Sex Differences in Cerebral Blood Flow

NCT04265053

5/4/2023

University of Wisconsin-Madison
Consent to Participate in Research
and
Authorization to Use Protected Health Information for Research

Study Title for Participants: Sex Differences in Cerebral Blood Flow

Formal Study Title: Human cerebral blood flow regulation: sex, mechanism, and stress differences

Principal Investigator: William G. Schrage, Ph.D. (phone: 608-262-7715)

Co-Principal Investigator: Marlowe W. Eldridge, MD.

Where Lead Researcher Works: University of Wisconsin-Madison; Department of Kinesiology; 1300 University Ave; Madison, WI 53706

Invitation
We invite you to take part in a research study examining the control of brain blood flow. You are invited to take part because you are between 18 and 40 years old and generally healthy. Approximately 111 individuals will participate in this study.

The purpose of this consent form is to give you the information you need to decide whether to be in the study. It also explains how health information will be used for this study and for other research in the future and requests your authorization (permission) to use your health information. Ask questions about anything in this form that is not clear. If you want to talk to your family and friends before making your decision, you can. When we have answered all your questions, you can decide if you want to be in the study. This process is called “informed consent.”

Why are researchers doing this study?
The purpose of this study is to test brain blood flow responses when the body is challenged by stressors. We want to know: 1) whether and how males and females differ in control of brain blood flow, 2) whether males and females differ in brain blood flow responses to breathing less oxygen (hypoxia) and more carbon dioxide (hypercapnia). We will test if males and females respond differently and how they respond differently. Funding for this study is provided by the National Institute of Health (NIH).

What will my participation involve?
If you decide to participate in this research study you will be asked to come in for four separate visits: a screening visit (~1hour), exercise and gas challenge visit (~2 hours), AND two study visits (~2 hours each). These two study visits are considered visit A and visit B and are described below. Note that you may be asked to come back for an additional screening visit in the event that we are unable to obtain a blood sample or technical difficulties occur during the initial screening visit.

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What will happen in this study?

Screening Visit (~1 hour): The screening procedures are described below. After you complete the screening, you may be enrolled in the study if you qualify.

1. Medical History: After providing informed consent, you will be asked to fill out a detailed health history questionnaire. You may skip any question on the questionnaire that you do not wish to answer.
2. Anthropometric (Body) Measurements: We will measure height, weight, waist and hip circumference, and blood pressure.
3. Urine Pregnancy Test (Women only): Female subjects will be **required** to have a negative urine pregnancy test which will be reviewed and confirmed by research staff.

Venipuncture: Blood will be drawn from a vein in your arm by a trained and certified person. You will have a total of up to 1 tablespoon or 20mL taken from you. This blood will be used to test for circulating substances in your blood such as sugar, cholesterol, and fats.

Exercise and Gas Challenge Visit (~2 hours):

1. Maximal Aerobic fitness test (VO_2): This test is used to measure your fitness. You will complete a maximal exercise test on a treadmill. You will wear a heart rate monitor (Polar Heart Rate Monitor), and mouthpiece or mask that will capture your breath but will allow you to breathe normally. This test increases in difficulty over time, but usually only lasts 8-12 minutes for most people.
2. Gas Challenge: This procedure is used to familiarize you to the gases you will experience during the MRI study visits. You will be fitted for the mask and will experience the hypoxia (low oxygen) and/or hypercapnia (high CO_2) stimulation.

Pre-Study Visit Procedures: Specific pre-visit procedures to be followed are outlined below:

1. Fasting: You will fast for a minimum of 8 hours prior to the study visits. Plain drinking water is allowed.
2. Withholding exercise, caffeine and NSAIDs; We ask that you refrain from vigorous exercise for 24 hours, and refrain from caffeine and NSAIDs like Ibuprofen for at least 24 hours prior to the study visits. You may and should drink water as normal.
3. For women only: If you are currently taking hormonal birth control for contraception (e.g. the Pill, patch, or ring), you will need to temporarily stop taking these medicines while you are in the study. This time may last from 1-6 months (depending on MRI visits-see below). You will need to be off hormonal birth control for at least one menstrual cycle before Study Visit 1. If you are unwilling or unable to stop birth control, you will not be eligible to participate in this study. An endocrinologist who specializes in these medicines will work with you and the study team to make a plan to temporarily stop birth control and complete the study visits.

Study Visit Procedures (Study Visits)

1. Urine Pregnancy Test (Women only): Female subjects will be **required** to have a negative urine pregnancy test on the day of the study visit, which will be reviewed and confirmed by research staff.
2. Measurements: Heart rate will be monitored by electrocardiogram (ECG) or by pulse oximeter on your fingertip. Blood pressure will be monitored by a cuff on your upper arm similar to clinics. Blood oxygen will be measured with a pulse oximeter on your fingertip; your breathing will be measured using a breathing mask.
3. Intravenous (IV) Catheterization: A highly trained person will place a catheter in a forearm vein. This catheter is used for blood sampling.
4. Blood Sampling: Blood will be drawn from the arm catheter (up to 10 tablespoons; ~150 mL) to test for blood values (sugar, cholesterol, hormones, etc.) and other research values.

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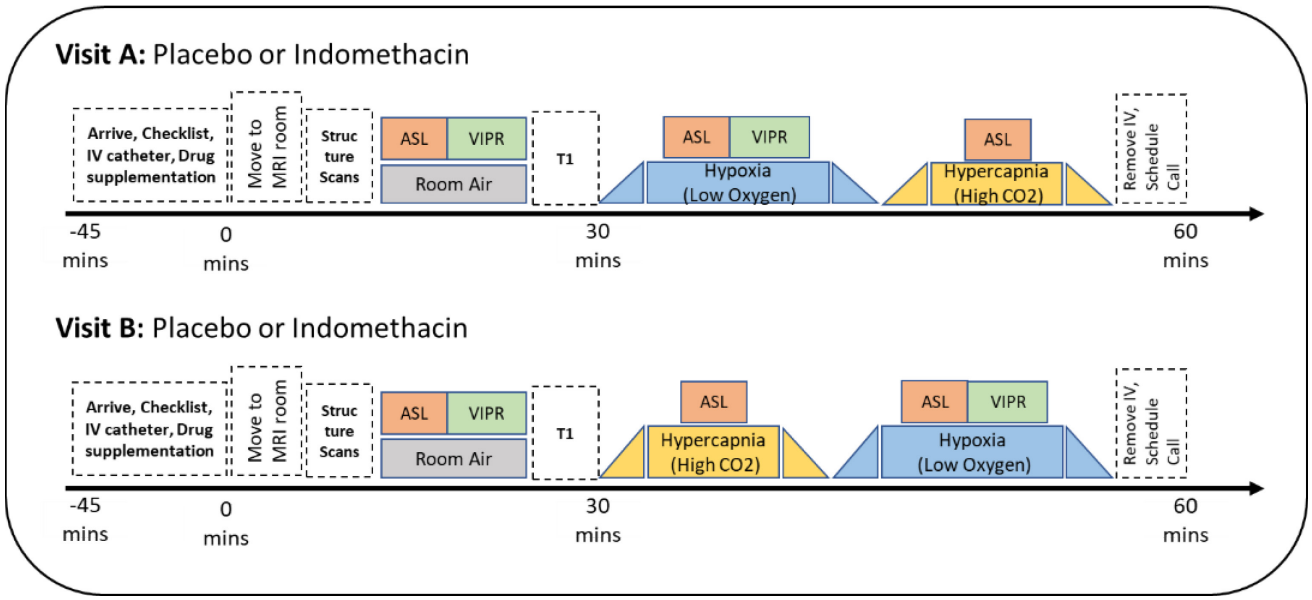
Most of these are research values and not clinical values (such as lab tests you would get at a doctor's office or hospital visit), so we are not allowed to share this information with you.

5. Magnetic Resonance Imaging (MRI): An MRI is a medical imaging technique used to visualize detailed images of internal structures. We are using it to collect images of your brain blood vessels and measure brain blood flow. The scanner looks like a large hollow tube. You will lie flat on your back on a moveable table. The table will slide inside the scanner to take measurements for baseline, and during all study trials (hypoxia, hypercapnia, hyperoxia). Scans (See figure below) taken during study visits will typically last around to 5-6 minutes each, but you will remain in the scanner between scans as well. Total time in the scanner will be about 60 minutes per visit.
6. Low Oxygen (Hypoxia): While you are in the MRI scanner, you will breathe in air through a mask over your mouth/nose that has lower amounts of oxygen than room air. You will breathe this air for ~30-35 minutes. Once the trial is over you will be immediately returned to room air and remain in the scanner while we complete other steps of the study visit.
7. High Carbon Dioxide (Hypercapnia): While you are in the MRI scanner, you will breathe in air through a mask over your mouth/nose that has elevated carbon dioxide. This air will contain normal levels of oxygen. You will breathe this type of air for ~15-25 minutes. Once the carbon dioxide breathing is over, you will be switched back to room air and remain in the scanner while you return to baseline values.
8. Drug Supplementation:
   During the MRI Visits, you will receive either Indomethacin or a placebo. This study is double-blinded; meaning neither you nor the researchers will know which drug you received. You will receive only one of the drugs per visit.
   a) Indomethacin: Indomethacin is a drug similar to NSAIDs like ibuprofen (Advil). Indomethacin is a drug used commonly in research to cause blood vessels to stop dilating (cause them to narrow). We are administering indomethacin to see if it changes brain blood flow.
   b) Placebo: Placebo is substitute for the active treatment. There are no active ingredients or properties in the placebo.
   c) Antacid: During both visits, you will receive an antacid to counteract expected gastrointestinal distress.

Summary of Visit Procedures:



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Procedure	Screening Visits	MRI Study Visit
Fasting (8 hours)	X	X
Medical History	X	
Body Measurements	X	
Maximal Exercise Test	X	
Breathing Challenge Familiarization	X	
Blood Sample	X	X
Vital Signs	X	X
Females stop birth control temporarily (if applicable)	X	X
24-hour abstinence of Caffeine, vigorous exercise, NSAIDs		X
Pregnancy Test (females)	X	X
MRI Scan (ASL and VIPR)		X
Breathing Challenge		X
IV Catheter		X
Drug Supplementation (Indomethacin or Placebo)		X

Protected health information (PHI) used in this study:
Protected health information, also called PHI, is information about your physical or mental health that includes your name or other information that can identify you, like your date of birth or medical record number. To do this study, we will use the following kinds of PHI:

From you: Name, sex, date of birth, home address, phone number, diet, use of tobacco, medications, and medical history.

From medical tests or other procedures performed for this study: Heart rate, blood pressure, blood sampling, and urine pregnancy test (female only).

How long will I be in this study?

Your participation will last ~1 hours for the screening visit, ~2 hours for the exercise visit and gas challenge, and ~2 each for the MRI Study visits (~6-8 hours total). After screening, we will try to schedule your 2 study visits in the same week, although these visits can happen over a 6-month period. After each MRI study visit, we will follow-up with you by telephone approximately 24 hours after the visit to make sure you are feeling well.

The researchers may take you out of the study, even if you want to continue, if

- your health changes and the study is no longer in your best interest
- you do not follow the study rules or no longer meet the requirements to be in the study
- the study is stopped by the sponsor or researchers

Do I have to be in the study? What if I say "yes" now and change my mind later?

No, you do not have to be in this study. Taking part in research is voluntary. This means that you decide if you want to be in the study. If you decide now to take part, you can choose to leave the study at any time. If you stop being in the research, already collected data may not be removed from the study database.

If you decide to be in the study, the researchers will tell you about new information or changes in the

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study that may affect your willingness to continue in the study.
Let the researchers know if you choose to leave the study. If you decide not to take part in the study, or if you choose to leave the study, your choice will not affect any treatment relationship you have with healthcare providers at UW-Madison, UW Health or any affiliated organizations, or any services you receive from them. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

Your authorization for researchers to use your protected health information (PHI) will last until the research study is done. However:

- You can choose to take back your authorization for researchers to use your health information. You can do this at any time before or during your participation in the research.
- If you take back your authorization, information that was already collected may still be used and shared with others, but the researchers will no longer be able to collect NEW information about you.
- If you take back your authorization, you will not be able to take part in the research study.
- To take back your authorization, you will need to tell the researchers by writing to the Lead Researcher, William G. Schrage, Ph.D., at University of Wisconsin-Madison, Department of Kinesiology, 1300 University Ave, Madison, WI 53706.

Will being in this study help me in any way?

Being in this study will not help you directly. But your participation in the study may benefit other people in the future by helping us learn more about how men and women regulate brain blood flow differently.

How is being in this study different from my regular health care?

This study is not part of your health care.

Will I receive the results of research tests?

Most of the tests that are part of this study are for research purposes only. Because of this, we will not tell you or your doctors the results of these research tests. As noted above, one blood sample will be tested at UW Health, and those blood values will be entered into your medical record.

MRI Scans: Whenever an MRI of the brain is done, there is the chance of finding something unexpected. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The MRI we are using in this research study is not the same quality as an MRI that you may have as part of your health care. The images from the MRI will not be reviewed by a physician who normally reads such images (such as a neuroradiologist). As a result, you will not be informed of any unexpected findings. The results of your MRI will not be placed in your medical record. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

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What are the risks?

Study procedures and the associated risks are described below.

1. **Fasting:** Fasting can make you feel, hungry, irritable, light-headed, and/or tired. There are no long-term effects of fasting. If you feel dizzy or nauseous stop the fast and contact the research team.
2. **Urine Pregnancy Test** (women only): There are no risks associated with a urine pregnancy test.
3. **Venous Blood Sample:** Blood sampling from a vein poses very little risk to subjects. There is a small chance that drawing your blood will be painful or will cause bleeding, infection (less than 1%), or dizziness. We will minimize the chances of these risks by drawing blood while you are lying down and by using only trained personnel.
4. **Maximal Exercise (fitness) Test:** The maximal exercise test may leave you with feelings of exertion, fatigue, and breathlessness. You may feel some discomfort due to the monitoring equipment (e.g. mouthpiece or mask). Serious complications including orthopedic injury, myocardial infarction (heart attack), arrhythmia (abnormal heart rate), hemodynamic instability (blood pressure changes), and death are rare.
5. **Temporarily stopping hormonal birth control (some women only)**: The biggest risk of stopping birth control is the risk of pregnancy. If you are sexually active and are stopping your hormonal birth control, you will need to use a backup method of birth control such as condoms or abstinence. If you were to become pregnant, you would need to notify the study team. Pregnant women cannot participate in the study.

   Additional risks of stopping birth control may depend on the reasons that you may have started birth control. Your periods will return to what they were like before starting birth control. This means that for some women they will not notice a change but for other women their periods could get heavier, more painful, or more irregular and they may notice worsening of menstrual symptoms such as bloating, mood swings, or headaches.

   If you feel any side effects are not tolerable and you want to restart your birth control, that is your choice. However, you must tell the study team, as you will need to stop participating in this study.

6. **Magnetic Resonance Imaging:** Before your scan, you will be asked a series of medical history questions to make sure you are safe to go into the scanner. The MRI scanner uses a powerful magnetic field to create images of the body. Some people should not participate in MRI studies. These include persons with shrapnel or certain metallic implants, such as prostheses, aneurysm clips, or persons with electronic implants, such as cardiac pacemakers or implanted hearing devices. The magnetic field generated by the MR machine can cause a displacement or malfunctioning of these devices. There are no other known risks to body tissues associated with the magnetic field strength used in this study. Women who are pregnant should not participate in MR studies. The potential risks to a fetus are not known.
   Some people report anxiety or claustrophobia in the MR scanner since the head must be placed fully inside the scanner tube. If anxiety or claustrophobia occurs, please let us know and we will stop the scan and bring you out of the scanner. In addition, fatigue and physical discomfort are possible. The MRI scanner makes a great deal of noise when taking images. To minimize the level of noise, you will be fitted with disposable earplugs or headphones to wear during the procedure. These may be a bit uncomfortable to wear, and will not eliminate all sound so that communication with you is still possible
7. **Lying down**: you will be asked to lie down for 1-2 hours. This might make you feel tired, stiff,

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and/or bored. There are no known long or short-term risks for lying down for 1-2 hours.

8. **IV Catheter:** Risks of placing an IV catheter in the arm include bruise or clot formation and infection. However, a qualified person will place the IV catheter and will take precautions to avoid bruising. Minor risks may be: pain at the site of catheter insertion, bruising after we remove the catheter and soreness over the site. These should all be short-lived and will decrease after several days. Serious complications are unlikely.
9. **Low Oxygen (Hypoxia):** Hypoxia exposure will last approximately 30 minutes total but may be increased to 45 minutes to obtain all research data. Short-term exposure to breathing air low in oxygen generally causes an increase in breathing and heart rate, similar to visiting higher elevations in the Rocky Mountains. Possible sensations as a result of breathing air low in oxygen are limited to slight discomfort, lightheadedness or mild headache. This trial will be performed while lying down, minimizing the risk of injury. If this procedure makes you feel too uncomfortable, you can stop at any time.
10. **Indomethacin:** Indomethacin is a drug similar to ibuprofen. In research, it is used to cause blood vessels to stop dilating (getting larger). Blood pressure may increase slightly. However, indomethacin should not increase your blood pressure more than exercising (like climbing a flight of stairs) or mental stress. You will be monitored continuously for any side effects.

    Adverse reactions: The most common adverse reactions to indomethacin, as reported by clinical trials with repeated daily dosing, with an incidence of greater than 1% (more than 1 out of 100 people) are as follows: gastrointestinal (GI) and nervous system symptoms. Other adverse events reported were whole body edema, high blood pressure, skin rash, GI distress (nausea, pain, diarrhea, vomiting), headache, drowsiness, dizziness.

    Adverse reactions: The least common adverse reactions to indomethacin, as reported by clinical trials with repeated daily dosing, with an incidence less than 1% (less than 1 out of 100 people) are as follows: weight gain, fever, heart palpitations, dizziness; GI distress (including bleeding, rectal bleeding, anorexia, or bloating); nervous conditions (like anxiety, insomina, muscle weakness, syncope, drowsiness, dry mouth, inability to concentrate excessive or reduced movement); breathing difficulty, runny nose, cough; altered taste sensation, vision or hearing; pulmonary edema, dyspnea, rapid fall in blood pressure, acute anaphylaxis.

11. **Antacid:** Antacid is a drug used for the relief of acid indigestion, heartburn, sour stomach, upset stomach, and pressure and bloating (gas). Adverse reactions can occur if you have kidney disease or a magnesium-restricted diet. This product may interact with certain prescriptions and not allow them to be fully absorbed in the stomach.

12. **High Carbon Dioxide (Hypercapnia):** Breathing carbon dioxide increases brain blood flow. It is unlikely you will feel any effects of breathing higher concentrations of carbon dioxide. The most likely response to this condition is an increase in breathing rate. There is also a possibility that you might feel lightheaded or dizzy; these symptoms stop after you change back to room air. These trials will be performed while you are laying down, minimizing risk of injury. If this procedure makes you feel too uncomfortable, you can stop at any time.
13. **Breach of Confidentiality:** There is a risk that your information could become known to someone not involved in this study. Personal information such as name, gender, date of birth, and medications will be stored in a locked file cabinet in Dr. Schrage's laboratory. Study records will be coded with a number and only study personnel will have access to the link connecting your name to the collected data. After the study is complete, we will remove all identifying information so that study data is coded during analysis and

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publication. Your information will be coded to remove any personal identifiers during data analysis or research publications.

Will being in this study cost me anything?

There will be no cost to you for any of the study activities or procedures. If you need treatment for side effects while you are on the study, you or your insurance will need to pay for this treatment.

Will I be paid or receive anything for being in this study?

Visit or procedure	Payment amount
Screening Visit	$20
Exercise and/or Gas Challenge Visit	$20
MRI study visits	$30/per hour; rounded to the next half hour
Completing both MRI study visits	Bonus $50
If you complete all procedures and visits	~$210 total

If a rescreening visit is required, you will be paid the same amount as for the initial screening visit ($20). Payment will be provided at the end of the study. If you choose to leave early or we take you off the study for any reason, you will receive a pro-rated amount based on the total number of hours in which you participated in the study visit.

What happens if I am injured or get sick because of this study?

If you are injured or get sick because of this study, medical care is available to you through UW Health, your local provider, or emergency services, as it is to all sick or injured people.

If it is an emergency, call 911 right away or go to the emergency room.
For non-emergency medical problems, contact the study team for instructions.
Call the Lead Researcher, William G. Schrage, Ph.D., at 608-262-7715 to report your sickness or injury.

Here are some things you need to know if you get sick or are injured because of this research:

If the sickness or injury requires medical care, the costs for the care will be billed to you or your insurance, just like any other medical costs.
Your health insurance company may or may not pay for this care.
No other compensation (such as lost wages or damages) is usually available.
UW-Madison and UW Health do not have a program to pay you if you get sick or are injured because of this study.
By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. You keep your legal rights to seek payment for care required because of a sickness or injury resulting from this study.

How will the researchers keep my research information confidential?

We have strict rules to protect your personal information and protected health information (PHI). We will limit who has access to your name, address, phone number, and other information that can identify you. We will also store this information securely. Since this study will be funded by the National Institutes of Health, we will obtain a Certificate of Confidentiality when the funds are granted. A Certificate of Confidentiality prohibits researchers from disclosing information or biospecimens that may identify you in a legal proceeding or in response to a legal request without

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your consent. We may publish and present what we learn from this study, but none of this information will identify you directly without your permission.

However, we cannot promise complete confidentiality. Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. These groups will maintain your confidentiality. By signing this consent form, you are authorizing this access to your records. We may also have to tell appropriate authorities, such as child protective services or health care providers, if we learn during the study that you or others are at risk of harm (for example, due to child or elder abuse, or suicidal thoughts).

Authorizing the research team to use your PHI means that we can release it to the people or groups listed below for the purposes described in this form. Once your health information is released outside UW-Madison or UW Health it may not be protected by privacy laws and might be shared with others. Also, with appropriate institutional permissions and confidentiality protections, we might use information and biospecimens that we collect during this study for other research or share with other researchers without additional consent or authorization from you or your legally authorized representative.

Who at UW-Madison can use my information?

Members of the research team
Offices and committees responsible for the oversight of research
Personnel who schedule or perform medical tests or procedures, handle accounting and billing, or do other tasks related to this study
Other researchers at UW Madison

Who outside the UW-Madison may receive my information?

U.S. Office for Human Research Protections
The U.S. Food and Drug Administration (FDA)
The study sponsor, NIH
Companies or groups performing services for the research team, such as laboratories outside UW-Madison

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

Will information from this study go in my medical record?

Only a small amount of the information we collect for this study will go in your medical record about the number and types of cells in your blood. The researchers are not required to release health information to you if it is not part of your medical record.

What will happen to my data and biospecimens after my participation ends?

We will keep your blood test results, MRI data, and some of your blood samples (biospecimens) for an indefinite period of time, meaning we have no plans of ever destroying your data. Keeping data for future research is called “banking.” The banked data will be kept in a secure location for use by researchers. The data that will be banked will be obtained during the course of the study; you will

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NOT need to undergo any additional procedures. The banking of data is required for participation in the study.

This is what will happen with your banked data and biospecimens:

- We will use the data or biospecimens in future research projects about brain blood flow or sex differences. We may also use them for other types of research.
- The data or biospecimens may be shared with other researchers at the University of Wisconsin-Madison
- The banked data or biospecimens will be labeled with a code instead of your name.
- When we give your data or biospecimens to other investigators for research projects, they will not be able to use the code to figure out which data are yours.
- The research team will maintain a link between your data or biospecimens and your identifiable information kept by the study team.
- You can request to have your data or biospecimens removed from the bank by contacting the research team at any time.

This is what will NOT happen with your banked data:

- Banked data or biospecimens will not be shared with your health care providers or used in your treatment outside this study.

The risk related to banking of data is a breach of confidentiality. There is a risk that your information could become known to someone not involved in this study. If this happens, it could affect your relationships with family and friends, affect your employment, or make it harder to get insurance or a job.

How long will my permission to use my health information last?

By signing this form you are giving permission for your health information to be used by and shared with the individuals, companies, or institutions described in this form. Unless you withdraw your permission in writing to stop the use of your health information, there is no end date for its use for this research study. You may withdraw your permission at any time by writing to William G. Schrage, Ph.D., University of Wisconsin-Madison, Department of Kinesiology, 1300 University Ave, Madison, WI 53706.

Beginning on the date you withdraw your permission, no new information about you will be used. Any information that was shared before you withdrew your permission will continue to be used. If you withdraw your permission, you can no longer actively take part in this research study.

Use of email

We are requesting your email address so we can schedule study visits and send out study visit reminders. Email is generally not a secure way to communicate about your health as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, please contact William G. Schrage, Ph.D. at (608) 262-7715. You do not have to provide your email address to participate in this study.

What if I have questions?

If you have questions about this research, please contact the Lead Researcher, William G. Schrage, Ph.D., at 608-262-7715

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If you have any questions about your rights as a research participant or have complaints about the research study or study team, call the confidential research compliance line at 1-833-652-2506. Staff will work with you to address concerns about research participation and assist in resolving problems.

Agreement to participate in the research study

You do not have to sign this form. If you refuse to sign, however, you cannot take part in this research study.

If you sign the line below, it means that:

- You have read this consent and authorization form.
- You have had a chance to ask questions about the research study, and the researchers have answered your questions.
- You want to be in this study.
- You give authorization for your protected health information to be used and shared as described in this form.

_____

Printed Name of Participant

_____

Signature of Research Participant Date

_____

Signature of Person Obtaining Consent and Authorization Date

Time: ☐☐ : ☐☐ (using 24 hour format)

****You will receive a copy of this form****

Applicable to females only:

□ **I do not currently take hormonal birth control and do not intend to start during this study**

□ **I am currently taking hormonal birth control and consent to stopping while participating in this study**

This study is considered Phase 1 of a larger study. We would like your permission to contact you about participation in Phase 2. In order to participate in Phase 2, you need to successfully complete all of Phase 1 noted above. Second, the study team will need to determine if you are eligible for Phase 2. The phase 2 activities are very similar to the phase 1 study activities. We will explain this in more detail if you agree to be contacted about phase 2

□ **Yes, you may contact me about participation in Phase 2.**

□ **No, I do not want to be contacted about participation in Phase 2.**

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