The U.S. Army Research Institute of Environmental Medicine (USARIEM)

CONSENT TO PARTICIPATE IN RESEARCH

Title of Protocol: Effects of severe negative energy balance on inflammation, iron absorption, nutritional status, skeletal muscle and whole-body metabolic homeostasis, cognitive, and physical performance during a simulated sustained operation (SUSOPS)

Principal Investigator: Stefan M. Pasiakos, PhD

Funding Source: Military Operational Medicine Research Program

INTRODUCTION

You are being asked to participate in a research study conducted at the United States Army Research Institute of Environmental Medicine (USARIEM) Natick, MA by Dr. Stefan M. Pasiakos, Nutritional Physiologist, at the Military Nutrition Division, USARIEM. You are being asked to participate in this research because you are representative of active duty male Soldiers, are healthy, and routinely participate in exercise (such as weightlifting or jogging) 2-4 days/week.

You may choose whether or not to participate in this research. It is important that you read what is written below and ask questions about anything you do not understand. You may talk to your family, friends or others to help you decide if you want to be part of this study. When you feel that your questions have been answered, you will be asked if you agree to be part of the research or not. If you agree, you will be asked to sign this consent form. You will be given a copy of this form to keep.

WHY IS THIS RESEARCH BEING DONE?

Military personnel commonly perform strenuous exercise, with minimal rest, during short-term (3-7 days), sustained training and combat operations (SUSOPS) that causes your body to burn more calories than you are able to consume, causing weight loss and reductions in many markers of physical health. For example, the physical stressors that military personnel experience can cause inflammation that reduces your body's ability to absorb key nutrients, such as iron, and lowers your body's ability to fight off infection, repair damaged muscle, and maintain gut (i.e., stomach) health, and optimal physical and mental performance. The purpose of this study is to see if consuming enough food to match the daily calories burned during SUSOPS protects against inflammation and the negative effects that can result from it. Results from this study will be used to help combat ration developers design field-feeding strategies that limit the negative effects of short-term training and combat-related stress.

Sixty volunteers will be enrolled in this study. All screening will stop once complete data has been collected from 15 volunteers. Although you may consent and desire to participate in this study, if the investigators are able to get enough data from past subjects, then you may not be tested and your participation will end.

You can participate in this study if you:
- Are a male, active duty Service member, who is 18-39 years old
- Have a stable body weight in the past 2 months (± 5 pounds (lbs))

- Have no signs of chronic illnesses, medication use or muscle or bone injuries as determined by USARIEM Office of Medical Support and Oversight (OMSO)
- Are recreationally active (2-4 days/week of aerobic and/or resistance exercise)
- Don't take any pain-relievers (e.g. Tylenol), nonsteroidal anti-inflammatory medications (e.g., aspirin, Advil®, Aleve®, Naprosyn®), or any other aspirin-containing product for 10 days before starting and at least 5 days after completing the study
- Don't drink alcohol, smoke (including e-cigarettes), vape, chew tobacco, drink caffeine, take dietary supplements, eat probiotic-containing foods (e.g. yogurt, cottage cheese, sauerkraut, etc) and probiotic-containing supplements (e.g. VSL#3, PRO-15, etc) during the entire study (vitamin/mineral supplements cannot be taken for at least 2 weeks before starting the study)
- Have supervisor approval if you are a non-Human Research Volunteer (HRV) Active Duty military person working within the U.S. Army Natick Soldier Systems Center
- Have a bowel movement at least as frequently as every other day (see Table 1 fecal collection)

You cannot participate in this study if you:

- Show signs of muscle or bone injuries or chronic illnesses as determined by OMSO
- Have abnormal cardiovascular (e.g. heart, blood vessels) or metabolic systems (e.g. kidney disease, diabetes) as determined by OMSO
- Have any history of disease or abnormality of the gastrointestinal tract (gut) such as Crohn's disease or diverticulosis
- Are anemic or have sickle cell anemia/trait as determined by OMSO
- Have a high C reactive protein (i.e., a lab value that indicates inflammation) level as determined by OMSO
- Have abnormal blood clotting as determined by OMSO
- Have bad reactions to lidocaine (i.e., a shot used to numb a body part to reduce pain or discomfort with minor medical procedures)
- Show signs of any physical, mental, and/or medical condition that would make this study harmful to you as determined by OMSO
- Engage in heavy drinking or have any substance abuse issues, or use of anabolic steroids
- Donated blood within the last 4 months
- Used oral antibiotics within the last 3 months
- Have had a colonoscopy within the last 3 months
- Use laxatives, stool softeners, or anti-diarrheal medications more than once/month
- Currently use benzodiazepines (e.g. Xanax, Ativan that are commonly prescribed for anxiety), anti-depressants or anti-histamines (e.g. allergy medications)
- Have a pacemaker or other implanted electronic medical device
- Are unwilling or unable to eat study diets and foods provided and/or follow exercise prescriptions

Health problems found during the screening process will be documented, and you will be provided a copy. You are encouraged to make an appointment with your doctor to follow up with a full evaluation of the identified health concerns. If you have any evidence of existing physical, mental and/or medical conditions that would make the proposed study more hazardous, you will be excluded.

WHAT WILL HAPPEN DURING THIS RESEARCH?

If you agree to participate in this research, you will be a study volunteer for about four to five weeks. The below study overview and table provide more details on what you will be asked to do:

Study Design:

The study is divided into seven parts: pre-study testing, a 3-day testing period before SUSOPS begins, a first testing period (SUSOPS 1), a 7 day recovery period, a second testing period (SUSOPS 2), and another 7-day recovery period.

Pre-study testing occurs 1-2 weeks before the actual study begins and consists of medical screening, height/body weight measures, diet and physical activity records, resting calorie expenditure measure, aerobic fitness test, appetite measures, muscle carbohydrate normalization and vertical jump practice tests, behavior and mood practice tests (see Table 1 for complete explanation of procedures). This period is meant to inform study staff of what your nutritional needs will be during the study, and it provides you chances to practice some of the tests and procedures you will be asked to perform during the study.

The 3-day testing period before SUSOPS begins consists of a muscle carbohydrate normalization procedure on an exercise bike, the first of three iron absorption studies, urine sample collection to measure protein status and calorie expenditure, and body composition will be measured on an x-ray machine called a DEXA (see Table 1 for complete explanation of procedures). Your body weight will be measured daily throughout the study from the start of this testing period.

Both of the SUSOPS periods will last 3 days (72 hours). The research staff will feed you all of your meals during both SUSOPS testing periods as well as during the two days immediately before each SUSOPS. The meals that you will be fed during the two day period before each SUSOPS period will be made up of commercially available grocery store foods, and the meals you will be fed during both SUSOPS periods will be made up of primarily combat ration items. In random order, you will be fed enough calories to maintain your body weight during 1 SUSOPS period, which will also account for the amount of calories you will burn during the study. In the other SUSOPS period, the amount of calories you will be fed will be only 45% of what your body is expected to need in order to maintain weight. This will mimic the amount of calories Soldiers are commonly deprived of during SUSOPS. You will perform the same amount of activity in both SUSOPS periods. During both SUSOPS testing periods, you will not be allowed to eat any food or perform any exercise that is not already part of the study because this could interfere with study results. You will live and sleep at the Doriot Climatic Chambers during each SUSOPS period and will be monitored by study staff. Two days prior to each SUSOPS period, you will check into Doriot and will begin living and sleeping there at that time (the time you will live in Doriot for each test period will be the 2 days before SUSOPS + 3 days of SUSOPS for a total of 5 days). The activities that you will be asked to perform during SUSOPS will be outdoor hiking/light jogging (within the Natick Soldier Systems Center, where USARIEM is located), with or without carrying extra weight in a backpack, and Warfighter operational tasks so that you will burn enough calories to mimic real-life operations. On a daily basis during SUSOPS, your mood, behavior, overall alertness, and appetite will be assessed. You will be asked to provide urine samples, blood samples, saliva samples, and fecal "poop" samples. At night, you will only be permitted to sleep four hours to mimic real-life SUSOPS. You will have a muscle biopsy sample taken before and after each SUSOPS period. The SUSOPS periods will also be followed by an iron absorption study after the last exercise session. You will be released at the end of the iron absorption study.

During the 7-day recovery periods, fasting (no food or drink in the past 8 hours) blood samples will be collected and 3 day diet and physical activity records will be kept. You will be asked to provide some samples (saliva, poop) and do a vertical jump test. Your body composition will be measured on the DEXA machine. Another muscle carbohydrate normalization procedure will occur 2 days before the second SUSOPS period begins. There will be a final fasting blood draw on the very last day of the study.

Screening Procedures:

Screening tests will determine if you are able to join this study. After signing the consent form, if you still wish to be in the study, you will be asked to answer questions about your medical history, exercise and eating habits, and make an appointment for a medical screening visit.

Medical Screening: You will meet with OMSO staff to undergo a general medical clearance. This will include drawing less than a tablespoon of blood from your arm to see how quickly your blood clots and well as markers of how 'inflamed' you are before starting the study. Volunteers who are briefed while at their home duty station (through coordination with the NSSC Soldier Squad Interface Team) and consent to volunteer may undergo medical clearance at this location prior to traveling to USARIEM. For other volunteers who are not medically cleared in advance, the medical screening visit will be done at USARIEM. You will be told about any possible medical concerns found from the screening.

Study Procedures:

SUSOPS Physical Activity:

The daily exercise and warfighter tasks you do during the SUSOPS periods will contribute to a large portion of your daily calories burned. Your specific exercise prescription will be different from other volunteers based on how many extra calories your body needs to burn in order to reach a certain level of calorie expenditure. The purpose of this high level of calorie expenditure you will have during SUSOPS is to reproduce the sort of prolonged strenuous exercise and stress that Warfighters experience during real-world SUSOPS. The physical activity that will be used in your exercise prescription consists of the daily exercise and Warfighter operational tasks. You will be closely monitored throughout all exercise bouts. Water will always be available so that you can remain hydrated throughout all physical activity. More information is provided below:

Daily Exercise:
During each SUSOPS period, low to moderate aerobic exercise will be the main type of exercise you do. You will have 3 exercise sessions per day (lasting 1-2 hours each) outdoors on the fitness trail. The first and third exercise sessions will be loaded ruck marches. The additional weight worn and carried during the loaded ruck marches will total about 70 lbs (i.e., wearing approximately a 12 lbs basic uniform, carrying simulated weapon and wearing tactical equipment totaling approximately 25 lbs, and carrying a ruck sack loaded to approximately 33 lbs). For the second session, you will not carry extra weight.

Warfighter Operational Tasks:
Move Under Fire: During this task you will wear a basic army uniform, while carrying a backpack and tactical equipment that weighs about 70 lbs (see description above for loaded ruck marches), and carry a fake weapon that weighs about 12 lbs. You will begin lying face down, and upon command, will sprint approximately 6 meters (m) to a marker and either kneel or lie face down. You will remain in this position for approximately 5 seconds. Upon signal, you will get up and sprint approximately 5 to 8 m to the next marker and either kneel or lie face down. This will be repeated until you have covered a total of 100 m (15 rushes of ~6.6 m). Time to complete the task will be recorded. Each testing session will take approximately 1-2 minutes.

Casualty Evacuation Drag: You will drag a fake casualty (dummy weighing about 270 lbs) up to 15 m as fast as possible in 60 seconds (sec), while wearing a fighting load with a fake weapon (see description above for loaded ruck marches). If you are unable to pull the casualty the full 15 m in 60 sec, the distance the casualty was dragged will be measured to the nearest 0.25 m.

Sandbag carry: You will wear the same gear described above the ruck marches but not carry the fake weapon (about 58 lbs). You will lift a total of 16 sandbags weighing 40 lbs each, carry them 10 m, and place them on the floor in a 4 bag wide x 2 bag deep x 2 bag high formation as quickly as possible. The completion time will be recorded. The test is expected to take approximately 3-5 minutes.

Please refer to Table 1 for a list of the standard testing procedures you will be asked to do. Please refer to Table 2 for the timeline of these procedures.

Table 1: Standard Testing Procedures

Study Procedures	Description	Study Days
Height, body weight and body composition (DEXA, InBody)	Height is measured once at the beginning of the study, body weight is measured daily. We will use an x-ray (DEXA, Dual Energy X-ray Absorptiometry) and a bio-electrical impedance scale (InBody) to measure the amount of muscle, fat, bone, and water there is in your body. For the DEXA, you will lie on your back and remain still for about 10 minutes while the x-ray scanner moves over your body. For the InBody, you will stand on the scale for about 30 seconds.	2, 6, 12, 16
3 day diet and physical activity records	You will report your routine eating and exercise habits on forms we provide. This information will help us determine how many calories you need to eat per day to stay the same weight	Pre-study testing, 6-8, 16-18,
Resting calorie expenditure	We will measure the amount of oxygen breathed in and carbon dioxide breathed out by placing a clear plastic hood attached to a machine over your head, while you lay awake for about 30 minutes. This test, which will tell us how many calories you normally burn while resting, will happen early in the morning after not eating for at least 8 hours.	Once during pre-study testing
Iron absorption studies	These studies will tell us how well your body absorbs the iron in your diet while resting and recovering from strenuous exercise, especially while you're not eating enough calories to maintain your body weight. You will drink a stable isotope-labeled iron drink (dissolved in artificially flavored water). The isotope drink is safe, non-radioactive, and already present in your body. We will give you a larger amount of these molecules than what is already present in your body so we can track how your body absorbs the iron in the drink. We will determine iron absorption by collecting 7 blood samples over the next 6 hours from an intravenous catheter (IV, plastic tube) paced in your arm. The blood is taken from the IV so you are not stuck with a needle each time.	2, 6, 16
Calorie expenditure and protein status studies	Like the iron isotope studies, we will provide you other stable isotope-labeled drinks; one water (i.e., known as doubly labeled water, DLW), and the other protein (dissolved in artificially flavored water). The DLW isotope study will help us determine how many calories you're burning during the SUSOPS periods. The protein isotope study will help us determine how your body builds and breaks down muscle during strenuous exercise, while not eating enough calories to maintain the same body weight. For both of these assessments, we will collect your urine in plastic tubes before and after consuming the drinks. For DLW, we will collect a urine sample (2^{nd} urination of the morning) every morning during the SUSOPS periods. We will provide you tubes for your daily urine collections and ask that you record (or tell us) the time you urinated into the tube. For	DLW, drink on day 2, daily urine collections (2-6, 13-16) Protein, drink and 24 hour urine collections on days 2, 5, 15

	the protein drink, you will be provided a urine container and asked to collect all of your urine for the next 24 hours. These isotopes are safe, non-radioactive, and already present in your body. Like the iron studies, we will give you a larger amount of these molecules so we can track how they are used in your body.	
Muscle biopsy	To examine how SUSOPS affects muscle health, we will obtain a muscle sample from your thigh by performing a muscle biopsy. This procedure will take about 10 minutes to complete. A local numbing medicine (lidocaine) will be injected into outer portion of your mid-thigh. A small cut (1 cm) in the skin will be made and a biopsy needle will be inserted to remove a small piece of muscle tissue (about the size of an un-popped popcorn kernel). If we are unable to obtain enough muscle for our tests, we will make a second attempt (2nd pass) after asking for your consent. After the biopsy, the cut will be covered with a gauze pad, transparent sterile dressing, and an elastic bandage. The elastic bandage should be kept in place for 5 hours after the biopsy and can then be removed. The principal investigator will remove the sterile dressing and gauze pad the next morning. You will be provided specific care instructions. OMSO will check how you are healing within 72 hours after finishing the muscle biopsies.	3, 6, 13, 16
Aerobic fitness test	Your peak aerobic fitness will be determined on a stationary bike, while wearing a heart rate monitor and breathing through a mouthpiece connected to machine that measures the amount of oxygen breathed in and carbon dioxide breathed out. The result will be used to better estimate how long and hard you need to exercise to burn your prescribed number of calories during SUSOPS. The test result will also help us determine how hard you need to exercise during the muscle carbohydrate storage procedure (see below). You will be given 5 minutes to warm-up at a low intensity. The test will start immediately after the warm-up and every minute thereafter, we will increase how hard you have to pedal until you get too tired to continue or maintain pedaling at a steady rate.	Once during pre-study testing
Muscle carbohydrate normalization procedure	You will complete a very hard bike ride to reduce the amount of carbohydrate stored in your muscles so that we can refeed you a carbohydrate-rich diet for the next 2 days to establish pre-SUSOPS carbohydrate storage level that is similar between SUSOPS periods. You will ride a stationary bike at different intensities based on your aerobic fitness assessment. After warming-up for 5 minutes, we will increase the intensity to about 80 ± 5% of your peak fitness level. You will pedal at this intensity for 2 minutes followed by a 2 minute recovery period at about 50 ±5% of your peak fitness. You will complete this 2 minute exercise to recovery interval 12 total times in about 50 minutes.	One practice session during pre-study testing, 1, 11
Saliva collection	We will collect your saliva to understand how stress affects genetics. We will provide you with a small tube with a cotton swab inside, and ask that you open the tube and place the swab in your mouth. After 45 seconds (gentle chewing possible, but not required),	2, 6, 9, 16, 19

	you will place the saliva-soaked swab back in the tube. You will do this twice within 30 minutes. On each morning of SUSOPS, including the morning before the first SUSOPS period, a second saliva sample will be collected to measure your immune function in the same manner as stated above.	2, 3-5, 13-15
Fecal "poop" collection	We will collect fecal "poop" samples to identify the types and activities of bacteria that are present in your stomach and intestine and to determine how different nutrients and exercise during SUSOPS influence the growth and activity of these bacteria. You will be given a 2-3 day window to collect a single sample. If you do not provide a fecal sample during this window, the collection period will be extended until a sample is provided. If the sample you provide is too small for us to analyze, you will be asked to collect another sample, and the collection period will be extended until a sample large enough to be analyzed is provided. If you produce a sample at a time when you cannot return it to study staff within 12 hours (recovery periods), you will be instructed not to collect the sample, and the collection period will be extended until you produce a sample and give it to study staff within 12 hours of collection. You will be given detailed instructions on how to collect a sample and the supplies needed to do it.	Once during pre-study testing, Once during each SUSOPS period, once during each recovery period
Sugar substitute test	We will assess the health of your gut (intestines) by asking you to drink water sweetened with 2 different artificial sweeteners. These sweeteners are safe and used as low-calorie substitutes for sugar in a variety of common commercial food products. Over the next 24 hours you will collect all of the urine that you produce.	Once during pre-study testing, 4, 14
Gut health	We will ask about the health of your gut (stomach and intestines) using a questionnaire that asks how your gut feels and the frequency of your bowel movements. This questionnaire will take under 5 minutes to complete.	Once during pre-study testing, 3, 6, 13, 16
Appetite measures	We will ask you to tell us how hungry (or full) you are by marking a scale on paper or electronically throughout the day. This scale will take under 5 minutes to complete.	Once during pre-study testing, 3-5, 13-15
Food preference and cravings	We will ask you how much you like and want to eat certain foods by completing an electronic food preferences questionnaire before and after lunch. This questionnaire should take under 15 minutes to complete.	Once during pre-study testing, 5, 15
Behavior and mood tests	We will assess your behavior by testing your ability to remember, react, and maintain your attention. We will also assess your mood by asking how you feel using a mood questionnaire. You will be trained on how to complete these tests before the SUSOPS periods. If at any time you are uncomfortable answering a specific question, you may	Four times during pre-study testing, 3-5, once during 7-12, 13-15

	skip that item and move on to the next. Behavior and mood tests will be done twice daily during each SUSOPS and will take about 1 hour to complete.	
Alertness and sleep monitoring	We will track your sleep and alertness during pre-study testing and SUSOPS by asking you to wear two lightweight devices on your wrist, similar in size to wristwatches. The devices contain sensors that can assess environmental conditions, such as light, as well as alertness and patterns of rest and activity. You will be asked to only wear one of the devices while sleeping. The other device will be pre-programmed so that sometimes during the day it will trigger (e.g. vibrate, flash and/or sound a tone) that will require you to push a button to stop it.	Pre-study testing, 3-6, 13-16
Vertical jump test	We will assess physical performance during SUSOPS by asking you to perform a vertical jump test. To perform this test, you will stand on a flat, clean surface, with your feet at shoulder width with your knees slightly bent. You will then swing your arms behind you and bend your knees to a comfortable depth and then attempt to jump as high as you can while extending your two hands as high as possible as you jump, tapping colored fins on the testing equipment at the peak height of your jump. You will perform 3 jumps with approximately 60 seconds of rest between jumps. You will practice this test during the pre-study period and will receive instructions before each test is performed. This test will take about 5 minutes to complete.	Twice during pre-study testing, 3, 5, 7, 9, 13, 15, 17, 19
SmartPill	We will assess how fast food passes through your digestive system using an electronic pill. The SmartPill is a sterile, ingestible Food and Drug Administration-approved wireless capsule similar in size to a large multi-vitamin pill that passes through the stomach and intestines while sending data to a receiver worn on your waist or around your neck. You will be asked to swallow the SmartPill under supervision, and to inform staff when you poop so they can confirm the pill has left your body. The pill passes through most people's bodies in under 48 hours. If the signal from the pill is lost before exit from your body can be confirmed, we may ask you to swallow another pill and begin collecting poop samples so that we can visually confirm the pill exited your body. Only 9 volunteers will participate in this test. These volunteers will be randomly selected (like flipping a coin) by study investigators. If you are selected but have trouble swallowing large pills or have certain medical issues (see page 12), please inform study staff so that an alternate participant can be selected. For the time that the ingestible SmartPill is in your system you should not have a magnetic resonance imaging (MRI) test. A wristband notifying medical personnel of this will be placed around your wrist. This band may be removed after you have excreted all SmartPills given to you during the study.	Once during pre-study testing, 4, 14

Table 2. Timeline of Standard Testing Procedures

	Pre-Study Period			SUSOPS 1				Recovery 1						SUSOPS 2				Recovery 2					
Day	-14 - 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Task																							
Height, body weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Body composition			x				x						x				x						
3 day diet and physical activity records	x						x	x	x								x	x	x				
Resting calorie expenditure	x																						
Iron absorption studies			x				x										x						
Calorie expenditure and protein status studies			x	x	x	x	x							x	x	x	x						
Muscle biopsy				x			x							x			x						
Aerobic fitness test	x																						
Muscle carb. normalization procedure	x	x										x											
Saliva collection			x	x	x	x	x			x				x	x	x	x			x			
Fecal "poop" collection	x				x					x					x								
Sugar substitute test	x				x										x								
Gut health	x			x			x							x			x						
Appetite measures	x			x	x	x								x	x	x							
Food preference and cravings	x					x										x							
Behavior and mood tests	x			x	x	x					x			x	x	x							
Alertness and sleep monitoring	x			x	x	x	x							x	x	x	x						
Vertical jump test	x			x		x		x		x				x		x		x		x			
SmartPill	x				x										x								

WHAT ARE THE POTENTIAL RISKS AND DISCOMFORTS FROM BEING IN THIS RESEARCH?

Dietary Intervention: The foods that you will be given to eat in this study pose no known risk. The meals that you will be fed during each four day SUSOPS period will be made of mostly Meals, Ready to Eat (MRE) combat ration items. The meals that you will be fed for the two days before each SUSOPS period will be made of store-bought grocery food items. Sudden changes to your diet can cause gas, cramping, bloating, constipation or other abdominal discomfort in some people. You may still feel hungry when eating a low-calorie diet. In addition, low-calorie diets may be low in specific vitamins and minerals. You will be shown the study menus before the study begins. You can expect to lose about 5 lbs during the energy deficit SUSOPS period.

Body Composition: You could be exposed to a small amount of radiation during the DEXA scan. The amount of radiation you will receive from both tests will be equal to about 1/30 of a chest x-ray. The health risks of very low levels of x-ray exposure are unknown but are probably very small. There are no known risks associated with bio-electrical impedance (InBody).

Blood Draws: Providing blood samples has few risks. You may experience bruising or swelling where the needle entered. A person may sometimes feel faint or actually faint during or right after the blood draw. If you have fainted during past blood draws, it is more likely to happen again. So, you should let us know if this has happened to you before. Trained staff will wash their hands, wear rubber gloves, apply rubbing alcohol to the area and use a sterilized needle before drawing your blood. However, in spite of being careful there is a chance of infection. You should not give blood for 4 months before and 2 months after this study.

Intravenous (IV) Catheter Placement: The risks related to inserting an IV are small. A needle will be inserted in your arm (same as *Blood Draws*) and, once the needle is removed, a small tube will remain for blood sampling throughout the day. A person may sometimes feel faint or actually faint during or right after the IV is placed. If you had problems with fainting during catheter placement in the past, it is more likely to happen again, and you should let us know. In addition, the catheter can cause irritation, bruising, swelling, infection or an allergic reaction. Trained staff will use hygienic practices to place your catheter and will watch closely for any signs of infection. If the catheter becomes clogged, we will have to replace it to continue blood sampling. This will require inserting another needle. Despite being careful, there is a chance that the site may become infected.

Muscle Biopsies: A muscle biopsy is a research procedure that involves making a small cut on the skin to get a small muscle sample from your leg using a needle. Like blood draws, there is a risk that volunteers will feel faint or may actually faint during or right after a muscle biopsy. If you have had problems with fainting during past blood draws or muscle biopsies, it is more likely to happen again. The most common risks in muscle biopsies are pain (1-2%), reddening of the skin (1-2%) and bruising (1-2%). Panic episode (less than 1%), bleeding (less than 1%) and swelling (less than 1%) have also been reported. These problems do not normally interfere with normal walking and heavy exercise. Permanent or long-term numbness may be possible but has not been reported. You may feel moderate stiffness and swelling around the cut after the biopsy, but this usually stops within several days. There might be minimal scarring as the cut heals. Permanent scars are possible, but the chance of this happening is 5-10% for dark-skinned people and is even rarer for fair-skinned people. The cut will be closed as soon as possible to prevent scarring. A qualified researcher will perform the biopsy under sterile conditions to prevent infection or pain. If you bleed during the biopsy, the researcher can quickly act by applying direct pressure to the cut. You cannot take aspirin or other medications that interfere with blood clotting for 10

days before or 5 days after the muscle biopsy. You will receive careful instructions on preventing bruising and infections. We will also watch you for any sign of infection, bleeding or bruising.

Lidocaine Shot: You might feel a slight, brief pain when you get the lidocaine shot. Rare, but possible side effects could include: dizziness, confusion, shakiness, visual changes, nausea, unusually slow heartbeat and convulsions. Allergic reactions, including swelling, itching, rash, hives, difficulty swallowing or difficulty breathing, are also possible. Trained researchers will watch closely for any of these signs throughout the entire procedure. If you have a bad reaction to lidocaine, medical staff will be called immediately.

Exercise:
Aerobic Exercise: Strenuous exercise can uncover or worsen hidden heart problems such as not enough blood flow to the heart muscle and irregular beats. Local muscle discomfort and fatigue may occur in active muscles during and shortly after daily exercise sessions, aerobic fitness testing and muscle carbohydrate normalization. Muscle soreness, ranging in intensity from mild to severe, may persist for 1 to 7 days. Muscle cramps, blisters, fatigue, trauma due to falling, or overuse injuries following loaded and unloaded outdoor exercise sessions may occur. You will be instructed to be well hydrated prior to aerobic exercise to reduce risk of muscle cramps. Water will always be available to you in order to remain hydrated through all exercise regimens.

Warfighter Operational Tasks: You may feel discomfort, muscle soreness, and fatigue in the muscles you use during and shortly after these exercise bouts from the weight of the equipment you will be carrying or dragging. You may experience falling or bruising from quick position changes during the move under fire task or muscle strain from the casualty evacuation drag and sandbag carry tasks.

You will have practice sessions during pre-study testing to become familiar with the exercises you will be doing to limit the likelihood of injuries. You will be closely monitored during all exercises by highly trained staff to ensure exercises are done safely. These monitoring staff are investigators and research assistants with experience in exercise testing and standard safety procedures. They have been involved in exercise monitoring and testing in previous USARIEM protocols and have undergone USARIEM credentialing to certify competency. All exercise monitors and test administrators will be CPR-certified. Medical clearance for exercise will occur prior to study inclusion. This decreases the likelihood you will have problems with your heart or circulatory system. A medical officer will be on call or on site at all times, as determined by the medical monitor using standard guidelines. Should you develop symptoms of any medical problems, testing will be stopped immediately and the medical officer of the day will be notified.

Vertical Jump Test: The risks due to the vertical jump test may include ankle or knee sprains when jumping or landing. However, we will monitor you closely during testing and provide you with detailed instruction and demonstration in order to perform the test safely.

Sleep Restriction: You will be limited to 4 hours of sleep each night during the SUSOPS periods. You will likely feel tired, irritable, be in a bad mood and/or not think clearly. Upon completion of each SUSOPS period, you will be allowed to sleep in-between blood draws during the 6 hour iron absorption study. If you withdraw or need to be withdrawn during a SUSOPS period, then you will be released in the care of someone else who will escort you home/to your living quarters and ensure that you receive an adequate amount of sleep.

Sugar substitutes: Sugar substitutes can cause bloating, cramping, gas or diarrhea in some people when consumed in high amounts. The amount you will consume in this study is not likely to have this effect.

Isotopes: The isotopes used in this study are safe, non-radioactive, occur naturally in foods, and are already present in your body.

Smart Pill: The Smart Pill is a large pill that may be difficult to swallow for some people. Risks include choking. There is a very small risk that the pill becomes stuck in your stomach or intestines. To minimize risks, study staff will monitor you while taking the pill and will monitor the pill as it moves through your body. Only 9 volunteers will be chosen to participate in the Smart Pill testing. If you are chosen but have a history of the following, please inform study staff immediately so that an alternate volunteer can be selected to replace you:

- History of a packed food ball that is unable to exit the stomach
- Swallowing problems with food or pills (known as dysphagia)
- Strictures, fistulas, or physiological/mechanical gut obstruction (damage)
- Implanted or portable electro-mechanical medical devices
- Currently using any of the following medications: proton pump inhibitors (i.e., Omeprazole, Nexium), histamine$_2$ blockers (i.e., Zantac), gut motility-altering medications (i.e., Reglan), antiemetics & 5HT3 antagonists (i.e., Zofran, Kytril), macrolides (i.e., Erythromycin, Zithromycin), anticholinergics (i.e., Phenergan, Compazine), 5HT4 partial agonists (i.e. Zelnorm), antacids (i.e., Maalox, Mylanta, Rolaids)

In addition to the risks listed above, loss of privacy/confidentiality is also a risk of study participation.

WHAT ARE THE POSSIBLE BENEFITS FROM BEING IN THIS RESEARCH?

There is no direct health or other benefits related to participating in this study. Information gathered from this research may benefit other people in the future.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH?

You will receive a total of $1,050 for completing the study, based on the amount of $25 per blood draw (42 total draws). If you do not complete the entire study, you will receive money for every successful blood draw that you did complete. You will not be eligible for any other form of compensation during this study.

Your Social Security Number (SSN) will be needed to process your payment, as required by law. This information will be carefully protected. Your social security number and banking information will be destroyed immediately after your payment has been confirmed. The Defense Finance and Accounting Service will report total payments of $600 or more within 12 months to the Internal Revenue Service (IRS). This may require you to claim the compensation that you receive for participating in this study as taxable income.

WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH?

If at any time you believe you have suffered an injury or illness from participating in this research, please contact:

Stefan M. Pasiakos, PhD
U.S. Army Research Institute of Environmental Medicine
Building 42, Room 219
10 General Greene Ave
Natick, MA 01760
Phone: 508-233-6474
Email: stefan.m.pasiakos.ctr@mail.mil

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at Army hospitals or clinics.

For DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the Principal Investigator (PI). If you have any questions, please contact the Pl.

HOW WILL YOU PROTECT MY PRIVACY AND THE CONFIDENTIALITY OF RECORDS ABOUT ME?

The principal investigator will keep records of your participation in the research. To protect your privacy, any of your research-related records will be labeled with an assigned research participant number that will not include your name or Social Security Number. Dr. Stefan M. Pasiakos will keep the link between your participant number and your research records in a locked cabinet. The principal investigator and study coordinator are the only people who will be able to match your research participant number with any of your personal identifying information.

Biological samples will be stored in a designated laboratory freezer and will either remain at USARIEM until analysis or will be shipped to the US Army Center for Environmental Health Research (USACEHR), the Energy and Environmental Sustainability Laboratory at Pennsylvania State University (EESL PSU), Metabolic Solutions Inc., or Pennington Biomedical Research Center (PBRC) for later analysis. All biological samples will be stored using your subject identification number only. The master list linking your identifiers to your data and biological samples will be deleted upon study closure. Your coded data, in a password-protected file, may be transmitted between USARIEM, USACEHR, and the University of Leeds via encrypted email, a secure file transfer site, or on approved removable media. USACEHR, PBRC, EESL PSU, Metabolic Solutions, and University of Leeds will not have access to any identifiable data. A portion of some or all of the biological samples you will provide during this study will be frozen and retained at USARIEM indefinitely, for either re-analysis under this research effort or under approved, future research plans. If you do not wish your samples to be retained for future use by any organization listed, you should not participate in this study.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity to others. If photographs, videos or audiotape recordings of you will be used for educational purposes, your identity will be protected or disguised. Names and faces will be covered in any photographs unless volunteers agree to sign a photo release form. If you do not sign the photo release form, any photographs taken of you will be destroyed.

Authorized representatives of the following groups may need to review your research and/or medical records as part of their responsibilities to protect research participants:

- U.S. Army Medical Research & Materiel Command (USAMRMC) Institutional Review Board (IRB)
- U.S. Army Human Research Protections Office and other DOD offices charged with oversight of human research
- USARIEM Office of Research Quality and Compliance (ORQC)

Complete confidentiality cannot be promised for military personnel because required health information may need to be reported to appropriate medical or command authorities.

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information entered into this confidential data base includes your name, address, Social Security Number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research conducted within the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

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 IF I DECIDE NOT TO PARTICIPATE IN THIS RESEARCH?

Your participation in this research is voluntary. You may decline to participate now or stop taking part in this research at any time without any penalty or loss of benefits to which you are entitled. Deciding not to participate now or withdrawing at a later time does not harm, or in any way affect your benefits to which you would otherwise be entitled to regarding future relationships with USARIEM. If you do not complete the entire study, you will be compensated for the number of successful blood draws you did complete.

WHAT COULD END MY INVOLVEMENT IN THE RESEARCH?

The investigator or study sponsor may withdraw you from participating in this research if:

- You are not willing to follow study diets and exercise prescriptions
- You become ill or injured, or to protect your health and safety

The investigator will make the decision and let you know if it is not possible for you to continue. Your taking part in the study may be stopped without your consent if it is determined by the investigator that remaining in the study might be dangerous or harmful to you.

If you are withdrawn or decide to withdraw during the study, no further data will be collected from you. You will be asked to return any study food and/or wrappers that you had been provided, in addition to any diet and exercise logs that you had started to complete. The data that has been collected from you up to that point may still be used for analysis. You will be compensated for any blood draws that you completed up to the point that your participation ended.

WHAT IF ANY NEW INFORMATION IS FOUND OUT?

During the course of the research, the investigators will tell you of any new findings that might cause you to change your mind about continuing in the study. If new information is provided to you, the investigators will obtain your consent to continue participating in this study.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR CONCERNS ABOUT THIS RESEARCH?

If you have questions about the research at any time, you should contact:
Stefan M. Pasiakos, PhD
U.S. Army Research Institute of Environmental Medicine
Building 42, Room 219
10 General Greene Ave
Natick, MA 01760
Phone: 508-233-6474

If you have questions regarding your rights as a research participant, you may contact the HQ USAMRMC IRB Office at 301-619-6240 or by email to usarmy.detrick.medcom-usamrmc.other.irb-office@mail.mil or USARIEM ORQC at phone (508-233-6306/4811) or by email at usarmy.natick.medcom-usariem.mbx.usariem-rqc@mail.mil

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SIGNATURE OF RESEARCH PARTICIPANT

I have read the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date