University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: August 7, 2018
IRB Study # 17-2303
Title of Study: A phase II randomized, double blinded, placebo-controlled study of gamma tocopherol-enriched supplement on lower airway responses to inhaled wood smoke in healthy adults
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What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.
You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

Wood smoke comes from people using wood to heat and cook, as well as from wildfires. Exposure to wood smoke particles causes symptoms, even in healthy people, such eye irritation, cough, shortness of breath, and increased mucous production. A form of Vitamin E, called Gamma Tocopherol, and found mostly in food, may have the ability to reduce, or even prevent, these symptoms. The purpose of this study, is to see if gamma tocopherol supplements will have an impact on these short term symptoms, and in the way the lungs respond to the wood smoke. The exposure will be to 500ug/m3 of WSP for 2 hours, with intermittent exercise on a bicycle and rest. The wood is burned in a typical wood stove and piped into the chamber.

Are there any reasons you should not be in this study?

You should not be in this study if you have asthma or other chronic health problems, if you have problems with blood clotting, if you are a smoker, or if you are pregnant, trying to get pregnant, or if you have orthopedic problems which prevent you from riding a bicycle.

How many people will take part in this study?

There will be approximately 20 people in this research study.

How long will your part in this study last?

Before you participate in this study, you should have completed our general screening protocol, IRB #98-0799, and our woodsmoke screening protocol, IRB #15-1775. There are 7 visits for this study, and it should take approximately 3 months to complete all of these visits. The baseline visit takes around 4 hours and the training visit will take about 4 1/2 hours. You will be given the study drug at the training visit, and you will take the medication 2 times a day for 2 days, with the last dose just before the exposure. The exposure visit will last all day. You will return for a follow up visit 24 hours after the exposure. There will be a 4-week washout, and you will return for a visit to receive your second round of study drug. After the 2 days of study medication, you will return for your second exposure and the 24 hour follow up. We will ask you to return within 5-10 days for checkout visit. We will call you in about a month to see if you have any questions about your health related to the study.

What will happen if you take part in the study?

You will arrive for the baseline and eligibility visit, or **Visit 0.** You will be given an opportunity to read the consent form, and the study will be explained to you. We will answer all of your questions. We will then collect your **medical history**, including any **medications** that you take. If you are female, you will have a *urine pregnancy test*, and it must be negative. We will check your **vital signs**, including your temperature, your heart rate, your respiratory rate and the oxygen concentration in your blood. We will listen to your chest to be sure you aren't wheezing. One of the study doctors will do a **physical exam**. We will do an **EKG** – we will place patches on your chest, your arms and legs to collect a ready of the electrical activity of your heart. You will do a **lung function** test for us, you will take a full breath in and blow it out as hard and as fast as you can. You will do this several times, and we will coach you through it each time. You will have a **methacholine challenge**. Methacholine is a FDA approved inhalation agent that is used to diagnose asthma. In this study we are not looking for asthma, however we want to see if your lungs are more sensitive after the wood smoke exposure to the methacholine. This test is

done by having you inhale a dose of methacholine, and then repeating the lung function test. You will inhale the next dose of methacholine, and repeat the lung function test. This is continued until you inhale all of the methacholine, or until your lung function drops by 20%. If your lung function drops that much, we will give you a medication, called albuterol, to relieve the effects of the methacholine. It should bring your values quickly back to normal. Then you will have a **sputum induction**. For this test, you will inhale a heavy mist made from salt water, at a concentration that is higher than the concentration of salt normally found in your body. This loosens secretions in your lungs, and allows you to cough the sample into a cup. We will monitor your lung function between levels of salt water, and you will inhale 3 different levels, starting at 3%, then 4% and finally 5%. We will draw about 20cc of **blood** from you, including blood to go to Labcorp to measure your complete blood count, your cholesterol and other lipid values, your values for blood clotting, and to look for markers of inflammation. The rest will be used for labs just for the research. You will be sent home with contact information for a study doctor in case you have questions about your health related to the research. When your lab values come back from Labcorp, we will calculate your 10 year risk of having a heart attack with a tool called the Framingham Risk Calculator. Your risk must be less than 5% for you to continue.

You'll come back at within the month for your training and medication visit, or **Visit 1.** This will be at least 2 days before your exposure visit, but no more than 3 weeks. We will ask you to come in fasting and this visit will be scheduled in the morning. We will:

1. Review any changes in your health or medications since the last visit.
2. Collect your vital signs, and ask you to complete a GI symptom questionnaire.
3. Do a Urine pregnancy test for females.
4. Lung function testing

You will have a baseline **heart rate variability (HRV)** measurement. This is done by putting a heart monitor on you with chest patches, much like the EKG, and having you lie quietly in a darkened room for 30 minutes. Go to the ultrasound lab for a **brachial artery ultrasound (BAU)** for **flow-mediated dilatation (FMD)** measurements**.** These tests measure the reactivity/responsiveness of the brachial artery, a blood vessel in your upper arm. You will rest quietly on a bed as ultrasound pictures are taken of the artery, using an ultrasound probe that is positioned above the elbow. This is not painful and non-invasive. You will wear an inflatable blood pressure cuff on your test arm below your elbow, and your heart rate will be monitored with three adhesive electrodes applied to your chest. After you rest quietly for 15 minutes, the first ultrasound scan will be performed. Then the blood pressure **cuff on your test arm will be inflated** for 5 minutes in order to stop the flow of blood. You may feel sensations in your hand similar to those when your foot "goes to sleep", such as "pins and needles" and tingling. Immediately after the pressure is released, a second scan will be taken in order to assess flow-mediated dilatation. You will then rest quietly for 10 minutes at which time a third ultrasound scan will be obtained. This may be repeated if the technician decides the images obtained are not optimal. Then we will perform an **ultrasound of the left ventricle your heart**. You will be asked to rest quietly while this is performed, which should take less than 15 minutes. A wand will be placed on your chest and moved around to make the measurement. A "jelly" that

makes the movement smooth will be used. You'll use a towel to wipe off the excess when we have finished, and we'll ask you to wear a hospital gown for this test. It is not painful and is non-invasive.

When you have the exposure, you will be exercising on a bicycle. We will show you the bike at this visit and how it works, and we will measure your breathing to be sure you are exercising enough for the study. This is measured by minute ventilation, which will be based on your body surface area. We will place an EGC monitor on you to watch your heart rate and rhythm during the exercise. We'll show you how to place the finger probe, so we can monitor your oxygen, and how to connect the blood pressure cuff. We will monitor your blood pressure intermittently during the exposure.

Finally, we will send you home with the study medication. The study medication will either be a placebo (safflower oil) or gamma tocopherol, 700 mgs in each capsule, and you will take 2 capsules each time. The medication is blinded, meaning neither you nor the study team knows if it's the gamma tocopherol or the placebo. We can find this out if we need to know. You will take the first dose at 9:30 pm, 2 evenings before your exposure, again the next morning at 9:30am and then that evening at 9:30pm. Please bring the final dose back with you, you will take it in the research lab at 9:30am, prior to going into the exposure chamber. We strongly encourage you to take the study medication with fatty foods, such as peanut butter, eggs, cheese. The vitamin is fat soluble, and it will digest better with fatty foods. We will send you with a diary to tell us when you take the vitamin, and to collect any symptoms you might have.

You will come back at least 48 hours later or up to 3 weeks for **Visit 2,** which is the first wood smoke exposure. We will call and remind you when to begin taking your study medication. When you arrive, we will:

1. Review any changes in your health or medications since the last visit.
2. Collect your vital signs, and have you complete a symptom questionnaire. The questionnaire is to monitor any symptoms you might have as a result of the wood smoke exposure, and it is important that we collect this information, though you are not obligated to complete the questionnaire.
3. Collect your symptom diary
4. Do a urine pregnancy test for females
5. Perform lung function
6. Draw about 20cc of blood, for Labcorp and for the research labs
7. You will enter the wood smoke chamber, and place the finger probe on and connect the blood pressure cuff. You will be in the chamber for 2 hours, alternating 15 minutes of exercise with 15 minutes of rest.
8. You will complete a symptom questionnaire just before you leave the chamber.
9. You will do a lung function test as soon as you leave the chamber.
10. You will have a 60 minute rest to eat a provided low fat lunch
11. 90 minutes after you leave the chamber, we will obtain HRV, FMD, and LVS
12. Four hours after the end of the exposure, we will collect your vital signs
13. Then we will draw blood again, 20 cc, for Labcorp and the research labs.

14. You will complete the symptom questionnaire
15. And finally, another sputum induction

We will check your vital signs before you are discharged, and we will send you home with contact information for a study doctor in case you have any concerns about your health related to the study.

You will return the next day for a follow up visit, or **Visits 3.** We will:

1. Review any changes in your health or medications
2. Collect your vital signs, and have you complete a symptom questionnaire
3. Draw about 20cc of blood, to go to Labcorp and for research labs
4. Check your lung function
5. Have you do a methacholine challenge
6. And have you do a sputum induction

We will be sure your vital signs are back to your baseline, and we will send you home with contact information for a study doctor.

After at least 4 weeks, but no more than 8 weeks you will return for your next study medication, at **Visit 4:**

1. Review any changes in your health or medications since the last visit.
2. Collect your vital signs, and ask you to complete a symptom questionnaire.
3. Do a urine pregnancy test for females
4. If more than 8 weeks has passed since your last visit, we will draw 10cc of blood to send to Labcorp, this time just to check your complete blood count and your clotting numbers.
5. Send you home with study drug and a diary. The study drug will again be either the gamma tocopherol or placebo, whichever one you did not receive the last session.

You will repeat the sessions, with **Visit 5** just like Visit 2 (the low fat lunch you select for visit 2, must be identical to your low fat lunch on visit 5), and **Visit 6** just like Visit 3.

You will come back to the research lab 5-10 days after you finish the exposure session for **Visit 7,** for a check out visit. We will:

1. Review any changes in your health or medications
2. Check your vital signs, and have you do a symptom questionnaire
3. Have you do a lung function test
4. If you have any health symptoms or concerns, a study doctor will do a physical examination.

We will call you in a month to see if you have any questions or concerns regarding the study. All the samples we collect from you, including the sputum and blood, will be kept until all the analysis is complete.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit

personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

Wood smoke: Breathing wood smoke in this study might cause coughing, wheezing, shortness of breath, irritation of the eyes, ears, nose, throat or lungs, heartbeat changes, or increase your chance of catching a cold. These effects typically last no more than a few hours, but could last longer if you are especially sensitive. No permanent health effects have been seen following exposure over short periods of time in studies like this.

A lifetime of exposure to air pollution is known to increase your risk of developing lung cancer. However, the two hours of exposure to wood smoke emissions in this study is unlikely to increase your risk in any meaningful way, just as smoking a single cigarette would carry much less risk than a lifetime of smoking.

Gamma Tocopherol: There is a rare (less than 1%) chance that higher doses of vitamin E may affect your body's clotting system. We will monitor your clotting levels throughout the study In a previous study, nausea, vomiting, bloating and/or diarrhea were commonly reported. These symptoms generally occurred in the first day or two of dosing. You are encouraged to take the study treatment with food containing fat, such as cheese or peanut butter, to minimize these effects.

Blood draw: There is a small risk of pain or bruising with blood draws. Rarely, some get light headed, so we will allow you to lie down during the blood draw. Our staff is experienced in this procedure.

Lung function: You might have the sensation of being lightheaded, or feeling faint. You will be seated in a non-rolling chair for security.

Sputum induction: This can make you short of breath, or cause you to wheeze or cough. We will monitor you closely, and we will stop the procedure if we, or you, feel that you are not tolerating the procedure.

Exercise: The moderate exercise on the bicycle could potentially cause leg cramps or soreness. We encourage you to stay well hydrated with water.

Brachial artery ultrasound: There are no significant risks associated with ultrasound imaging of the brachial artery, or with the 5 minutes of reduced blood flow that is part of the test. Cutting off blood flow to the arm may result in mild discomfort or temporary sensations of tingling or numbness in the hand until the blood pressure cuff is released. About 1 in 200 patients develops a painless rash on the arm where the blood pressure cuff is placed; this disappears over several days.

Ultrasound of the heart: There is no risk to this procedure.

HRV: You may have minor skin irritation in the area where the electrodes are attached to the skin. Prior to electrode application, the skin will be treated with alcohol and a cleansing solution. If you are male, the skin will be shaved in the area where the electrodes are attached. You should not participate if your skin is highly sensitive to electrode adhesive or gel. You will not be able to do activities which would result in the monitor getting wet, such as showering or swimming while the monitor is on you.

ECG patches: On rare occasions we have seen some skin irritation or blistering from these patches. If this occurs, please use a mild over the counter topical steroid cream, such as hydrocortisone 1%.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

Pregnancy tests will be done on all females who might be able to get pregnant at the start of the study and again if more than 7 days have passed. The study pays the cost of these tests.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about you be protected?

Your personal information, including your name, will go into a database called REDCap, which is designed for research studies. Only individuals who need to see your identifying information will have access to this part of the database. All study data will be coded with your study number. Any hard copy item with any personal identifying information, such as the study worksheets, will be secured in a locked office when not in use. No one outside of the study staff will have access to these records. We will need to use your date of birth for the lung function program.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

What is a Certificate of Confidentiality?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: if you require medical treatment for any medical problems you might have related to the research.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. You do not give up any of your legal rights by signing this form.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving $1,150 for taking part in this study.

Subjects will be paid for participation as detailed below:
V0: $80
V1: $125
V2/5: $275
V3/6: $125
V4: $25
V7: $50

Total for completing all visits: $1,080

In addition subjects will receive $10 for each study medication diary completed, for a total of $20 if diaries are completed for both treatment periods, and a completion bonus of $50 (paid for completing all study procedures). This is a total compensation of $1,150.

Your name, address, and social security number (SSN) are required to process payments and/or to report taxable income to the IRS. You will be asked to sign a separate Social Security Number Collection form. If you do not provide your SSN (or ITIN), we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

Who is sponsoring this study?
This research is funded by the National Institutes of Health. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Signature of Research Participant Date

_____

Printed Name of Research Participant

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent