Strategies to Augment Ketosis: Ketone Conferred Resiliency Against Sleep Restriction (STAK-Sleep)

The Ohio State University

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The Ohio State University Consent to Participate in Research

Study Title: Strategies to Augment Ketosis: Ketone Conferred Resiliency Against Sleep Restriction (STAK-Sleep)

Principal Investigator: Jeff Volek, PhD, RD

Study Sponsor: Department of Defense

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

Sleep deprivation is a major problem in military populations. Some major consequences of sleep loss are inability to concentrate, poor work efficiency, and increase in errors during daily tasks. There is some evidence that ketone ester supplements may lessen the adverse effects of sleep restriction. The main purpose of these supplements is to raise your blood concentration of ketones, which are safe, small molecules that appear in the blood during fasting, when following a ketogenic diet, or consuming ketone supplements.

The main purpose of this study is to examine if ingesting a ketone ester supplement, twice daily, can improve cognitive and physical performance during short-term sleep restriction.

2. How many people will take part in this study?

We are planning to enroll a total of 60 men and women.

3. What will happen if I take part in this study?

Overview

Eligibility for participation in this study is dependent on the results of the tests conducted during the screening visit. Participants who qualify will be familiarized with all testing. All subjects who participate in this study will undergo a 5-day testing period that includes 4 consecutive nights of sleep restriction (50% of usual sleep). This 5-day testing period will be done twice separated by at least a 2-week washout period (see **Fig 1**).

During one testing period you will receive a ketone ester supplement and during the other period you will receive a placebo. This will allow us to determine if ketone supplements have any impact on cognitive and physical performance under sleep loss conditions. You will be taking one single dose of the ketone ester (Juvenescence Labs MetaSwitch®); this dosing is considered an average serving size for humans by the FDA and has been previously tested in one of our OSU approved studies (#2020H0005, approved on 13th March 2020). We expect no significant side effects besides potential GI discomfort (i.e., nausea, flatulence) immediately after consuming the ester, although this response varies between people.

On Days 1 and 5, you will undergo a series of cognitive and physical tests. Throughout the study, you will also be asked to wear several wearables such as a watch fitted with heart rate and sleep monitoring, a sensor on your arm that measures ketones and glucose, and a heart rate monitor during workouts. After you complete 5 days in the

study, you will then wait two weeks and return to the lab for another 5 days to receive the other supplement.

Screening

The purpose of the screening meeting is to determine if you meet our qualifying criteria, inform you of your rights as a participant, and to confirm your willingness to participate. We will provide you with a few questionnaires including medical history, physical activity history, dietary history, and a sleep screening form. If you meet inclusion criteria we will draw a small amount of blood to perform a metabolic panel to make sure all values are normal. You cannot participate in this study unless you are deemed safe to do so based upon the full screening process and you read, fully understand, and sign this informed consent document providing us with written consent.

Eligibility Criteria

We are looking for healthy men and women with a body mass index (BMI) <35 kg/m^2 between the ages of 18 and 40 years. We will exclude you for any of the following reasons:

- You are <18 or >40 years of age
- You do not fit the body mass index (BMI) requirements
- No diagnosed sleep disorders (i.e., sleep apnea, insomnia)
- You have gastrointestinal disorders or suffer from food allergies that would interfere with consuming the study supplements.
- Drink alcohol in excess of 3 drinks/day or 14 drinks/week
- Have any conditions or contraindications to blood draws.
- Have been diagnosed with diabetes, liver, kidney, or other metabolic or endocrine dysfunction, or use diabetic medications other than metformin
- Currently consume a low carbohydrate or ketogenic diet or have done so in the last 3 months
- Have experienced weight loss of >10% of your body weight within the last 6 months
- Are pregnant, lactating, or planning on becoming pregnant during the study
- Have any major psychiatric disorders (e.g., schizophrenia, bipolar disorder)

Taking certain dietary supplements or beginning any exercise programs outside of your normal physical activity may interfere with testing results that will be conducted during study. You will be asked to discontinue any new training programs or usage of these supplement(s) for the full duration of the study.

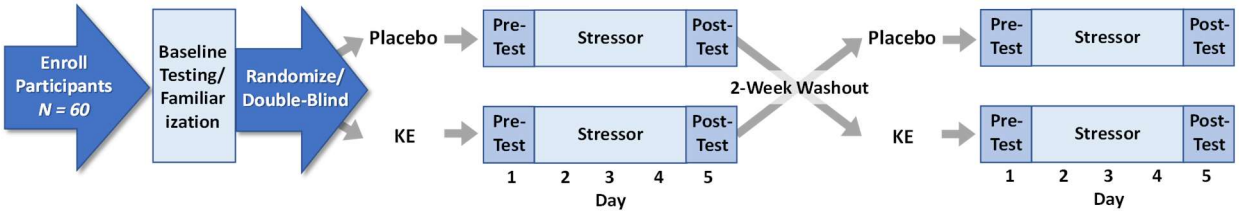

Figure 1 | Experimental Design

Familiarization:

1. The primary goal is to make you feel comfortable with all the tasks in the study.
2. You will receive a wrist-based HR monitor and a sensor to apply to the back of your arm for measuring glucose and ketones a week before starting each 5-day testing period. This familiarization protocol is intended to capture a week of normal free-living data, including your typical sleep pattern.
3. We will show you each of the experimental tests, such as surveys, computer/iPad assessments, virtual shooting scenarios, squat jumps on a force plate, and Quick Board reaction time.
4. We will provide proper weightlifting lifting and running form expected during training days to minimize exposure to injury.

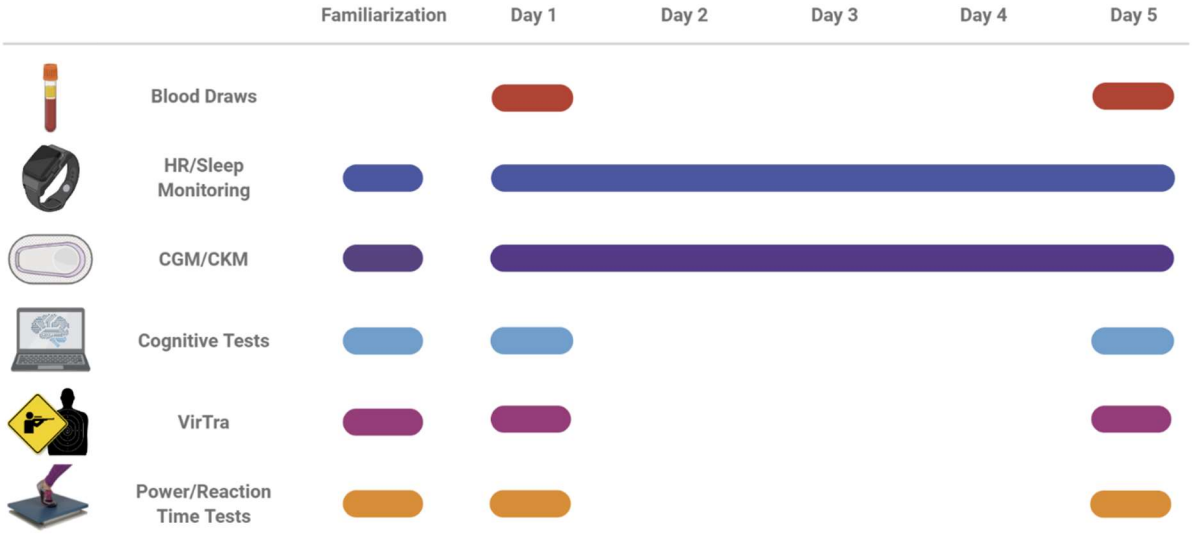

Figure 2 | 5-day overview.

Sleep Restriction Protocol:

1. At the consent session you will have filled out a Pittsburgh Sleep Questionnaire about your sleeping habits.
2. After the familiarization session we will monitor your sleep the week before the intervention to assess your normal sleeping patterns.

3. When you return for day one testing the team will assign you 50% of your habitual sleep to follow for 4 consecutive nights. The goal is to provide you a consistent start time for the new sleep restriction:
    a. Example 1: if you usually sleep **6** hours per night, then 50% reduction will mean that you will sleep **3** hours per night for 4 nights in a row. A target sleeping schedule for you will be from **3am – 6am**.
    b. Example 2: if you usually sleep **8** hours per night, then 50% reduction will mean that you will sleep **4** hours per night for 4 nights in a row. A target sleeping schedule for you will be from **3am – 7am**.
4. You will resume normal sleeping habits after Day 5 testing.

Test Day 1 & 5:

1. You will arrive at the testing lab (305 Annie and John Glenn Avenue, Columbus, OH 43210) between 6:00-9:00h, hydrated and after an overnight fast (<8h).
2. *Blood Draws:* After 10 minutes of rest, a trained phlebotomist will obtain a small amount of blood (20 mL or 4 teaspoons) from an arm vein using a small needle.
3. *Supplement Ingestion:* The first supplement dose (either KE or PL) will be consumed before commencing the cognitive testing battery.
4. *Cognitive Tests:* A series of computer and iPad-based cognitive tests will be administered to measure your attention, information processing, memory, function, inhibition, and social and emotional domains.
5. *Surveys:* A secondary assessment of well-being will be administered in the form of questionnaires: McGill Pain Questionnaire, the Shortened Profile of Mood States, and the Pittsburgh Sleep Quality Index.
6. *VirTra:* You will be tested on shooting competency using compressed gas weapons. The system is designed to record each weapon action (pistol/rifle) and simulate bullet trajectory and recoil without firing an actual projectile (i.e. bullet). Measures of reaction time, accuracy, precision, and spread will be recorded by a trained team member present in the room.
7. *Force plate*: Whole body power will be assessed with a repetitive 10-jump test performed on a force plate.
8. *Response time*: Upper body and lower body reaction time will be measured using the Quick Board. The Quick Board system is comprised of an iPad Quick Board application and a footpad with 5 sensors placed equidistant from each other, with two at the front of the footpad, two at the back of the footpad, and one in the middle of the footpad. Upper and lower body reaction time will be measured using hands and legs, respectively. Prompts will be displayed by the iPad software to instruct the participant with quick time tasks.
9. After Day 1, you will be instructed to restrict sleep to 50% of your normal sleeping duration. After testing on Day 5 (i.e. after 4 nights of consecutive sleep restriction) you can resume regular sleeping habits for two weeks until you return to the lab for the second cross-over condition.

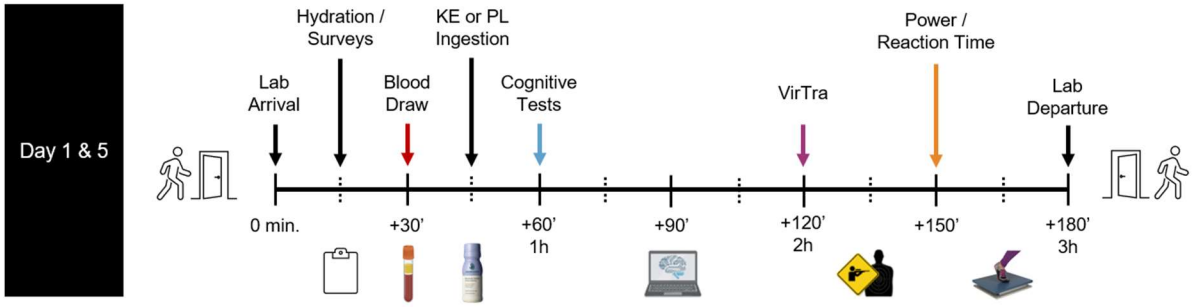

Figure 3 | Day 1 and 5 Timeline.

Day 2, 3, & 4:

1. You will be asked to maintain normal training schedule during these days.
2. The goal is to maintain training across conditions.
    a. For example, if you have to run and train in the gym during between testing dates, you should be able to replicate these exercises during the second experimental condition
3. To measure your exercise we will provide you with a survey (IPAQ) to note the exercises you will perform and how intense you performed those exercises.

Participant Completion

After you complete the study, an exit meeting will be scheduled with a member of the study team. You will receive your payment for participating in the study and any personal data that has been analyzed. This information will psychological and physical results, plus other blood analysis results completed at that time. Analysis of most of your data will be completed after you have finished the study, and we will make that available to you as well. You will only receive your own data.

Analysis

All the blood we collect from you (we refer to them as biological specimens) will be kept in cold storage at -80^{o}C in our biochemistry lab. Your biological specimens will be labeled with your subject identifier and not your name to maintain confidentiality. During sample analysis some of your biological specimens will be sent to collaborators who will perform some of the analysis, but your name will not be shared with them. Only your subject identifier will be provided to our collaborators. We will be measuring several markers in your biological specimens related to metabolic health. Samples may be stored for up to five years for analyses of health-related markers related to this research project.

Table 1 | Experimental Checklist.

	Blood Draw	HR Monitoring	CGM/CKM	Cognitive Tests	Surveys	VirTra	Power
Familiarization		x	x	x	x	x	x
Day 1	x	x	x	x	x	x	x
Day 2		x	x				
Day 3		x	x				
Day 4		x	x				
Day 5	x	x	x	x	x	x	x

HR, heart rate; CGM/CKM, continuous glucose/ketone monitoring; VirTra, Virtual Training; RT, reaction time.

Continuous Glucose/Ketone Monitoring

We plan to incorporate the use of a novel, continuous glucose, and ketone monitoring (CGM/CKM) system developed by Abbott Biowearables. The sensor is applied to the back of the arm where it will continuously measure your glucose and ketones. The sensor is worn for a period of 2-wk. The first sensor will be inserted with assistance from the study team after familiarization. A new sensor will be applied halfway through the washout period. The sensor will always be removed after the end of each intervention. You will be given written instructions on how to remove and dispose of monitor.

4. How long will I be in the study?

The study is approximately ~5 weeks long and requires 30h of in-person time commitment.

The run-in period is 1-week long. Each intervention spans 5 days. Every in-person visit is approximately 3h long (15h weekly commitment to in-person research duties x 2 intervention). The wash-out period between interventions is 2 weeks. Duration between supplement phases (wash-out) could also be extended if we cannot find a good time for you to come in for testing due to scheduling issues.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

CGM/CKM Monitoring

The glucose/ketone monitor may cause a slight immediate discomfort at the skin application site. Under normal conditions, there are minimal risks to you when a CGM/CKM monitor is applied properly. Rare side effects include: bruising; light-headedness or dizziness due to fear of skin patches; and infection.

Blood Draws
Blood draws may cause discomfort at the skin puncture site and a small bruise may develop that may persist for several weeks. There is also a small possibility of an infection. Every precaution to avoid infection will be taken including the use of sterile disposable needles and gauze and the practice of aseptic (sterile) techniques during the blood draw.

GI Distress
Drinking the supplement beverage could cause some people to have discomfort such as stomach cramps, nausea, vomiting or diarrhea. Additionally, this study is designed to offer the supplement twice daily; therefore, it is possible that you may not like the taste of the product at first but may get used to it after the first dose.

Surveys
Surveys administered in this study are designed to evaluate psychological aspects of mood, satiety/hunger, which may make participants uncomfortable. The surveys have potential to cause you to feel anxiety, stress, depressive feelings, etc. You can skip any question(s) that make you uncomfortable. Research key personnel will help to provide contact information for resources such as the student health center, medical center, or emergency department if necessary to aid with intense psychological distress induced by surveys.

Sleep Restriction
According to the National Institute of Health, sleep deprivation is known to affect driving safety. You may be prone to falling asleep when stopped at a light and while driving. This situation increases the likelihood of motor vehicle accidents and traffic law violations, respectively. To avoid these risks we plan to collaborate with OSU-approved ride services (i.e., Lyft) to provide you with transportation at no additional cost to you. 100% of the ride-sharing costs will be re-imbursed using university accepted PCards or check.

7. What benefits can I expect from being in the study?

You may be persuaded to continue taking ketone ester supplements if you see benefits from consuming it daily during the study. The data that is collected during the study (i.e., heart rate, sleep quality, reaction time, shooting performance) will all be provided to you. This may help you make informed decisions in the future about how to sleep and perform in military duties.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

For all the data collected over the course of the study (i.e. records, biological samples and questionnaires) a unique subject identifier (i.e. a code) will be assigned and used instead of your name. This identifier, which links your name to your data, will only be available to research personnel. Any records that contain your name and identifier together will either be stored in the Kinesiology file storage room in a locked file cabinet or protected on a computer via password protection on the individual digital file and password protection on the computer the file(s) are stored on. All other records that only contain the subject identifier will be kept in either a file cabinet in our locked file storage room or on a password protected computer. Your name will never be used in any presentation or publication resulting from this study. The records will be maintained until the data are published and up to a maximum of five years after the completion of the study.

There may be circumstances where your information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Any potential incidental findings (psychological results, physical outcomes, blood biomarkers, etc.) will be shared with the participant. This information is non-diagnostic and will be provided so the participant may choose to share with their physician if they would like to address potential findings and receive diagnostic medical screening or testing. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information. Unpublished research information/findings from this research study will be kept confidential. Study related information will not be shared with ROTC leadership, cadre, etc.

10. What are the costs of taking part in this study?

Other than your time, there are no costs to participate in the study. You may need to pay for parking if you do not have an Ohio State University parking pass, but we have temporary passes that we can provide you with.

11. Will I be paid for taking part in this study?

Yes, if you complete the study you will receive a total of $300 in the form of a PCard or a check. No compensation will be provided for completing the screening visit.

If you do not complete the full study, compensation may be prorated:

- Completion of one condition will result in compensation of $150.
- Completion of both conditions will result in compensation of $300.

By law, payments to subjects are considered taxable income.

12. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable,

according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact **Alex Buga, M.S.** His email address is buga.1@buckeyemail.osu.edu.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Jeff Volek**. His office number is 614-688-1701 and his email address is volek.1@osu.edu.

15. Who is sponsoring this study?

The Department of Defense is sponsoring this study.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study. I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**