (e.g. flipping a coin). There are no direct benefits for participating in this study and your alternative to taking part in the research study is to not participate.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, should you choose to take part, you should feel free to ask them and should expect to be given answers that you completely understand. After your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?
Dr. Steven K. Malin, PhD is the Principal Investigator of this research study. The Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Dr. Malin is located at 70 Lipman Dr, Loree Gymnasium New Brunswick NJ 08901 and may be reached at: (848) 932-7054 or steven.malin@rutgers.edu.

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Sponsor of the Study
School of Arts and Sciences at Rutgers University

Why is this study being done?
The number of people with type 2 diabetes has increased dramatically over the last decade and it is now estimated that 30 million people in the U.S. (almost 10% of the population) has the disease. Type 2 diabetes raises your risk for heart disease and other health problems such as stroke, cancer, and dementia. Risk factors are traits, conditions, or habits that increase your chance of developing a disease and can include a large waistline, high levels of fat in the blood, high blood pressure and high fasting blood sugars.

A large study funded by the National Institutes of Health showed that people with type 2 diabetes can improve their blood sugar control, also known as glucose control, by increasing physical activity and/or losing weight. In recent years, circadian rhythm and time of day in which exercise is performed has become an area of interest in understanding how to maximize improve weight loss and cardiometabolic health. However, more research is needed to determine whether exercising in the morning or afternoon promotes greater health adaptations in this population.

The purpose of this study is to determine whether exercise time of day differentially enhances appetite regulation, glycemic control and vascular health. If so, it is possible that individuals can greatly reduce their risk for developing cardiovascular disease by exercising at certain times of the day. Information that is gathered from this study could potentially lead to improved recommendations for treatments that specifically target cardiovascular risk reduction.

Who may take part in this study and who may not?
You are being asked to be in this study because you are a non-smoking adult with either prediabetes or type 2 diabetes. Individuals 30-80 years are eligible with a body mass index (a value comparing an individual's height and weight) of 25-45 kg/m2 who are not currently engaged in > 90 minutes a week of exercise may participate. Following blood work to confirm having either prediabetes or type 2 diabetes and no kidney/liver disease, people will be required to have at least high blood sugar. People taking insulin, who have lost or gained weight recently, have history of significant disease (e.g. congestive heart failure, cancer, etc.), on weight suppression medication or known hypersensitivity to perflutren are not eligible for safety reasons.

Why have I been asked to take part in this study?
Your participation in this study is voluntary and you are not obligated to participate. We are recruiting participants through flyers and people eligible are encouraged to inquire about the study. Subjects who call the inquiry phone number at (848) 932-7059 will reach the study team. At the time of the phone call, researchers will record your name and contact information (telephone number and/or email address). During the inquiry call, you and the researcher will determine a time for screening visit to discuss study eligibility and informed consent. At the time of your inquiry call, the team researcher will record your name and contact information on paper and keep this information in a locked file cabinet in the lab office.

How long will the study take and how many subjects will take part?
Your participation in this study will require about **17** study visits over about 2 weeks. Each visit will last between **1-6** hours depending on whether it is for research purposes (e.g. about 3-6 hours) or exercise training (e.g. 1-1.5 hours). There are 2 Screening Visits and 3 Test Visits. We can split up some the visits, if need be, for convenience. Thus, the majority of visits include exercise training (10-12 visits).

Up to **40** people will be in this study.

What will I be asked to do if I take part in this study?
Note: All assessments outlined in this consent are being done for research purposes only. In light of COVID-19, we will follow routine safety checks per University guidelines until otherwise deemed unnecessary. These checks will be implemented at time of in person visits and consist of: temperature check and questions related to exposure yourself or to others with COVID-19. Face masks should also be worn unless otherwise indicated.

PHASE 1: SCREENING AND TESTING PROCEDURE
*Note: Portions of screening visits 1 and 2 can be combined to ease your burden and number of visits.

Screening Visit 1 at the Clinical Research Center (CRC) or Institute for Food, Nutrition and Health (IFNH) (Day 1) (will last about 1- 2 hours)

Prior to signing this consent, you were contacted by a member of the study following your interest in this study. If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. You are to be fasted (nothing to eat or drink after midnight) for blood work. These include the following:

- Health history and Physical Activity Readiness Questionnaire (PAR-Q) that will take about 30 minutes to complete.
- Vital signs (blood pressure, heart rate)
- Your height, weight, and waist circumference will be measured.
- Blood draw will also be performed for laboratory testing.
- Your body mass index (BMI) will then be calculated. It must be between 25-45 kg/m^2 for you to be able to continue in this study.
- Resting electrocardiogram (ECG) to see the electrical activity of your heart will be done as well as assessment of vital signs (blood pressure, heart rate).

We will also measure your resting metabolic rate, a measure of the amount of energy it takes to burn calories. While laying down you will wear a canopy (cover) that is connected to a special device (metabolic cart) that measures your exhaled carbon dioxide (CO_2) and oxygen through indirect calorimetry. Indirect calorimetry is a way to measure how your body is using fat and carbohydrates. These measurements are then used to calculate the number of calories you burn to determine food needs.**PLEASE NOTE:** Your continued participation in the study after this point will depend on the results of the vital signs and confirmation of diabetes status. Further, if you are a woman who is able to have a child, you will have a pregnancy test that must be negative in order to participate – this will be determined via urine collected at the screening.

Screening Visit 2 at the Clinical Research Center (CRC) or IFNH or Foran Hall
(will last about 1-2 hours)

IMPORTANT: You must fast (not eat) for 4-10 hours before this visit. During the second screening visit the following assessments will take place at the CRC or IFNH or Foran Hall:

- Review of your medical history
- Resting electrocardiogram (ECG), if not completed during the screening visit.
- Physical exam will be conducted in person or Zoom platform. Zoom calls will not be recorded. If needing to perform Zoom based exams, health information (e.g. age, race, weight, blood pressure, heart rate, allergies, medications, will be shared with the physician electronically through the Rutgers secured email platform without your name. Emails will be sent prior to physician appointment and contact with physician will occur to confirm receipt.
- Resting metabolism test, if not completed during the screening visit.

If you continue to qualify for the study the remainder of the visit will involve the study procedures described below:

A. Body Composition

- You must be fasting for at least 4-10 hours before this procedure.
- Your weight will be measured without shoes and while wearing minimal clothing.
- Your waist and hip circumference ratio will be obtained with a tape measure to determine how much fat is located in the central part of your body.
- We will measure the total amount of fat and muscle in your body with the DXA in Foran Hall. DXA is a machine that uses a very small dose of radiation to create pictures of the inside of your body to look at where fat is located.
- You will be required to wear clothes without metal on them (including zippers and bras with an underwire). If your clothes have metal, we will ask that you change into a pair of shorts and a t-shirt or wear a hospital gown provided by the lab.
    - If there are technical issues with the DXA machine, we will measure the total amount of fat and muscle in your body with the BodPod® in the IFNH. The BodPod® looks like a large white egg and has a window on the door. It analyzes the way air is moved within the machine once an individual is in the device.
    - We will provide a swimsuit and swim cap for you to wear during this procedure to help standardize your results. The swimsuit and swim cap are provided to get accurate results. You will not get wet at any time during this measurement. You will enter the device and sit down. A door will close while you sit in the BodPod®. You are asked to breath normal and be still.

B. Treadmill exercise testing for cardiovascular fitness (i.e. VO2max):

- You will be asked to perform a maximal treadmill or bicycle exercise test in the CRC or the IFNH. The test will begin with low speed on the treadmill or bicycle, and the resistance, or incline will increase gradually every 2 minutes. You will be asked to go as long as you can, that is, until you feel exhausted.
- During the test, you may have continuous electrocardiogram (ECG) heart monitoring and blood pressure monitoring

if you are considered at risk.

- During exercise testing we will also measure your metabolic rate, a measure of the amount of energy it takes to burn calories. During exercise you will wear a facemask that is connected to a special device (metabolic cart) that measures your exhaled carbon dioxide (CO_2) and oxygen through indirect calorimetry. These measurements are then used to calculate the amount of calories you burn.
- During the exercise test, you will wear a mask over your nose and mouth. This allows us to measure how much oxygen you are using and will tell us what your fitness level is.
- The visit ends after you complete the exercise test. You will receive the results of your test after the completion of the study.
- You will also be provided with an **accelerometer** and instructions on how to use the accelerometer after the test. The accelerometer is a small device, similar to a pedometer, which is worn on your belt and records the amount of activity you perform. Data will be downloaded when the device is returned.

C. Physical Activity questionnaire

- *Minnesota Leisure Time Physical Activity:* This is a checklist of 60 physical or recreational activities you may have participated in over the last 12 months. This takes about 10 minutes to complete.

D. Diet logs and appetite questionnaires

- You will fill out a daily record of your eating habits for 3 days at weeks before, during and near the end of the 2 weeks. You will also answer questions that test your response to the food you eat. This takes about 30 minutes to complete.

E. Quality of life questionnaires

- Physical activity enjoyment: We will also provide you with a questionnaire to understand your feelings about the exercise program at weeks 0 and 2. This takes about 5 minutes to complete.
- Sleep History: You will fill out questions to understand sleep patterns throughout the study at weeks 0 and 2. This takes about 5 minutes to complete.
- Morningness-Eveningness questionnaire: You will answer questions about your daily activity at weeks 0 and 2. This will take about 5 minutes.
- Sleep Disorders Symptom Checklist: Subjects will fill out questions to screen for six sleep disorders (insomnia, obstructive sleep apnea, restless legs syndrome/periodic limb movement disorder, circadian rhythm sleep-wake disorders, narcolepsy, and parasomnias) throughout the study. This takes about 5 minutes to complete. Subjects will complete this questionnaire during Week 0 and 2.
- Social engagement questionnaires: You will answer questions about your social activity at weeks 0 and 2. This will take about 10 minutes.
- Veteran Rand-36: You will also complete a series of questions related to stress, anxiety, overall happiness, etc. that will have you think objectively about your quality of life at weeks 0 and 2. This takes about 10 minutes to complete.
- Three Factor Eating: You will answer a series of questions related to emotional and behavioral eating patterns. This will be completed at weeks 0 and 2. This takes about 10 minutes to complete.

PHASE 2: TESTING CONDITIONS AND PROCEDURES

Study test Visits Related to blood work and vascular health.

- While you are in the study you will be asked to maintain your normal activity levels.
- You will be provided standardized meals and snacks the day prior to and during all test visits (listed below) consisting of 55% carbohydrate, 30% fat, 15% protein.
- **You must not drink alcoholic or caffeinated beverages for at least 24 hours before the oral glucose tolerance test (OGTT) study testing visit begins.**
- You must not use allergy, prescription or pain-related medicines (over the counter or prescription) or antioxidant dietary supplements for at least 24 hours prior to each OGTT testing visit. Prescription meds may be taken after testing.
- You must not perform any vigorous exercise (outside of this training study) for 72 hours prior to each test day.
- **The OGTT tests must be performed in the fasted state, so you may not eat or drink anything (except water) after about 9:00 pm the night before.**
- You will be asked to report to the CRC by approximately 6:30-9:00am on the morning of each test.

Pre and Post Study Testing days:

Blood draws:

- In the morning of the pre and post study testing days in the CRC, an IV catheter will be inserted into a vein in either the forearm or hand. An IV is a small flexible tube that is inserted into a vein guided by a needle. Once the tube is in place the needle is removed and replaced with cap that allows blood to be withdrawn or fluids or medications to be given.
- The IV catheter will be in your arm for the remainder of each visit (about 4 hours) and removed before you leave the CRC.
- We draw blood to measure sugars, lipids (fats), and hormones that estimate blood sugar and vessel health.
    - Visits 3 and 14: about 11 tablespoons of blood will be drawn per visit.
    - Additional blood (about ½ tablespoon) may be drawn to verify results of the screening visit at the discretion of the investigator.
- When the blood draws are completed, you will be fed lunch and discharged to go home.

The amount of blood collected pre and post study is approximately half the amount as donating a pint of blood. As a result, you are advised not to donate blood while participating in this study.

Glucose Metabolism test (i.e. blood sugar): Visit 3 and 14

Oral Glucose Tolerance Test (OGTT) (approximately 4.5 hours)

- You will report to the CRC fasted for about 10 hours and participate in an OGTT (oral glucose tolerance test), and we will put an intravenous catheter (IV) into a vein in your arm and obtain baseline blood samples.
- The OGTT is used to help determine how quickly sugar is removed from the blood. After the blood sample is taken for the fasting blood sugar test, you will drink a sugary solution. Five more blood draws will be taken at 30, 60, 90, 120, and 180 minutes after you receive the drink.
- This procedure will also include a measure of blood flow (see below).
- Appetite questionnaires will be provided at 0, 30, 60, 90, and 120 minutes. This will take about 2 minutes to complete.
- You will also have a see-through canopy (cover) over your head before and at the end of the OGTT. This procedure uses the same machine used during exercise in screening visit 2, part B above. This device allows us to measure how much sugar and fat you are using to create energy. Also, by measuring and analyzing the oxygen and carbon dioxide levels in your breath it is possible to estimate if you are storing glucose as glycogen, which is how blood sugar is stored in the body for future energy use.
- You will complete items on the NIH toolbox for related to working/episodic memory, executive function, and attention. The NIH toolbox is an iPad application that consists of cognitive, emotional, motor, and sensory function assessments. This will take about 20 minutes and will be completed prior to consuming the sugary solution.

Urine Collection:

- You will be provided with a plastic container and asked to collect one urine container on visit 3 and 14. The amount and time of your urine collection will be recorded and analyzed for nitrogen, protein and metabolites, which are all substances that are used in your body's metabolism.

Blood flow to be done at Visit 3 and 14:

Blood pressure:

- Your blood pressure will be taken at the beginning of each testing visit. This test takes about 5 minutes.

Large artery flow-mediated dilation (FMD):

- This test allows us to measure the blood flow through your arteries.
- This procedure uses an ultrasound device to measure blood flow in an artery in your upper arm and leg. Ultrasound is a diagnostic procedure that creates a picture image using sound waves. Unlike X-rays, ultrasound does not involve radiation.
- Just prior to the test you will be asked to lie down on a bed quietly for 20 minutes. During this time, you will have your blood pressure taken, and you will be connected to an electrocardiogram (ECG) that will monitor your heart

rate. After the 20 minutes have passed, an ultrasound probe will be lightly pressed against the inside of your upper arm and leg. Images will be taken.

- Next, we will place a blood pressure cuff on your forearm only and pump it up tightly. This portion of the test may cause some discomfort in your forearm and fingers (such as pain, tingling, and numbness).
- We will keep the cuff inflated for 5 minutes, take images, then release it, and measure the increase in blood flow in one of the arteries in your upper arm using the ultrasound probe.
- This procedure takes about 15 minutes. We will perform this procedure just before the glucose beverage during the OGTT, and then again at 1, and 2 hours after you drink the glucose beverage.

Augmentation Index (AI):

- This measures the pulse wave of the vessel and its characteristics that assess the stiffness of the aorta, which is the largest vessel that pumps blood to the rest of your body from the heart. We will use a waveform analysis from SphygmoCor, which is a way to measure the pulse wave of the vessel on a computer.
- This is done by placing a blood pressure cuff on your upper arm. The blood pressure cuff will inflate three different times to capture your brachial waveform.
- This will take about 5 minutes. We will perform this procedure at 0, 60, 120 and 180 minutes of the

Pulse Wave Velocity (PWV):

- This measures the time difference between the pulse wave at the carotid artery (the artery in your neck) and the pulse wave at the femoral artery (the artery in your leg) A blood pressure cuff will be placed on your upper thigh to measure your femoral pulse while we measure your carotid pulse with a doppler pen, which looks similar to a normal pen. This will allow us to assess the “stiffness” of the larger vessels. The shorter the time difference, the stiffer or less elastic the vessels are. When the vessels are more elastic, it means that blood has an easier time traveling through the vessels, which is better for your overall health.
- We will use the same SphygmoCor device as described above for AI.
- This will take about 5 minutes. We will perform this procedure at 0, 60, 120 and 180 minutes of the OGTT.

Contrast Enhanced Ultrasound (CEU):

- This is used to look at muscle and heart blood flow at the microcirculation (or closest part of blood flow to muscle/heart).
- We will infuse the microbubbles (brand name is Definity) that are approved by the FDA for imaging of the microvasculature using similar techniques to FMD described above with ultrasound.
- This will take approximately 10 minutes and will occur at 0 and 60 minutes of the OGTT.

Common carotid artery intima-media thickness (CCA-IMT)

- An ultrasound will be used to measure the level of blood vessel wall thickness, vessel diameter, and blood flow of the inner left carotid (neck) artery.
- Prior to the test you will be asked to lie down on a bed quietly for 15 minutes. We will measure vitals, ECG, and heart rate. Then at about 15-20 minutes, we will use the ultrasound to measure the carotid artery intima-media thickness, diameter, and blood flow in the neck.
- We will perform this procedure before the OGTT

RANDOMIZATION and STUDY PROCEDURES
You will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups. You have an equal chance of being assigned to any one of the groups. Neither you nor your doctor can choose which treatment you are assigned

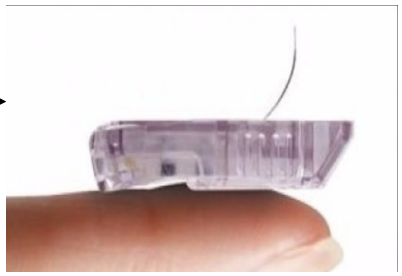
PHASE 3: INTERVENTION PERIOD (Visits 4-13)

Continuous Glucose Monitoring:
Inserting the continuous glucose monitor (CGM) (~30-45 minute lab visit).

- You will be asked to come to Loree Gymnasium, IFNH or CRC for a CGM insertion. CGM is a small device that measures your blood continuously for 24-h. The small CGM sensor will be placed on the skin of your stomach area by a person trained by the CGM manufacturer. The CGM sensor has a small piece that is inserted under your skin with a small needle (less than 1 cm long). The needle is then removed and only the flexible piece remains under your skin. Tape will be placed over the CGM to hold it in place. A picture of the CGM is shown in the figure below. Inserting the CGM should take no more than 5 minutes. During this lab visit you will be given a small booklet containing important information about the CGM. The CGM will be worn for up to 10 days (includes 4 diet days and 5 training sessions, plus 1 rest day). It will be removed at the end of the approximate 10 days. The first 2 days using the CGM you will be asked to eat the provided food and then repeat this diet during the last two days of wearing the CGM (1 exercise and 1 recovery day).

Figure: A continuous glucose monitor.

Note: Only the flexible piece is inserted under the skin. →



You will be provided an accelerometer (see "Screening Visit 2" section B) to wear during the blood pressure monitoring and CGM period during the intervention.

Prior to the intervention you will be randomized (like the flip of a coin) to receive 1 of 2 treatment options. *Note, due to COVID-19 if supervised exercise sessions need to vary for safety reasons, virtual sessions will be established within reason to maintain "supervised" sessions.*

Morning Supervised High-Intensity Exercise: If you are randomly assigned to this group, you will participate in supervised exercise training during the hours of about 7:00AM to 11:00AM. You will be asked to attend 10 total supervised exercise sessions. This will take place with the exercise physiology staff at the Loree Gymnasium or IFNH on Cook-Douglas Campus. Your heart rate will be monitored continuously, and you will be asked to exercise at an intensity near 85% of their previously measured fitness level for 60 minutes. To acclimate you to exercise and foster safety, day 1 of exercise will be 30 minutes at 70-75% VO_2max and day 2 of exercise will be 45 min 75-80% VO_2max. Thereafter, you will exercise at 60 min at 85%

VO_2max for the remainder of the time.

Daily sleeping habits will be tracked via self-reported logs.

Afternoon Supervised High-Intensity Exercise: If you are assigned to this group, you will participate in the same exercise program, but it will take place in the afternoon during the hours of about 4:00PM to 8:00PM.

PHASE 4: POST INTERVENTION TESTING (Visits 14-15)

After the 2 week intervention you will be asked to undergo the following testing that you completed in phase 2. You cannot drink alcohol or take medications/supplements 24 hours prior to testing unless approved by the study team. In addition, you cannot eat or drink foods that contain caffeine 24 hours prior to testing. We also ask that you refrain from any structured exercise for 72 hours prior to testing and limit exercise to your normal everyday activities. All study testing visits highlighted above in Visits 2 and 3 (Body Composition, Fitness, AI, PWV, OGTT, etc.) will be repeated (except physical screening, resting EKG). The order of the tests post-intervention will be:

1. OGTT (Visit 14)
2. Body Composition and Fitness (Visit 15)

*Intervention may be extended or shortened by approximately 1-2 day(s) if scheduling requires to complete visits 16 and 17. Visits may be combined too if timing allows.

END OF STUDY:

After subjects have completed Phase 4, the study will be complete.

Study Screening and Testing Schedule Visit Overview

Study Visit	Screening Visit 1	Screening Visit 2	Pre-Test OGTT Visit 3	Exercise Training (Intervention Period) Visits About 4-13	Post-Intervention OGTT Testing Visit 14-15
Informed Consent	X				
Blood Draw	X		X		X
History and Physical, ECG	X	X (If not collected at screening)			
Urine Collection			X		X
VO2peak (Treadmill testing)		X			X
Body Fat measurement (Waist and Hip circumference, DEXA, or Bod Pod)		X			X
Indirect Calorimetry	X	X (If not collected at screening)	X		X
Exercise* Indirect Calorimetry				X*	
24-hour Blood Glucose			X**	X**	
Blood Pressure, AI, and PWV tests			X		X
FMD, CEU, AND IMT			X		X
Diet Record		X		X	X
Appetite Questions			X	X	X
Quality of Life Questions			X		X
Accelerometer		X		X	
NIH Toolbox			X		X
Heart Rate Monitors				X	

Exercise Training will be performed at Loree Gymnasium or IFNH on Cook-Douglas Campus for 5 consecutive days followed by 1 day off (rest) and then another 5 days of exercise. All exercise will be supervised by an exercise physiologist/research team member. Participants will be asked to either wear a pedometer or use their smart phone to track their step count during exercise.
*** 24-hour glucose will occur before the first day of training. Post-testing for 24 hour glucose will be determined or finished on the rest day. Accelerometers are worn for a total of about 3 weeks (1 week before testing and 2 weeks of training).*

What are the risks of harm or discomforts I might experience if I take part in this study?

Research studies often involve some risks. We will do all we can to prevent bad results for you.

Risks and side effects related to the study procedures include:
Likely

- Fatigue and soreness associated with exercise.
- Soreness associated with the placement of the IV catheter.
- Mild to moderate discomfort (e.g. pain, tingling, and/or numbness) in the forearm and hand during the 5 minutes when the blood pressure cuff is inflated.

Less Likely

- There may be mild skin irritation caused by the application of electrodes for the heart monitor.
- Possible unpleasant reaction to the glucose drink such as nausea or feeling sick to your stomach
- There is an overuse injury risk as a result of exercise resulting in pain of the muscle/tendons in your legs.

Rare but serious risks related to exercise.

- Abnormal blood pressure responses
- Faintness, dizziness, disorders of the heartbeat
- Heart attack, stroke, or even death (the risk of death during or immediately after an exercise test is less than 1 in 10,000). Every effort will be made to minimize risks by observations during each exercise session. Emergency equipment and trained exercise physiologists will be present during the exercise tests.

Blood draw, CGM and Intravenous catheter placement (IV): When a needle is inserted into a vein/skin there will be some temporary pain (common) and possible bruising. Infection is very rare as your skin is cleansed prior to needle insertion and only sterile needles are used. Some people also feel dizzy when they have their blood drawn.

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for: hepatitis, HIV (Human Immunodeficiency Virus), or other infections. You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV, we will tell you how to find counseling. You may want help in understanding what the results mean for you.

ECG: Men may need to have a small amount of chest hair shaved off for the ECG pads to stick correctly. A small amount of adhesive might remain on your skin when the pads are removed, or the adhesive might pull on hair when removed. You can easily remove any remaining adhesive with rubbing alcohol or soap and water.

Urine Collection: There are no risks to collecting urine samples. However, some people may find it uncomfortable or embarrassing to collect samples.

Risk of Saline Flush: Saline works by preventing blood clots from forming in IV catheters when they are not in use. Saline is a salt solution. There are no known risks to saline flush other than mild pain at the injection site.

Study Diet: You may find it difficult to adhere to a special diet for a long period of time. You might have to fight cravings to eat or drink items that are not part of the approved and provided research diet.

Questionnaires: You might find it boring or time-consuming to complete the questionnaires. There is the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential, however, this cannot be guaranteed. Some of the questions we will ask you for this study may make you feel uncomfortable.

Accelerometer: You might find it burdensome, uncomfortable, or unsightly to wear the activity monitor for extended periods of time.

Indirect Calorimetry: For some people, the plastic canopy over their heads/mouthpiece makes them feel claustrophobic or anxious. This feeling is temporary and will go away when the canopy is removed. The canopy is “see through” and does not restrict movement.

Oral Glucose Tolerance Test: You could react to the ingestion of nutrients, namely glucose. These reactions could include nausea, low blood sugar, and an increase in blood pressure, flushing and/or sweating.

Definity Microbubbles: Occasionally you could experience flushing and temporary changes in your taste . Back pain occurs in 1-3% of subjects, although this is uncertain why it happens but resolves within 1-5 min after stopping the microbubble infusion. The infusion will be stopped in anyone noting onset of back pain during the microbubble infusion. There is a potential concern for the microbubbles to disturb the circulation of blood from the heart and lungs. However, the microbubble infusion used here is < 1/600 of that used in studies of myocardial perfusion, which is a test to determine how well blood flows through the heart muscle. Infusion of microbubbles also includes a slight possibility of an anaphylactic reaction (fever, drop in blood pressure, shortness of breath). To avoid this, solutions infused are sterile.

Serious cardiopulmonary and hypersensitivity reactions are rare, but may occur, including fatal heart or respiratory (lungs) attack, shock, loss of conscious, arrhythmias (irregular heart rhythms), hypertension (high blood pressure), convulsions, throat tightness, swelling of the face, eye, upper airway, rash and flushing.

In the event of a medical emergency, study personnel will call the Rutgers Emergency Services line and call the physician on call for immediate assistance.

Exercise: You may find it difficult to adhere to our exercise program for duration of this study. You might also have to fight cravings to eat or drink items that are not part of the approved and provided research diet.

DXA Scan: This study involves radiation exposure from DXA scans of your whole body. As part of everyday living, everyone is exposed to a small amount of background radiation. Background radiation comes from space and naturally occurring radioactive minerals. The radiation dose you will receive in this study will give your body the equivalent of less than 1 days’ worth of this natural radiation. This radiation dose is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. The risk from this dose is considered small. This radiation exposure is not necessary for your medical care but is necessary to obtain the research information desired.

Reproductive Risk: If you become pregnant during the course of this study, you should notify the study doctor of this fact as soon as possible. While there no evidence of birth defect or complications, you will be encouraged to exit the study.

Drug to drug interaction: You should share over-the-counter medicines, herbal products, vitamins, or food supplements prior to starting this study and avoid new drugs unless you tell the study doctor and get permission from the study doctor to go on taking these medicines. You will follow the instructions of the study doctor about the use of any of these products.

You should also tell the study doctor about all medicines that other doctors may have prescribed for you to take.

A caution about giving too much blood:
Because of the amount of blood being taken, you should not give blood for other reasons while in the study. For example, avoid giving blood at a blood bank or in another research study. You should wait 2 months after the study is completed before donating blood at a blood bank.

Unforeseeable risks: There may be risks or side effects related to the study that are unknown at this time. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study. Contact the study manager (Emily Heiston, 848-932-7059; emily.heiston@rutgers.edu) if you have any symptoms or problems.

Are there any benefits to me if I choose to take part in this study?
You may or may not benefit from being in this study. However, some possible benefits to you include: knowledge of fitness, body fat, metabolism, blood sugars and cardiovascular health**.** In addition, information researchers get from this study may help others in the future. Society in general will benefit from greater understanding of the importance of exercise with or without a mobile app for improving vascular function as well as hypertension and glucose control.

What are my alternatives if I do not want to take part in this study?
You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include careful follow-up with your primary care physician.

How will I know if new information is learned that may affect whether I am willing to stay in the study?
During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?
During the study your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time you can ask for more information about the study results. For instance, upon completion you will receive a report detailing your individual results (e.g. body composition, fitness, effects of exercise on post prandial hyperglycemia).

Will there be any cost to me to take Part in this study?
All of the tests outlined this research study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study visit. You will be provided parking costs.

Will I be paid to take part in this study?
You will be compensated $300 for completion of the study, made in one total payment at the end of your time in the study. You will be paid by check. You should get your payments about 4-6 weeks. The income may be reported to the IRS as income.

By agreeing to be in this study, you are donating your blood for research, and giving up any property rights you may have in them. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

How will information about me be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. This includes keeping files in locked cabinets, rooms and using password protected devices. Moreover, you will be provided an ID number that minimizes use of your name to protect privacy/confidentiality.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

A description of this clinical trial will be available on *http:// www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What will happen to my information or biospecimens collected for this research after the study is over?
After information that could identify you has been removed, de-identified information collected for this research may be used by or distributed to investigators for other research without obtaining additional informed consent from you.

What are your responsibilities in the study?
You have certain responsibilities to help ensure your safety, including:

- You must be completely truthful about your health history and answer all of the study-related questions completely.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over the counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications.
- You cannot drink alcohol 24 hours prior to study tests and are advised to avoid alcohol throughout the entire study.

- You cannot eat or drink foods that contain caffeine 24 hours prior to study tests. Common foods containing caffeine include coffee, tea, soda and chocolate. If you have questions on foods containing caffeine, please ask one of the team members before your study begins.
- We also ask that you refrain from any structured exercise for 24 hours prior to testing and limit exercise to your normal everyday activities.

What will happen to my information or biospecimens collected for this research after the study is over?
Research samples will be collected on the day of your research visits. We will take 1½ tablespoons of blood during Visit 1 and about 11 tablespoons during the oral glucose tolerance test. After the tests for the study are completed, there may be samples left over. Normally, these leftover samples would be thrown away. We are asking you to allow us to collect this leftover material for specimen banking.

You are being asked to provide samples of your blood to be used for future research. Along with specimens, researchers may need to collect some health information about you. Combining information from the specimen with information from your health records may be useful for this research. For this research, the following types of information could be included: vital signs, lab results, age, gender, medications you are taking, whether or not you have diabetes, family history of cardiovascular disease and other known medical disease.

In addition, if you agree, specimens collected for research will be added to a research specimen bank. The purpose of a specimen bank is to process, and store samples until researchers need them for future research. The long-term goals of the samples collected in this bank will be mainly used for research on diabetes and cardiovascular disease prevention. It is not possible, however, to list every research project that will include the samples because we cannot predict all of the research questions that will be important over the coming years. As we learn more, new research questions and new types of research may be done.

What will happen if I am injured during this study?
In this study, you will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment, which include descriptions outline above in “risks”. In addition, it is possible that during the course of this study, new adverse effects of exercise may occur that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject’s health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University. However, by signing this form, you are not giving up any legal rights to seek further compensation.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?
It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time.

If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include.

a) Your study physician is concerned about your health.
b) You do not follow the instructions of the study doctor or study staff.
c) The study sponsor closes the study for safety, administrative or other reasons.

If you decide to stop being in the study, we will ask you to contact the study coordinator (contact information listed below) by telephone, email, or written letter. If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can I contact if I have questions?
If you have questions about taking part in this study or if you feel you may have suffered a research related injury, you can contact the researchers listed below to:

Steven K. Malin, Ph.D. (Principal Investigator)
Department of Kinesiology and Health
Division of Endocrinology, Metabolism, and Nutrition
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7054; steven.malin@rutgers.edu

Emily Heiston. (Project Coordinator)
Department of Kinesiology and Health
Rutgers University, New Brunswick, NJ 08901,
(848) 932-7059; emily.heiston@rutgers.edu

EMERGENCY HEALTH CONTACT *if problems occur:*

- In case of emergency, call 911 or go to the nearest Emergency Department.
- During normal business hours, contact Dr. Shah, MD at (732) 235-6337.
- After hours or on the weekend, call (732) 401-5445 to reach Dr. Shah. Please DO NOT text as they will not be forwarded to Dr. Shah. Only phone calls please.

If you have questions about your rights as a research subject, you can contact the Rutgers IRB Director at:

Health Sciences IRB New Brunswick/ Piscataway
Office of Research Regulatory Affairs, Rutgers University
Liberty Plaza/ 3rd Floor / Suite 3100
New Brunswick, NJ 08901
732-235-9806

You may also contact the Rutgers Human Subjects Protection Program at (973) 972-1149, email us at humansubjects@ored.rutgers.edu, or write us at 65 Bergen St., Suite 507, Newark, NJ 07107.

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

PERMISSION (AUTHORIZATION) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

What Is the Purpose of The Research and How Will My Information Be Used?
You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What Information About Me Will Be Used?

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address, and date of birth.
- Your health information is required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.
- Social Security number ONLY IF you are being paid to be in this study.

Who May Use, Share or Receive My Information?
The research team may use or share your information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved in The Study
- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- Hospital Personnel as Necessary for Clinical (e.g., Robert Wood Johnson University Hospital, Barnabas health, University hospital, etc.).
- Non-Rutgers Investigators on the Study Team (e.g. Uta Erderbrugger, Eugene Barrett, Zhenqi Liu at University of Virginia, etc.).
- The Food and Drug Administration.

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I Be Able to Review My Research Record While The Research Is Ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I Have to Give My Permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I Say Yes Now, Can I Change My Mind and Take Away My Permission Later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind

later for use of your information in the research, you must write to the researcher and tell him or her of your decision: Dr. Steven K. Malin, PhD in the Department of Kinesiology and Health and Division of Endocrinology, Metabolism, and Nutrition at Rutgers University ((848) 932-7054; steven.malin@rutgers.edu).

How Long Will My Permission Last?
There is no set date when your permission will end. Your health information may be studied for many years.

AGREEMENT TO PARTICIPATE

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print):_____

Subject Signature:_____Date:_____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print):_____

Signature:_____Date: _____