

Exercise, Hypertension, and Gut Dysbiosis in African Americans
NCT03897777

COVER LETTER

Today's date: April 15, 2020

Study Title: Effects of Exercise on Hypertension and Gut Dysbiosis in African Americans

Principal Investigator: Marc D. Cook PhD

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Document was amended to increase subject payment.



Study Title: Effects of Exercise on Hypertension and Gut Dysbiosis in African Americans

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Purpose of the Study

You have been asked to participate in a research study about the effects exercise training has on the health of the bacteria in your intestines and blood pressure in African Americans. You have been asked because you are an African American between the ages of 30-50 years old and have pre-hypertension (mildly elevated blood pressure) or stage 1 hypertension (moderately elevated blood pressure) or normal blood pressure.

African Americans have hypertension (high blood pressure) more often than any other population in the United States. This makes hypertension one of the most important health concerns in the African American community. Most of the time, African Americans get hypertension at an earlier age and it causes more damage.

Recently, the bacterial make-up of the intestines has been found to be related to increased blood pressure. Researchers believe that specific types of bacteria that breakdown fiber may be lower in African Americans and related to greater blood pressure. Exercise can potentially increase these specific types of bacteria and increase the production of substances that are related to lowering blood pressure.

The purpose of this study is to understand how exercise affects specific types of bacteria in your intestines, in African Americans with and without hypertension, and if exercise-induced changes in those types of bacteria affect your blood pressure. To do this, we will measure your blood pressure and you will submit stool samples before, during, and after a three-month period of moderate-to-vigorous aerobic exercise training. In addition, we will obtain blood samples to measure your biomarkers (substances found in the blood that are linked to the health of intestines and blood vessels).

The primary researcher involved in this study is Dr. Marc Cook from the Department of Human Performance and Leisure Studies. If you do not have a primary care physician, you will be referred to Dr. Veita Bland M.D. of the Cone Health Hospital affiliated Bland PA Clinical Hypertension Clinic located at 1317 N Elm St # 7, Greensboro, NC 27401 (Phone: (336) 373-1557). Please ask the research study staff to explain any words or information that you do not clearly understand in this consent form. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. If you do not qualify for the study, none of your information obtained in the screening will be stored. Approximately 50 people may be involved in this research at North Carolina A&T State University.

This research is sponsored by the American Heart Association (AHA) grant number 18CDA34110444.

Procedures

If you qualify and choose to participate in this study, you will be asked to **1.** Complete (4) questionnaires providing information on your health history, physical activity, race/ethnic background demographics, and dietary habits (diet recall); and (3) psychological questionnaires to determine your stress levels, learning and memory and cognition.





Understanding stress levels and learning and memory has previously been linked to the healthy balance of gut bacteria. **2.** Perform an exercise test to measure your heart's response to exercise and measure your cardiovascular fitness level (4 times); **3.** Perform exercise training (12 weeks for 1 hour, five times per week) and not change your diet during this time; **4.** Provide blood samples (4 times) and stool samples (4 times); **5.** Perform body composition testing to measure your weight, fat mass, and fat-free mass (4 times); and **6.** Measure your blood pressure at home using a device you will be provided over a 24-hour time period (4 times). The exercise tests, blood and stool samples, and home blood pressure measurements will occur at the beginning of the study and at the end of every month (4 weeks) of exercise training to measure your exercise progression, changes in biomarkers in your blood and bacteria in your stool related to blood pressure, and changes in your blood pressure.

It is expected to take about 14 weeks in total. Again, the exercise test, blood and stool samples, body composition, and blood pressure measurements will be taken at the beginning (0 week), 4 weeks, 8 weeks, and 12 weeks (end of the study). The exercise tests will track your exercise training progress at 4 weeks, 8 weeks, and 12 weeks (end of the study). Participants in this study should:

- a) Be an adult between 30 - 50 years of age with blood pressure in the pre-hypertension stage (BP 120/80 - 139/89 mmHg) or stage 1 hypertension (140/90 – 159/99 mmHg).
 - a. If you have stage-1 hypertension, you will need to obtain written consent from your primary physician to participate in the exercise intervention study.
- b) Not have any other diagnosed cardiovascular disease (heart condition)
- c) Not exercise regularly (participate in less than 60 minutes of exercise/week)
- d) Not be pregnant or plan to become pregnant during the study and not be lactating
- e) Be free of active diseases that affect your intestines (i.e., chronic constipation, diarrhea, Crohn's disease, ulcerative colitis, irritable bowel syndrome, diverticulosis, stomach or duodenal ulcers, diabetes, hepatitis, HIV, and cancer)
- f) Have not taken antibiotics in the past 3 months
- g) Have not been regularly taking medications that impact intestinal function (i.e., laxatives, enemas, anti-diarrheal agents, narcotics, antacids, antispasmodics, antidepressants, diuretics, anticonvulsants, antibiotics, herbals, homeopathic and home remedies)
- h) Have no plans to travel out-of-town during the study period.

If you agree to participate, you will be asked to avoid alcohol and not to change your eating habits. This is because changing your diet can affect the types of bacteria found in your intestines and the goal of the study is to determine how exercise, by itself, changes the bacterial make-up in your intestines. If you are taking medications, you will be asked to continue taking them throughout the study period.

If you qualify for the study, you will be asked to complete the following:





1. *A supervised moderate-to-vigorous cardiovascular-based exercise training program for 12-weeks.* The exercise training will consist of walking, running, or cycling for 5 days per week, for up to 60 minutes each day, at an intensity that will range from somewhat hard to hard. The exercise intensity will be set at 70-85% of the highest heart rate you reach on your maximal exercise test you will perform at the beginning of the study. A maximal exercise test will also be performed at the end of each month (every 4 weeks) to record your fitness progress. All maximal exercise testing (4 in total) will occur in Corbett Gym, which is right next door to the campus recreation facility. Daily exercise training sessions will occur either in the campus recreation facility at North Carolina A&T State University or at North Gateway Research Park (10-minute drive north of campus).
2. *Body Composition Measurement.* Have your body composition (weight, height) taken by standing on a scale for approximately 2 minutes (total of 4 times).
3. *Blood pressure and heart rate measurement.* Your blood pressure will be taken just like they do at the doctor's office using a cuff that is placed on your arm. Your heart rate will be measured using an electrocardiogram (ECG). During the ECG, we will put some sticky patches (electrodes) across your upper body to measure the electrical activity that your heart produces. The exercise test, to measure your fitness, will be performed with the ECG electrodes on (total of 4 times).
4. *An exercise maximal oxygen uptake test.* You will walk/run on a treadmill where the speed and incline of the treadmill will increase every 2-3 minutes until you cannot walk/run anymore. It will also consist of a mouthpiece or face mask being used during the exercise to collect your breath. This will determine how much oxygen you use during the test and will be used as a measurement of your cardiovascular fitness level. This will occur 4 times in total (1 time before training and every 4 weeks).
5. *Questionnaires.* Completion of questionnaires about your health history and background as well as questionnaires to assess your perceived stress levels, learning, memory, and cognition (retaining and understanding information). It has been shown that the gut bacteria composition (make-up) may be related to the psychological factors associated with levels of stress and the ability to understand and retain information. Also, completion of one 5-day and three 3-day dietary records to assess your dietary habits before and during the study. The only restriction is that you agree to avoid alcohol and not consume any probiotic supplements or foods containing them. Further details about the food record procedure will be provided to you at the screening session. These will be performed before training and at the end of the study (12 weeks).
6. *Twenty-four-hour ambulatory blood pressure (ABP) monitoring to measure your BP.* This monitor will measure your BP for 24-hrs on a typical day. The 24-hr period will begin in the morning of a typical day, with the exclusion of Friday through Sunday. The BP cuff will be fitted to your non-dominant arm. Blood pressure measurements will be obtained every 30-min during the day (7am-10pm) and every 60-min at night (10pm-7am hours). You will be instructed not to exercise before or during the time your BP is being taken, and to pause momentarily and maintain your body position





- during each BP measurement. Throughout the duration of the recording period, you will be required to maintain a diary in which you will record your activity at the time of each measurement. Only recordings of good technical quality (80% of valid BP measurements) will be included in final analyses. This will occur 4 times in total (1 time before training and every 4 weeks).
7. Home stool collection. Within 24-hours of the day you wear the 24-hr ABP monitor, you will be asked to collect a stool sample at home and return to the laboratory the next day when you return the monitor. You will be provided with instructions on how to collect the sample as well as given the equipment to collect the sample safely. The equipment will include gloves, sterile cotton swabs with safety tubes, a storage container for storage in your freezer, and a container to transport the sample to the lab. The sample will need to be placed in the freezer until you return it to the study staff. This will occur at the beginning and every 4 weeks (total of 4 times).
 8. A 3-day controlled menu before each fecal collection at 4, 8, and 12 weeks. These menus will be based on your "normal" food intake from the 5-day food record you complete at the beginning of the study. We will not provide you this food, but emails will be sent to remind of your menu.
 9. Four blood samples. throughout the course of the study, which will be collected from a forearm vein by a phlebotomist. The phlebotomist will draw 1½ ounces (3 tablespoons) of blood from your forearm or hand vein the first time and 1 ounce (2 tablespoons) the following 3 times. A total of 4.5 ounces (9 tablespoons) of blood will be drawn for the entire 14-week study.
 10. Multivitamins, medications, or oral contraceptives being taken at the time of screening must be continued at the same dosage throughout the study. You must not begin taking any new supplements during the study or change your oral contraceptive during the study.

Screening Procedures and Assessments

Visit 1, 1.5 hour: Informed consent and questionnaires

1. Medical history and physical activity, and psychological questionnaires. We will review the medical history questionnaire to ensure all the questions and their answers regarding your health, current medication use, medical history and exercise pattern are clear. This is done to ensure you are eligible and that it is safe for you to participate in this study. You will also complete some questionnaires to understand how your gender and ethnic identity may be related to your health history. Completion of this questionnaire will take approximately 10-20 minutes. You also will fill out a physical activity readiness questionnaire (PAR-Q). Pre-menopausal women will be asked to confirm they are not pregnant by taking an over-the-counter pregnancy test that we will provide. This is the only time you will be asked to take a pregnancy test. **Risks** associated with the questionnaires and pregnancy test: You may feel a little uncomfortable sharing your personal health information and/or answering some of the questions related to stress levels or cognition. You are free to skip any questions you do not wish to answer. Concerning the psychological questionnaires (stress, learning,





memory, cognition, gender roles and ethnic identity), there are no right or wrong answers. These questionnaires will allow us to determine if your blood pressure and fecal microbiome characteristics are related to your individual levels of perceived stress, cognition, and additional psychological assessment and will not be compared to any other participant. None of these measures will be used to diagnose any potential condition. If you are female and test positive during the pregnancy test you may be surprised or experience distress if you were unaware. However, if you have hypertension and are pregnant, it may be dangerous for you to start an exercise program before consulting with your physician.

2. Completion of psychological questionnaires (4 total) to assess your perceived stress and depression levels, learning, memory, and brain processing speed (cognition: retaining, understanding, and speed of recalling information). These questionnaires will not be used to diagnose any psychological condition, but they are important to assess because gut bacteria are extremely sensitive to psychological stress and have been related to increased depression and reduced cognition. We hope to better understand how these psychological measures affect cardiovascular health. These questionnaires will be administered by study personnel and will approximately take 20-30 min to complete each time.
3. 5-day food record. We will educate you on how to complete a 5-day dietary food record. For this record, you will write down your food and beverage intake for the entire week following this initial screening. You will be given a paper food record diary to write down your daily food intake for 5 days before you start exercise training. There have been no **risks** identified in writing down your food intake. You will be asked to provide a stool sample, which you will collect at home, after you complete your 5-day diet record. (Explained below)
4. Familiarization with the 24-hour blood pressure monitoring device. We will introduce you to the 24-hour ambulatory blood pressure monitoring device. You will be fitted with a blood pressure cuff and sent home with instructions on how to use it. You will also be given instructions (verbal and written) on how to keep a blood pressure diary, where you will record your activities at the time the monitor was taking your blood pressure. **Risks** associated with the blood pressure monitoring device are that there is mild discomfort when the measurements are being taken during wake and sleeping hours. However, subjects infrequently report sleep disturbances as they become less sensitive to the measurements being taken throughout the day. If the monitor significantly disturbs your sleep, you may turn it off. Your skin may become irritated by the cuff. If this happens, you may remove the cuff as frequently as you need to, throughout the day, to relieve the irritation. If it causes significant irritation, you should remove it immediately and contact the research staff.
5. Stool samples. You will be asked to provide a stool sample after you complete the 5-day diet record and before you start exercise training (Week 0). You will also provide a stool sample each month (Week 4, Weeks 8, and Week 12). Stool samples will be collected by you at home and returned to researchers at the following exercise session. **Risks** associated with fecal sample collection include: experiencing emotional stress related to





working with your own feces. Mishandling the sample can lead to infections, however, personal protection equipment will be provided, and safe hand washing technique will be taught to reduce this risk to only rare cases.

Pre-exercise Assessment (Visit 2, 1.5 hours)

1. **Body height and weight.** Your height and body weight will be measured on a scale to determine your body weight, fat mass, muscle mass, and total body water. The scale requires you to stand on the scale barefoot and hold on to the arms of the machine. The test takes approximately 2 minutes to complete. If you are unaware of your body weight and fat mass, there is a **risk** that you may experience some emotional distress. However, your results will always be confidential.
2. **Blood draw.** Blood will be taken from the antecubital (forearm) vein by a phlebotomist. A small amount (about 3 tablespoons) of blood will be taken at this time. **Risks** associated with a blood draw include: mild pain, bleeding, bruising at the site of the draw and rarely, infection.
3. **Peak Oxygen Uptake (VO_{2max}) Test.** This test will involve walking/running to a maximal effort on a treadmill until you cannot continue. An experienced member of the research staff will measure oxygen uptake and respiratory rate on the Parvo Medics True Max 2400 metabolic cart.

This test will take place in the Exercise Core Laboratory, G-07 Corbett Sports Center (405 Benbow Road, Greensboro, NC 27411). After a 3-minute warm-up at 1.7 mph at a 5 % grade, a special testing protocol will be employed to determine your peak rate of oxygen consumption (VO_{2max}). The test is outlined below, with each stage lasting 2-3 minutes:

Stage 1 = 1.7 mph at 10% Grade
Stage 2 = 2.5 mph at 12% Grade
Stage 3 = 3.4 mph at 14% Grade
Stage 4 = 4.2 mph at 16% Grade
Stage 5 = 5.0 mph at 18% Grade
Stage 6 = 5.5 mph at 20% Grade
Stage 7 = 6.0 mph at 22% Grade
Stage 8 = 6.5 mph at 24% Grade

Heart rate, the ECG referred to earlier, will be taken during each work stage via a wireless Polar Monitor (Polar Electro, Lake Success, NY). The test will end when you are unable to continue, despite verbal encouragement from the researchers, or when you reach your maximum oxygen consumption after increasing your exercise level. It is expected that you will reach maximum oxygen consumption within 8-12 min (Stage 4-6). **Risks** associated with the exercise testing (VO_{2max}) include: those associated with exercise (small risk of sustaining minor muscle, bone and/or tendon injury during exercise or discomfort due to intensity of exercise and muscle soreness after the test). These risks are considered to be minimal. **Risks** associated with the ECG are minimal.





You may experience mild skin irritation when we remove the sticky electrode patches from your skin.

Exercise training period (Visits 3- 60, 1 hour & 15 min/visit)

1. Stool samples and 24-hour blood pressure monitoring. You will be asked to provide fecal samples at Weeks 0 (start of exercise), **and each month** (Weeks 4, 8, and 12). These samples will be collected at home, by you, and returned to researchers at the next exercise session. They will not be collected on a weekend. You will be sent home with instructions and all the protective equipment and accessories to collect the stool sample. Prior to collection at Weeks 4, 8, and 12, you will be asked to consume the same diet as you did 3 days prior to your Week 0 sample. This is to ensure that your diet does not cause significant variations in the bacteria in your intestines. Email and/or written reminders will be sent 3 days prior to and on collection days to remind you of the diet and the collection day, respectively. Within 24-hours of you providing the fecal sample, you will be sent home with the 24-hour blood pressure monitor you used at the beginning of the study to measure your blood pressure. **Risks** associated with fecal sample and the blood pressure monitoring device are listed above.
2. Exercise training. During this 12-week period you will be asked to come into the Campus Recreation Facility or the Exercise Lab at North Gateway Research Park for a supervised, endurance-based exercise-training program 5 times per week. The training will consist of running on a treadmill, cycling on a stationary bike, or exercising on an elliptical trainer for 45-60 minutes/day at a moderate to high intensity (~60-75% VO_{2max}). The exercise training will proceed in a progressive fashion over the 12-weeks of training. For the first week, training sessions will last only 30 minutes at a moderate intensity (~60% VO_{2max}). Training sessions for Week 2 will last 45 minutes at a similar intensity. Training sessions for Week 3 will last 55-60 minutes at that same moderate intensity. Over the remaining weeks of training the duration for each exercise session will remain at 55-60 minutes, but there will be a progressive increase in intensity each day of training, progressing up to ~75% VO_{2max} . At the end of 4-weeks and 8-weeks of training, one of your training sessions will be a VO_{2max} test that will allow us to determine your fitness level and change your exercise prescription appropriately. Exercise sessions will be completed indoors and may be completed with a group of study participants or by oneself, if you prefer. Training intensity will be monitored throughout the entire protocol by use of a heart rate monitor. Intensities of each exercise session will be based on a percentage of your heart rate reserve, which will be established during your pre-testing trials. A certified exercise physiologist (Dr. Marc Cook, PhD in Exercise Physiology and certified by the American College of Sports Medicine) will train all research staff, including undergraduate researchers who will help with your exercise training sessions. **Risks** associated with exercise training: There is a small risk of sustaining minor muscle, bone and/or tendon injury during exercise. In addition, you may experience a feeling of discomfort after the exercise session due to increased use of major muscle groups. There is a theoretical risk that heart irregularities or sudden death may occur during exercise. However, these events generally happen to





people who already have heart conditions. If you have been diagnosed with any type of heart condition, you cannot participate in this study. If, despite precautions, an emergency occurs during exercise; research staff is trained in CPR, first aid, and the use of an automated external defibrillator (AED) (which will be immediately on hand if it is needed). Research staff also will call 911, if appropriate.

Exercise Testing and Post Exercise-Training Assessments (Visits # 21 (4 week) and # 41 (8 week) and # 61 to Exercise Lab, ~1.5 hours each Visit)

After each 4-week period of exercise training, it is necessary to measure the parameters below and perform monthly VO_{2max} tests to update your exercise prescription to ensure you are exercising intensely enough.

1. ***Body composition:*** Your height and body weight will be measured on a scale that will determine your body weight, fat mass, muscle mass, and total body water. See above for details.
2. ***Blood draw:*** Blood will be taken from a forearm vein by a trained phlebotomist. A small amount (about 3 tablespoons) of blood will be taken at this time point.
3. ***Maximal Oxygen Uptake (VO_{2max}) Test:*** This test will involve walking or running to a maximal effort on a treadmill until you cannot continue. See above for more details.
4. ***Psychological questionnaires at Visit 61 only (end of study):*** Assess your perceived stress and depression levels, learning, memory, and brain processing speed. These are the same questionnaires you completed at the beginning of the study.

Risks and Discomforts

The risks related to your participation in this research study have been explained above and can be reviewed at any time.

To minimize the risk of breach of privacy or confidentiality, all health information and blood samples collected will be stored coded as to not be able to identify you.

If you think you are having a bad reaction during or after the study ends, contact your physician and when possible, also notify the lead researcher, Dr. Marc Cook at 336-285-3547 or at mdcook@ncat.edu.

Benefits

This study is for research purposes and may or may not provide benefits to participants. A possible benefit is that you may experience an improvement in cardiovascular health from the exercise training. Another benefit is that you may experience a reduction in your blood pressure. Additionally, you may receive a sense of fulfillment from personally contributing to medical knowledge about the use of exercise as tool to improve blood pressure and gut health. We hope to learn more about how specific types of bacteria in the intestines affect blood pressure in African Americans. We also hope to learn how exercise training changes these bacteria to reduce blood pressure.

Compensation or Costs to Study Participants

For your participation in this study, you will receive compensation totaling \$190 (in the form of gift cards). You will receive compensation of \$100 for completing the questionnaires, the





VO_{2max} test, submitting to the 1 blood draw and submitting 1 stool sample, and returning the 24-hour BP monitoring at the beginning of the study (pre-exercise training). At weeks 4, 8, and 12 (end of study) of the exercise training period, you will be compensated \$30 for completing the VO_{2max} test, submitting to a blood draw and a stool sample, and returning the 24-hour BP monitoring (total=\$190). (If asked to provide an additional sample due to improper storage/collection, additional compensation will not be provided.) If you to decide to leave the study early, monetary compensation would still be provided for each sample that you provided. You will not pay for any testing or procedures associated with this study. You will not be compensated for the cost of your transportation any visit to the lab for testing or the gym for exercise training.

Missed training sessions: You must complete 90% (total of 54) of training sessions for exercise training to be considered completed. If you have a family emergency or become ill and miss an extended period of training time, you will be allowed to continue if absence is no longer than 8 consecutive exercise sessions (make-up sessions will be required and extend their time in the study).

Confidentiality

Your samples will be coded with an identification number (rather than your name or initials) to maintain your confidentiality. Any questionnaires or records that identify you, and this consent form signed by you, may be inspected by the Department of Health and Human Services (DHHS) agencies, and the North Carolina A&T State University Institutional Review Board. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. However, to the extent permitted by the applicable laws and regulations, records identifying you will be kept confidential and will not be made publicly available. In general, we will not tell anyone any information about you. The results of this study may be presented at meetings or in publications, but your identity will not be disclosed in those presentations.

Your records will be kept in a locked cabinet in a locked office space with access limited to essential research staff. Research data collected will be transferred to a password protected excel file on a password protected laboratory computer. Access will only be given to essential research staff that will update these files. Records stored in this manner will be coded and will not be able to identify you in any way. These electronic files will be kept indefinitely. Biological specimens (blood and stool samples or bacterial DNA isolated from those stool samples) will be stored in a freezer, indefinitely. No one will be able to identify you from these samples, as they will be stored with the coded ID numbers.

Information that identifies you personally will not be released without your written permission (for example, to your primary physician), and if the results of this research are published or discussed in conferences, no information will be included that would reveal your identity. We are required to keep all data and records for at least four years after the close of the study. All paper records that may identify you as a participant in the study will be destroyed (via shredding) at that time.

Questions about the Study

If you have any questions about your involvement in this study, you may contact research staff at 336-285-3749 or by email at geilresearch@ncat.edu. You can also contact Dr. Cook at 336-285-3547 or by email at mdcook@ncat.edu. If you have any study-related concerns or any





questions about your rights as a research study participant, you may contact the Office of Research Compliance and Ethics at North Carolina A&T State University at 336 285-2961.

Voluntary Participation/Withdrawal

Your participation is voluntary, and you may end your participation at any time. Refusing to participate or leaving the study, at any time, will not result in any penalty or loss of benefits to which you are entitled.

Statement of Consent

I have read the above information and have received answers to any questions I had. I am at least 18 years of age or older and voluntarily consent to take part in this research study.

Participant's Name (Printed): _____

Participant's Signature: _____ Date: _____

Researcher's Signature: _____ Date: _____

