

CONSENT TO TAKE PART IN A RESEARCH STUDY

Title of Study: Carbon Dioxide: A Pilot Study of a Hypothesized Mechanism to Explain Cognitive Impairment

Principal Investigator: Howard M. Kipen, MD, MPH

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this study?

Dr. Kipen is the Principal Investigator of this research study. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team.

Dr. Kipen may be reached at 848-445-6091 or Rutgers-Environmental and Occupational Health Sciences Institute (EOHSI), 170 Frelinghuysen Road, Piscataway, New Jersey 08854.

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

Why is this study being done?

Carbon dioxide (CO₂) is a naturally occurring gas found in our air. High levels of CO₂ have been associated with temporary problems in thinking, also called cognitive impairment. The purpose of this study is to learn the biological reasons for these problems.

Who may take part in this study and who may not?

Inclusion criteria are:

- Age between 18 and 30 years
- History of COVID-19 vaccination
- Weigh at least 110 pounds

Exclusion criteria include:

- cardiovascular disease, including a history of stroke
- diabetes requiring the use of insulin
- pregnancy
- colorblindness
- asthma attack within the past five years
- history of a severe anxiety or panic disorder
- ever experienced a panic attack
- medications which may affect cognition such as beta-blockers or CNS depressants
- medications for anxiety disorders
- respiratory symptoms in the previous 4 weeks
- use of sedating cold/allergy medications in the previous week
- use of marijuana in the previous week
- consumption of alcohol in the previous 24 hours

Individuals with a history of head trauma or neurosurgery, or neurological disorder (other than headaches or peripheral nerve disease) should **not** participate in this study as these may impact neuroimaging results.

Other Contra indications for MR imaging:

- Ferrous material implanted in or on the body, including, surgical clips, bullets, or electrical devices such as a pace-maker, or nonremovable ferrous jewelry (fillings in teeth and permanent retainers are permitted).
- Individuals with surgical pins or plates above the neck are excluded. Surgical pins or plates below the neck are exclusions, except when the material is fixed to bone, and considered acceptable by the *Reference Manual for Magnetic Resonance Safety. Implants and Devices, 2020 Edition*. Almost all recent orthopedic implants are made of materials that are not ferromagnetic and therefore are safe for scanning, and even though some screws are still made of ferromagnetic materials these are firmly screwed into bone. In cases where the material is unknown or deemed unsafe for scanning by the *Reference Manual for Magnetic Resonance Safety. Implants and Devices the participant will be excluded*.
- History of eye injury involving metallic materials, shavings in eyes, or welding without a face mask
- Lead/iron tattoos
- Claustrophobia (history of significant anxiety in closed places).
- Back problem that would prevent the subject from laying still comfortably for up to 90 minutes.
- Deafness

Each exclusion is to ensure the safety of the participant, and to avoid unnecessary psychological or physical discomfort, or in the case of neurological disease because the individual's brain may show differences that make it harder to include in data analysis.

Why have I been asked to take part in this study?

You have been asked to take part in this study because you are a healthy adult who responded to an advertisement for volunteers.

How long will the study take and how many subjects will take part?

The study will take two study visits, each about 8 hours in length (16 hours total).
Up to 12 subjects will participate and the study will take 2 years to complete.

What will I be asked to do if I take part in this study?

You will participate in 2 study visits. You will be asked to refrain from using cold/allergy medications or marijuana one week before each study visit and refrain from alcohol the day before each study visit.

At the first study visit, your height and weight will be measured. If you are female, you will be given a pregnancy test.

- During each study visit, you will spend 2.5 hours sitting at a desk in the EOHSI Controlled Exposure Facility (CEF). Up to four study volunteers will be in the CEF. You will be given headphones and have access to a laptop. You will be asked to remove your face mask while you are in the CEF.
- In one study visit, you will be breathing clean air (with a normal CO₂ concentration which is about 600 ppm). During the other study visit, you will be breathing a higher level of ozone (2500 ppm). The order of these exposures will be random, like the flip of a coin.
- During the first hour in the CEF, you will be able to read or work on your computer. During the last 1.25 hours of the exposure, you will be asked to complete some tasks on a computer. One task



will take about one hour and will measure your thinking and decision-making. The other task, called the Wisconsin Card Sorting Test (WCST), will take about 15 minutes and involves matching cards on a computer.

- You will have a blood draw before (30 mL or about 2 Tablespoons), after (10 mL or about 1 Tablespoon) and four hours after each exposure session (30 mL or about 2 Tablespoons; the total amount of blood for each exposure will be 70 mL or about 4.5 Tablespoons).
- You will answer a brief (about 5 minutes) questionnaire about the air quality in the CEF and your physical health at the start and end of each study visit.
- After your exposure session, you will be brought to The Center for Advanced Human Brain Imaging (CAHBIR) where you will have an fMRI. After removal of any metal, you will be positioned in the MRI scanner to scan for up to 60 minutes. In the MRI scanner you will be completing cognitive tasks.
- After your fMRI session you will be brought back to the Environmental and Occupational Health Sciences Institute for the four hour post-exposure blood draw, detailed above.

What are the risks of harm or discomforts I might experience if I take part in this study?

Carbon dioxide exposure:

CO₂ itself is generally considered non-toxic at levels up to 5,000 ppm, the federal standard for workplaces set by Occupational Safety and Health Administration of the U.S. Department of Labor. The CO₂ levels used in the exposures are often found indoors in conference rooms and schools. Other studies have used these levels with no adverse events. There are no known persistent effect of acute exposures in healthy individuals. Although some studies have found a decrease in cognitive function with high CO₂ exposure, the decrease is temporary.

Blood draw:

When your blood is drawn, there may be a bruise, or bleeding, or infection, at the place where your blood is drawn. However, infection is rare.

MRI Risks:

There are no known health risks associated with the magnetic field produced by the scanner in healthy adults. Exposure to high magnetic fields is associated with primary or secondary risks in certain patient populations (e.g., patients with pacemakers), therefore such patients are excluded. Subjects with aneurysm clips, neural stimulators, possible metal fragments in the eyes, cochlear implants, artificial cardiac valves, iron based facial tattoos, and body piercings that are not removable are also excluded from participation. The only other risks associated with scanning are claustrophobia while in the magnet, physical discomfort from lying still in the magnet, and the loud sound of the magnet. You will be given a button to press should you need to exit the scanner or capture the experimenter's attention. The study team will review your MRI screening questionnaire with you to make sure that you do not have any issues that would make it hard or risky for you to complete the MRI scan.

Incidental findings: The MRI study is being conducted for research purposes only and is not a clinical evaluation. However, the MRI exam could reveal an abnormality in your brain. This finding may be distressing to you. Scans at the Center for Advanced Human Brain Imaging Research (CAHBIR) are screened for abnormalities. If there is any sign of an abnormality, the scan data is reviewed by a certified neuroradiologist through a contract with University Radiology Group (URG). The neuroradiologist provides a brief written evaluation that includes their recommendation as to whether any potential abnormality is clinically significant, and if it is, provides a recommendation for referral or further evaluation. Dr. Zald, the director of CAHBIR, is responsible for communicating this finding to you if it is deemed clinically significant.



Are there any benefits to me if I choose to take part in this study?

You will not receive any direct benefit from taking part in this study.

What are my alternatives if I do not want to take part in this study?

There are no alternative treatments available. Your alternative is not to take part in this study.

How will I know if new information is learned that may affect whether I am willing to stay in the study?

During the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I Receive The Results Of The Research?

In general, we will not give you any individual results from the study.

However, you will be shown and receive a picture of your brain if participating in the MRI session. The images obtained during this study are limited and are not gathered for clinical diagnostic purposes. However, if your scan reveals an unusual finding, we will have a neuroradiologist look at your scan at no charge to you. If the neuroradiologist thinks that there is something in the scan that may warrant further attention, we will convey the results of this evaluation to you at no charge. We try to get such evaluations accomplished within a week of the scan but cannot guarantee that this will always happen within a week. If the neuroradiologist does think there is something that requires further attention, Dr. Zald or a doctoral level member of the research team will contact you directly to discuss the finding with you. Learning that there is an abnormality on your MRI could cause you psychological distress. Therefore, we typically do not share information about any observed abnormalities until a neuroradiologist has evaluated the scan. Because the scans in the present study are being conducted solely for research, there will only be a very brief report even if an abnormality is observed. Neither Dr. Zald, nor the neuroradiologist, will contact your physician or insurance company regarding the findings. However, if you request it, and sign a release of information form, we can provide your doctor with the pictures from the study that show the observed abnormality and the neuroradiologist's brief report of the evaluation. If needed, we can also provide a referral to a doctor or clinic who specializes in the evaluation and care of the type of problem revealed by the scan.

Will there be any cost to me to take Part in this study?

There is no cost to you to participate in the study.

Will I be paid to take part in this study?

You will be paid \$175 in cash for each study visit (\$350 for completing the study). You will be paid after completing your participation.

How will information about me be kept private or confidential?

All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. All information about you will be stored in our secure electronic database. Only study investigators will have access to these data. All samples will be coded by a study identification number (study ID). Blood samples, coded only by study ID, will be analyzed both at Rutgers University and at Baylor College of Medicine. All staff associated with the project will be trained in procedures for maintaining confidentiality. Results of the research may be presented at meetings or in publications, but your name and identity will never be disclosed. Sometimes, however, researchers need to share information that may identify you with people that work for the University, government regulators, or study sponsor.



The only place that any medical information appears on a sheet with a name is the MRI screening form. The MRI form is kept in a locked file cabinet and is only accessible by the staff of the Center for Advanced Human Brain Imaging Research (CAHBIR) and individuals related to Rutgers University who are involved in research safety oversight

The research team may use or share your information collected or created for this study with the following people and institutions:

- The Rutgers University Institutional Review Board and Compliance Boards
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services

A description of this Basic Experimental Study Involving Humans (BESH) will be available on 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.

What will happen to my information—data and biospecimens—collected for this research after the study is over?

After information that could identify you has been removed, de-identified information and biospecimens collected for this research may be used for other research we conduct without obtaining additional informed consent from you.

What will happen if I am injured during this study?

Subjects in this study will be exposed to certain risks of personal injury as outlined on page 2 of this document. In addition, it is possible that during the course of this study, new adverse effects of carbon dioxide that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or TRICARE/CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University. However, by signing this form, you are not giving up any legal rights to seek further compensation.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?

It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time. If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of data already collected about you, but you must do this in writing to Dr. Howard Kipen, Rutgers-EOHSI, 170 Frelinghuysen Road, Piscataway, NJ 08854. After the study is closed, your data cannot be withdrawn because there may not be any identifiers to link the data with you.

Who can I contact if I have questions?

If you have questions, concerns or complaints about the research, wish more information or if you feel you may have suffered a research related injury, you can contact the Principal Investigator:

Dr. Howard Kipen



Rutgers – EOHSI
848-445-6091

If you have questions, concerns, problems, information or input about the research or would like to know your rights as a research subject, you can contact the Rutgers IRB Director at: Brunswick/Piscataway Health Sciences IRB 335 George St., Liberty Plaza Ste. 3100, New Brunswick, NJ 08901, (732)235-9806 or the Rutgers Human Subjects Protection Program at (973) 972-3608 or (732)235-9806, email us at human-subjects@research.rutgers.edu, or write us at 335 George Street, Liberty Plaza Suite 3200, New Brunswick, NJ 08901.

AGREEMENT TO TAKE PART IN RESEARCH

Subject Consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name (Print): _____

Subject Signature: _____ Date: _____

Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (Print): _____

Signature: _____ Date: _____

