Official Title: Sodium Regulation in Individuals on Known Dietary Sodium Intake

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University of California, San Diego
Consent to Act as a Research Subject

Sodium Regulation in Individuals on Known Dietary Sodium Intake
(MEASURE Study)

Introduction

Dr. Cheryl Anderson and associates are conducting this research and asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary - whether or not you join is your decision. You can discuss your decision with others (such as family, friends or your physician).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your health care or any other benefits you may be entitled to.
- You can say no even if the person inviting you is part of your healthcare team.
- Please ask questions or mention concerns before, during or after the research.

We are trying to find out if eating high-salt and low-salt diets has an effect on the storage of sodium (salt) in the skin, muscle, and bones of adults. Participation in the study may not benefit you directly, but may result in new knowledge that may help others.

If you decide to participate in the study, you will be assigned to two different diets (high-sodium and low-sodium), each lasting at least 14 days. During that time, all meals will be provided to you by the study. You will visit our UCSD research offices and/or check in with study personnel online via Zoom twice per week for procedures to measure the effect of the assigned diets. Each visit will last between 1-7 hours, depending on the procedures done.

The most commonly expected risks of the study are possible pain, bruising, and/or fainting from drawing blood.

The most serious risks of the study may include low-dose radiation exposure from the IVNAA bone measurements, and possible burns to the skin during MRI measurements. The risk of burns is rare. The risk of radiation exposure is small; the total effective dose of radiation is about 1/2 that of a typical chest x-ray.

Additional, detailed information about this research is provided below. Please feel free to ask questions before signing this consent.

Why have you been asked to participate, how were you selected, and what is the approximate number of participants in the study?
You have been asked to participate in this study because you are an adult with high blood pressure living in San Diego. There will be approximately 50 total participants in this study.

What will happen to you in this study, and which procedures are standard of care and which are experimental?
In addition to the information at the beginning of this form, here are some additional details about what will happen to you if you agree to be in this study. All questionnaires, measurements, and samples collected during study procedures are being done for research purposes.

1. **Baseline visit 1**: Up to a week before starting the study diet, you will complete a short questionnaire online via a Zoom call with study personnel to attain your current medication information and health status. We will also ask you to come into the study clinic to measure your weight, heart rate, and blood pressure. You will also be randomly assigned to 1 of 2 study groups. This means your chance of being assigned to each group is 50:50, like the flip of a coin. Neither you nor the researchers can choose the group to which you are assigned. During the research, the study team members collecting your data will not know which group you are in.
    a. If assigned to Group A, you will follow a high sodium diet for at least 14 days, your usual diet for 10 days, and then a low sodium diet for at least 14 days.
    b. If assigned to Group B, you will follow a low sodium diet for at least 14 days, your usual diet for 10 days, and then a high sodium diet for at least 14 days.
    c. For all participants (both groups), all meals will be provided to you during the two 14-day eating periods. All study procedures described below will be the same for participants in both study groups.

2. **Study foods**: Every day during the two eating periods (14 days per diet, at least 28 days total), you will be asked to eat only the foods provided to you by the study. Alcohol consumption is not permitted during those 28 days. You will also be asked to complete a food diary during each day of the eating periods.

3. **Check-in visits**: In order to determine the effect of the diet on blood pressure, you will be asked to complete a check-in visit every 3-4 days (approximately days 1, 4, 8, and 11of each dietary intervention period). For of these visits, you will measure and record your blood pressure and weight at home. You will also come to our study office to pick up your food for the following days. You will also eat one study-prepared meal online via Zoom as part of the check-in visit and complete an online questionnaire asking how you felt during the week.

4. **Additional blood pressure measurements**: On approximately the first and last day of each eating period (day 1 and day 14), you may have two additional blood pressure measurements taken using Laser Doppler Flowmetry (LDF) and Ambulatory Blood Pressure Monitoring (ABPM).
    a. Laser Doppler Flowmetry uses a weak laser probe that will be placed on your forearm for approximately 1 hour. The probe applies a small amount of heat to the skin that should not cause any discomfort. Then the probe measures blood flow in

small blood vessels in your skin (microvascular flow). This measurement will be done in our study office.

b. For ABPM measurements, you will be asked to wear a small portable, home blood pressure monitor for 24 hours. A trained technician will fit the monitor to you in the clinic, and you will continually wear the monitor for the following 24 hours. The monitor includes a blood pressure cuff that will inflate at predefined times, approximately every 55 minutes. The monitor is attached to a recording device, and your blood pressures will automatically be recorded and stored over the 24-hour period. You will be instructed to perform your usual activities while continuously wearing the blood pressure monitor and return the monitor to our study offices at your next study visit.

5. **Sample collection**: On approximately the first and last day of each eating period (day 1 and day 14), a small fasting blood sample (approximately 1 tablespoon) will be drawn from you at our study offices. You will also be asked to collect a 24-hour urine sample at home and may be asked to collect up to two 24-hour stool samples at home, with supplies that will be provided for you. These samples will be used to analyze mineral excretion as well as microbial content.

6. **Sign up with the American Gut Project (AGP)**: To collect one of the stool samples mentioned above, we will provide you with an American Gut Project collection kit (http://americangut.org/) that includes collection swabs, sample collection instructions, and instructions on signing up for the American Gut Project and registering the swabs as coming from you. The AGP is a separate project that will analyze your stool sample (from used toilet tissue) to better understand human gut health and will provide you with results from the microbiome analysis of your stool sample. If you choose to participate in the AGP, you will complete a separate consent form for that project and fill-in an online questionnaire about your health and eating habits. We predict it will take approximately 30 min – 1 hour to complete the registration and questionnaire. You may ask for help with signing up and kit registration online if that would be helpful at the time of your MEASURE study visit. Instructions on stool sampling will be provided with the kit. You may still participate in the MEASURE study even if you decide not to participate in the separate AGP project. If you would prefer not to enroll in the American Gut Project, please check and initial the box below.

   ☐ I do NOT wish to sign up for the American Gut Project (AGP). _____ (initial)

7. **MRI to measure sodium in muscle and skin**: On approximately the first and last day of each eating period (day 1 and day 14), ^{23}Na-MRI will be used to non-invasively measure the sodium in muscle and skin of 25 study participants using a 3.0T whole-body MRI system housed at the UCSD Center for Functional MRI. If you are eligible to complete the MRI measurements, you will be asked a set of screening questions to make sure it is safe for you to have the MRI done. Prior to entering the imaging room, you will be required to remove any metal objects, including jewelry, from your clothes and body. You will also be asked to empty your bladder since emptying the bladder will be more difficult once the procedure is under way.

During the MRI, you will be placed on the scanner bed with attention to your comfort and asked to remain as still as possible throughout the whole procedure. You are not required to do anything or perform any tasks during the exam. If you want, you may just sleep. A series of scans, each varying in length from 3 to 15 minutes, will be made to obtain images of your body and/or chemistry, focusing on the lower leg. During these scans the scanner will make tapping sounds.

8. **IVNAA to measure sodium in bone**: Sodium content in bone will be measured in 25 participants on approximately day 1 and day 14 of each eating period. We will measure this with a technique called in vivo neutron activation analysis (IVNAA) in the Biomedical Research Facility II building at the UCSD School of Medicine. If you are eligible for this procedure, you will thoroughly wash your lower arm and hand with soap to ensure the skin is clean prior to the measurement. Then your hand will be placed carefully inside a neutron irradiation cave, with the rest of your body shielded from the neutrons by wearing a lead apron. You will be required to sit relatively still for about 10-20 minutes. This technique generates characteristic γ-rays with fixed energies that will be used to identify the sodium content in bone. Your hand will then immediately be placed carefully inside a detection cave for up to two hours, to detect the sodium γ-ray signal. Four to six hours after irradiation, we will take a second measurement of sodium using the detection cave for up to two hours. You may also be asked to come back to the lab for a third measurement (in 24 hours). Radiation exposure only occurs for the first 10-20 minutes when your hand is irradiated; no additional radiation is involved when your hand is measured in the detection cave. After each detection session, you will be asked to thoroughly wash your hands again. During one of your measurement sessions, you will be asked to complete one of the following procedures to estimate the volume (size) of your hand; either 1) insert your hand into a container of room temperature water for a few seconds to measure the amount of water that spills out of the container, or 2) measure your hand using a ruler.

As a participant in this research study at UCSD, you will be expected to:

- Eat only the food and drinks provided to you by the study, as instructed.
- Not drink alcohol during the study eating periods (at least 28 days).
- Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigator or research staff if you believe you might be pregnant.
- Store the study foods as instructed, and in a safe place for your use only.
- Fill out your food diaries and complete questionnaires as instructed.
- Collect urine and fecal samples and home blood pressure measurements (ABPM) as instructed, and return all samples and monitors to the study office at the specified study visit.
- Ask questions as you think of them.
- While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

How much time will each study procedure take and how long will the study last?

Your participation in the study will last for approximately 40 days total. Each of the four main measurement visits (on days 1 and 14 of each eating period) will last approximately 3 to 7 hours, depending on the measurements you complete. During each measurement visit you will complete either an MRI measurement (lasting approximately 60 minutes each) or IVNAA measurements that will take approximately 2.5 hours each. Each of the 8 check-in visits will last approximately 1 hour.

What risks are associated with this study?
Participation in this study may involve some added risks or discomforts. In addition to the risks described at the beginning of this form, the following are possible risks or discomforts from study activities:

1. **Blood drawing**: There may be some discomfort, bruising, or bleeding at the site where the blood is drawn. Rarely, fainting occurs because of drawing blood. Precautions will be taken to minimize these risks by using sterile technique and applying pressure to the site after the needle is withdrawn.

2. **The nutrients given by the diet** in this study do not exceed the upper tolerable limits. As with all dietary studies, we will ask you regularly about any adverse events such as abdominal pain, nausea, vomiting, headache, diarrhea, constipation, or allergic-like reactions, in addition to the usual risks associated with eating and drinking a normal diet.

3. **Ambulatory Blood Pressure Monitoring**: This procedure requires you to wear a blood pressure cuff on your arm continuously for a 24-hour period. You will feel the cuff inflating as it measures your blood pressure approximately every hour during the day and night. This may be uncomfortable and may wake you up at night when it measures your blood pressure. You will be advised to take caution when driving or operating machinery if you did not get sufficient sleep while wearing the 24-hour blood pressure monitor.

4. **Laser Doppler Flowmetry**: This procedure utilizes weak laser probes that are taped to the skin on your forearm. The lasers can hurt your eye if you stare into the light for a long time. To avoid this, we do not turn on the laser until the probes are taped to a surface. During the procedure, the skin is heated with the laser and feels very warm but will not hurt. We measure the temperature of your skin under the holders. The heating makes the skin under the holder red, like when you take a hot bath. The redness goes away within several hours. Some people may be more sensitive to heating. If your arm feels too hot, tell us, and we will reduce or stop the heating. The sticky disks or tape used to attach the laser probe may irritate your skin or cause a temporary rash. We have ointment that you may use on the rash. Prior to the procedure, tell us if you are sensitive to tape. If a disk sticks very strongly, we may use an adhesive remover like that used in a doctor’s office to remove the disks. You could have an allergic reaction to the adhesive remover, which could include rash, itching, fever, or breathing problems. Also, an allergic reaction could include changes in pulse, and/or blood pressure, convulsions, shock, and/or fainting. If a bad reaction to the remover should occur, we will summon medical help right away.

5. **Questionnaires**: Some people become embarrassed or uncomfortable at being asked questions about their health. During the questionnaires, you can refuse to answer any questions that you do not want to answer, or you can terminate the session at any time.

6. **MRI**:
    a. Magnetic Field: Some individuals should not participate in an MRI study. These include persons with some types of metallic implants, such as aneurysm clips or some types of prostheses (fake body parts), or persons with electronic implants, such as cardiac pacemakers, in their body. The magnetic field in the MRI scanner can cause these devices to heat up and move or stop working properly. Dental fillings are not a problem. If you complete MRI measurements during the study, you will undergo a safety screening before entering the scanner room.

    b. Collision hazard: Due to the magnetic fields that are present in the MRI scanner, loose magnetic objects (pocketknives, key chains, pens, necklaces, earrings, etc.) can fly into the magnet with great force if brought into the environment of the MRI scanner. You will be asked to remove such objects from your clothes and body in order to prevent such an occurrence. All of these precautions will be reviewed with you immediately before you have the MRI, and we will set up a security zone to prevent objects containing iron from coming close to the magnet.

    c. Radio-wave effects: If metal wires or sensors, as used to measure your heart rate, breathing or electrical brain activities, are attached to a person being imaged, the energy of the imaging coils of the MRI scanner may, in rare cases, cause burns where the metal wires contact the skin. The scanner operator is aware of this risk and knows the proper handling and placing of such sensors and wires to avoid this problem.

    d. Nerve stimulation: Some subjects undergoing the rapid scanning procedures have experienced minor nerve stimulation effects, such as muscle twitches and tingling sensations. There are no known risks associated with these effects. The devices used in our research create varying magnetic fields that are within the limits specified by the Food and Drug Administration (FDA). If, however, the feeling causes you discomfort, notify the researcher at any time and the study will be stopped.

    e. Claustrophobia: Occasionally, some people experience feelings of claustrophobia (feelings of being “closed in”) due to the relatively restricted space within the MRI machine. Mirrors will be placed to allow you to see outside of the scanner or to watch a movie in order not to feel uncomfortable inside the scanner. If you experience claustrophobia during the study, the study will be stopped. If you are claustrophobic, you will not be able to participate in the study.

    f. Hearing: The MRI scanner produces tapping sounds during operation, which may be unpleasant. To minimize any discomfort, you will be provided with disposable earplugs and headphones.

g. Incidental findings: The series of scans being completed in this study are for research purposes only and are not sufficient for clinical diagnosis or treatment planning. They will not routinely be reviewed by a radiologist. However, it is possible that an incidental finding is discovered either during your participating in the study, or at some point in the future when researchers are reviewing and/or analyzing the MRI images. An incidental finding is a finding of potential medical importance that is beyond the aims of the study. Any suspected incidental findings will be reviewed by a radiology specialist. If the finding is confirmed, you will be contacted, and offered a copy of the radiology report to share with your doctor for further evaluation and follow up. If you would prefer not to receive information about incidental findings, please check and initial the box below.

☐ I do NOT wish to be contacted regarding incidental MRI findings. _____ (initial)

7. In Vivo Neutron Activation Analysis (IVNAA):

a. Radiation exposure: During your participation in this research study, you will be exposed to radiation from scheduled IVNAA scans, if you complete IVNAA measurements. The IVNAA procedure will be done to the hand 4 times during the 40 days of the study, at the beginning and end of each eating period. The total exposure resulting from these four imaging scans is calculated to be approximately 120-288 mSv for the hand dose and 0.096-0.116 mSv for the whole body effective dose. The hand dose range is approximately 24%-58% of the 500 mSv annual limit allowed for occupational radiation workers. The whole body effective dose is less than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6mSv.

Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, Dr. Cheryl Anderson, and/or your primary doctor.

b. Sitting: Additionally, for this test you will be required to sit relatively still for up to 2 hours during the bone Na measurements, and this may pose some discomfort.

c. Lead exposure: During IVNAA procedures there is a negligible risk of exposure to lead particles. The pieces of equipment used to irradiate your hand and to detect the sodium γ-ray signal in your hand bones are surrounded by lead shielding. This shielding is used to limit radiation exposure to other parts of the body, similar to using lead aprons during dental and other x-ray procedures, and to improve the equipment's ability to accurately measure the sodium stored in your hand bones. The lead shielding surrounding the equipment is covered with a plastic covering to prevent potential exposure to lead particles from accidentally touching the lead shielding. To further reduce your risk of exposure to lead particles, you will be asked to thoroughly wash your hands after each IVNAA detection session.

8. **Loss of confidentiality**: Loss of confidentiality is a risk related to the research. Although this risk is a possibility, safeguards are in place as listed in the confidentiality section.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Are there risks to the reproductive system or a developing fetus?

MRI and IVNAA procedures may involve risks to the embryo or fetus that are currently unforeseeable. For this reason, participants in this investigational study should not become pregnant. All female participants of childbearing potential will be tested up to for pregnancy 5 times throughout the study in order to be as sure as possible that you are not pregnant before completing MRI or IVNAA procedures. Using a small urine sample, pregnancy tests will be performed during the screening visit and each of the four main measurement visits. If you have a positive pregnancy test, we may withdraw you from the study. If, while participating in the study, you become pregnant or suspect you have become pregnant, please contact Dr. Anderson or research personnel immediately so that your continued participation in the study can be reevaluated.

What are the alternatives to participating in this study?

Participation in this research study is voluntary and the only alternative is to not participate.

What benefits can be reasonably expected?

There may or may not be any benefit for participation in this study. In addition to the information listed at the beginning of this form you may learn about how your diet can affect your body's sodium content, which could have implications for blood pressure and chronic disease risk. This study may benefit society by providing data on new and novel procedures for measuring sodium distribution in body tissues, which can potentially benefit many research topics and lead to new diagnostic and therapeutic tools.

What happens if you change your mind about participating?

If you decide that you no longer wish to continue in this study, simply inform a research team member in person or by phone at (858) 633-7251 or contact Dr. Cheryl Anderson at (858) 534-4456. You will be requested to return to the study office for a final measurement visit.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?

You may be withdrawn from the study for the following reasons:

1. If the researchers believe it is in your best medical interest to withdraw.
2. If you are unable to complete the required measurement procedures.
3. If you are unable or unwilling to eat the food prepared for you, throughout the entire eating period.

You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?

You will be provided with all meals, beverages, and snacks at no cost to you during each 14-day eating period (28 days total). In addition, as compensation for your time and travel, you will receive either $60 or $100 at the completion of each main measurement visit (day 1 and day 14 of each diet period; 4 days total). If you complete MRI measurements during your measurement visits, you will receive $60 upon completion of each visit ($240 total for completing all 4 visits). If you complete IVNAA measurements during your measurement visits, you will receive $100 upon completion of each visit ($400 total for completing all visits). If you withdraw from the study, you will only be paid for the measurement visits that you have completed at that time. UCSD will disburse your compensation payments in the form of a gift card.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. You will be assigned a unique study identification number that will be used on your research records instead of your name. This includes all MRI and IVNAA records. No identifying information will be stored in the computer database for the MRI scanner except for your study ID number. Microbiome samples, as well as data derived from their analysis, are also maintained in a confidential and secure manner. Microbiome data will be identified using your unique study ID and a unique identifier from the American Gut Project; all personal identifiers will be removed.

The list that matches your name with your study ID number will be separate from any other identifying information and will be kept in a locked file in the study office or on a secure server. All study documents will only be available to study staff and will be kept in a file cabinet in a locked room for at least 3 years after the end of the study. All study staff are trained and will adhere to the Health Insurance Portability and Accountability Act (HIPAA) regulations regarding your medical records. Research records may be reviewed by people and organizations responsible for conducting the research and for performing oversight of the research. This includes members of the research team and other authorized staff at the University of California, San Diego; the UCSD Institutional Review Board; the Federal Office of Human Research Protections; and the National Institutes of Health who is sponsoring this research.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. Researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research *unless* there is a federal, state, or local law that requires

disclosure (such as to report child abuse, elder abuse, intent to hurt self or others, or communicable diseases), you have consented to the disclosure, including for your medical treatment; or it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institutes of Health which is funding the project or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA). You should also understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research to release it.

This research does not include whole genome sequencing.

Personal identifiers will be removed from the information or biospecimens collected and stored for future use as part of the research; only your unique study code will be included on stored information and specimens. The stored information or biospecimens may be used for future research studies or distributed to another investigator for future research studies without your additional informed consent. The principal study investigator will keep information that links your personal health identifiers with the unique study code that is on the stored sample. This information will be kept in a secure location and would only be shared with research associates in or outside of UCSD with Institutional Review Board approval. If you would like to withdraw consent for future use of your samples or data, please contact Dr. Cheryl Anderson at (858) 534-4456 and she will destroy any of your remaining biospecimens and research data that has been stored. However, samples or related information that have already been used by researchers cannot be withdrawn or destroyed.

Biospecimens (such as blood or urine) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

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.

We may need to report information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may report such information to the appropriate authorities.

Will you receive any results from participating in this study?
Results that could be important for your clinical care will be shared with you. We will not share other results with you.

Who can you call if you have questions?
This study has been explained to you and your questions have been answered. If you have other questions or research-related problems, you may reach Dr. Cheryl Anderson at (858) 534-4456.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____ _____
Subject's signature Date

_____ _____
Signature of the person conducting the informed consent discussion Date

For participants who cannot read: An impartial, literate witness must be present during consent procedures and must read and sign the statement below:

I, the witness, attest that the information contained in this written consent form has been read and explained to the participant. The participant appears to understand the purpose, procedures, risks and benefits of the study and has voluntarily agreed to participate in this study.

_____ _____
Signature of witness Date