Ketogenic Intervention in Depression(KIND)

The Ohio State University

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IRB Protocol

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SUMMARY AND BACKGROUND

Major depression is a burgeoning problem that affects over five percent of adults worldwide[1] and is rapidly increasing in the United States. From the second quarter of 2019 to June of 2020, the prevalence of symptoms of depression spiked from 6.5 to 24.3% , which was largely attributed to the COVID-19 pandemic[2]. Major depression and suicidal ideation have increased markedly in young adults, particularly within college campuses. In 2020, counselors at the Ohio State University (OSU) experienced a surge in the number of students with various mental health issues with anxiety and depressive disorders being the most common. The escalating prevalence of depression bubbling under the surface of the ongoing COVID-19 pandemic represents a unique challenge that requires new and creative solutions.

Current psychotherapy interventions, such as Behavioral Activation, Cognitive Behavioral Therapy, and Interpersonal Psychotherapy are associated with clinically significant decreases in depression for approximately half of the people enrolled in these trials[3]. Further, depression is often treated with medications such as selective serotonin reuptake inhibitors and tricyclic antidepressants. However, these drugs are associated with side effects such as anxiety, decreased libido, nausea, and insomnia which may exacerbate the same depressive symptoms they are intended to treat[4].

Poor metabolic health significantly increases risk of depression. For example, people with obesity are more likely to meet criteria for depression and report symptoms of depression[5]. Thus, additional co-therapies[6], specifically those that might enhance current psychotherapy such as diet interventions[7], are warranted in the treatment of major depressive disorder. Further, examining nutritional interventions may be particularly important following the onset of the COVID pandemic, given restrictions on activities and increased isolation. Most nutrition studies examining effects on depression have focused on single nutrients (e.g., omega 3 fatty acids, B-vitamins, tryptophan, specific minerals) with mixed results[8]. A more consistent improvement in depressive symptoms may be achieved by improving eating patterns, such has been shown with a Mediterranean diet[9,10].

Another eating pattern shown to have consistent benefits in metabolic health is a ketogenic diet (KD). KD interventions have demonstrated therapeutic effects in obesity, metabolic syndrome, and type 2 diabetes[11-15]. It was recently demonstrated that a group of military-affiliated students at OSU prescribed a KD were uniformly able to adhere to the diet for 12-weeks as demonstrated by average ketone >1 mM. They exhibited highly significant improvements in body composition, loss of visceral fat, and improvement in a host of metabolic markers[16-18]. In addition to global improvements in body composition and metabolic health, KDs may target neurochemicals, such as brain derived neurotropic factors (BDNF)[19], and inflammation which may influence depression and cognitive functioning over time. For example, KDs may also have neuroprotective effects in the hippocampus, an important neural area cognitive function and mental health[20,21]. Recently, a KD was administered to adults who had been admitted to a psychiatric hospital and were suffering from various mental disorders. The dietary intervention lasted between 16 and 248 days and showed significant improvements in depression and psychotic symptoms[22]. Ketogenic diet interventions (and ingestion of ketone esters) have also been associated with more stable brain networks, assess with functional Magnetic Resonance Imaging (fMRI). Additionally, a novel but as yet under-appreciated effect of nutritional ketosis is to induce a broad-spectrum reduction in

inflammation in metabolically-impaired individuals[12,14,23,24]. Elevations in a range of inflammation biomarkers has been associated with severity of depression[25,26].
Although KDs have been proposed as a treatment option for mental health disorders, including schizophrenia[23] and depression[7], few human clinical trials have tested the efficacy of this eating pattern specifically in a population of adults with major depression. In patients with type 2 diabetes (n=262) prescribed a KD using a novel virtual care model (Virta Health), we observed significant improvements in depressive symptoms after 10-weeks, which were directly correlated with the degree of carbohydrate restriction and nutritional ketosis as assessed by blood concentrations of ketones[27,28].

IMPACT

The overarching goal is to perform a pilot study to: (1) demonstrate that a well-formulated KD can be implemented in a university counseling treatment program for major depression, and (2) test whether such a program results in reductions of symptoms of depression. We plan to recruit 60 students with major depression who will receive coaching and support on a KD over a 12-week period; this will demonstrate initial feasibility of the diet. We hypothesize that participants will demonstrate improvements in metabolic health, mental health, cognition, and brain function (using Magnetic Resonance Imaging; MRI)[29]. The data from this pilot study will be used to generate effect size estimates to inform the design of an intervention study to compare efficacy of a KD to standard diet and/or other diet treatment strategies. The results from this open-trial will also be valuable for providing safety information and providing relevant mechanistic information regarding KD-induced improvements in depression.

RESEARCH STRATEGY

This will be a single arm prospective trial assessing feasibility of implementing a KD in up to 60 participants with depression over 12-weeks. Participants who are MRI eligible will also have the option to complete pre- and post-intervention brain MRI. After enrollment, participants will complete a battery of baseline tests. The intervention will last 12-weeks with the primary efficacy outcomes assessed bi-weekly and other secondary/exploratory outcomes assessed at time points detailed in **Table 1**. Participants will receive standard of care clinical treatment for depression through the OSU Counseling and Consultation Services (CCS) throughout the intervention.

OUTCOMES

Primary Outcomes. Adherence will be determined by the number of participants completing the 12-week intervention. We expect >80% of enrolled participants to complete the 12-week trial. Additionally, we will determine the number of participants who consistently maintain a level of nutritional ketosis (average ketones ≥0.5 mM).

The primary efficacy outcome will be depression score as assessed by PHQ-9 and HRSD. The self-reported PHQ-9 is a measure of depression symptom severity. It maps onto DSM-5 criteria for Major Depressive Disorder and is widely used in both clinical and nutrition research settings. The HRSD is an observer-rated measure of depression mostly used in research settings; the HRSD will be used to provide objective and standardized ratings of symptom severity, including ratings

that require external observation such as psychomotor retardation. The PHQ-9 and HRSD will be administered bi-weekly to provide a trajectory of depression symptoms.

Secondary Outcomes. In addition to changes in symptoms of depression, we will assess changes in a number of metabolic markers and cognitive markers of psychological health. We will assess the following to quantify these changes: Body weight, body composition, blood pressure, glucose, insulin, HbA1c, chemistry panel, lipids, and cognitive measures, structural and functional brain MRI). To examine changes in inflammation, we will assess the following markers: interleukin 1, interleukin 6, C-reactive protein, tumor necrosis factor-alpha, and WBC count with differential.

PARTICIPANTS

We expect to enroll up to 60 young adults with major depression into a KD intervention over a 12-week period. Participants will be able to pick up study fliers or will be handed fliers by CCS team members. Study fliers will include all inclusion and exclusion criteria and will provide potential participants with research team contact information. Participants must meet all inclusion criteria and none of the exclusion criteria as indicated on a prescreening checklist before baseline testing. Pre-screening and BL inclusion/exclusion criteria is outlined below.

Inclusion Criteria:

- OSU students (age 18-30 years at the time of enrollment) with confirmed major depressive disorder as determined by SCID-5 diagnosis at baseline testing.
- Currently engaged in counseling treatment for depression at CCS
- Available for a 12-week period and indicate willingness and ability to eat KD foods as prescribed

Exclusion Criteria:

- Disordered eating, as evidenced by meeting criteria for Anorexia Nervosa, Bulimia Nervosa, Binge Eating Disorder, Other Specified Eating Disorder, Unspecified Eating Disorder, or Avoidant Restrictive Eating Disorder during the SCID-5 interview at baseline testing.
- Substantial imminent risk of suicide as assessed during the SCID-5 interview.
- Body mass index (BMI) < 20 kg/m^2
- Habitual consumption of a structured low-carbohydrate diet in the last 6-months
- Gastrointestinal disorders or allergies that would prevent adherence to prescribed diets
- Alcohol consumption in excess of 3 drinks/daily or 14 drinks/weekly
- Diagnosed diabetes, liver, kidney, or other metabolic or endocrine dysfunction, or use of diabetic medications other than metformin
- Inability to access or prepare appropriate KD foods/meals
- Pregnant, lactating, or planning on becoming pregnant during the study
- Unwilling to perform finger-stick blood testing or continuous glucose/ketone monitoring

Exclusion for optional MRI:

- The CCBBI screening form (https://redcap.osumc.edu/redcap/surveys/?s=N3XJ4WC7T9) will be used to assess MRI eligibility. Endorsement of items that contraindicate MRI will serve as exclusion criteria (pacemaker, stint, claustrophobia, etc.).

Recruitment:

OSU students will be recruited through the Office of Student Life's CCS, and through the recommendations of the 50+ counselors associated with the Health and Wellness Center who are

charged with the care and wellbeing of OSU students experiencing major depressive symptoms. All potential participants must be currently enrolled with the Student Life's CCS. Initial screenings for qualifying inclusion and exclusion criteria will be conducted by Dr. Patel and his team. We expect to enroll between 30 and 60 participants. The total number of students who received clinical services through CCS during the 2020-2021 academic year was 5,488. Thus, recruiting 30 – 60 participants who meet inclusion and exclusion criteria is an achievable goal.

METHODS

Study overview:

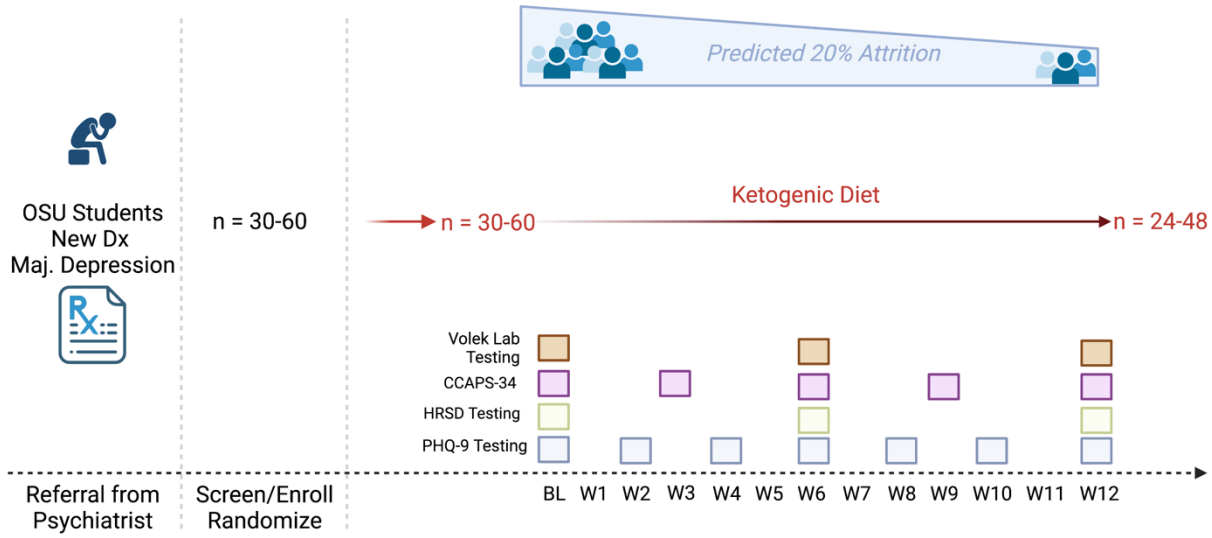

Fig. 1 Experimental Approach.
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Study Procedures

The timeline of various study procedures is detailed in **Table 1**.

Table 1: Study Assessment Timeline

Test	Week												
	BL	1	2	3	4	5	6	7	8	9	10	11	12
SCID-5 RV [1]	X												
WHO-5[2]	X		X		X		X		X		X		X
PHQ-9 [3]	X		X		X		X		X		X		X
Depression Scale [4]	X						X						X
CGM/CKM [5]	X	X				X	X					X	X
Finger Stick BHB [6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Survey/Side Effects [7]	X						X						X
Venous Blood Draw [8]	X						X						X
Body Composition [9]	X						X						X
Blood Pressure [10]	X						X						X
Cognitive Testing [11]	X												X
MRI [12]	X												X

1. SCID-5 RV: Structured Clinical Interviews will be used at baseline after Informed Consent to determine if participants are eligible to continue with the study's dietary intervention.

2. WHO-5: The WHO-5 is a short 5 item questionnaire that will be used bi-weekly to assess participants psychological well-being. This questionnaire will be administered digitally via RedCap or Qualtrics.

3. PHQ-9: The Patient Health Questionnaire-9 will be used bi-weekly to assess each participant's degree of depression (i.e., intensity and severity). This questionnaire will be administered digitally via RedCap or Qualtrics.

4. Depression Scale: The Hamilton Rating Scale for Depression is a questionnaire that will be given to participants and BL, week-6 and -12 of the intervention to evaluate improvements in depression symptoms.

5. CGM/CKM: Continuous Glucose/Ketone Monitors will be applied after Informed Consent. The sensor will be checked by the study team at each test day and will be removed and replaced by a fresh sensor at ~6-week intervals during the study. The sensor will be removed at the end of the final test day

6. Finger Stick BHB: Finger sticks will be taken daily in the morning, by the participant to determine ketone and glucose levels at a fasted state. Measurements will be reported daily in RedCap or Qualtrics.

7. Surveys/ Side Effects: Participants will complete the Automated Self-administered 24-hour Dietary Assessment Tool (ASA24®) at baseline. They will also complete behavioral and cognitive surveys during each testing day.

8. Venous Blood Draw: A fasting blood draw will be taken from the antecubital vein during each testing day.

9. Body Composition: Anthropometric data will include: Lean Body Mass by DXA, BMI, height and weight.

10. Blood Pressure: This will be determined by manual cuff and recorded by research staff.
Participants will wear a Bluetooth heart rate monitor chest strap throughout the test day.

[11.] Cognitive Testing: Cognitive tests will be conducted via iPad to provide measures of global cognition and specific cognitive domains.
[12.] MRI: Structural and Functional MR imagining will be done to assess changes in cortical thickness, brain volume, and functional connectivity.

***Pre-Study Screening*:** Students with depression who are currently engaged with counseling treatment provided through the CCS, will be made aware of the study during their therapy sessions. Potential participants will be provided with a research flier by their CCS therapist. If the potential participant takes interest in the study, they will complete a pre-screening checklist which includes a brief summary of the study and a series of inclusion/exclusion criteria to which they will answer 'yes' or 'no'. If the potential participant passes this pre-screening checklist, they will be scheduled to meet with study staff for an informed consent meeting to thoroughly discuss the study, review informed consent and HIPPA information. Upon consent, the participant will then meet with study team for eligibility determination.

Informed Consent and Eligibility Determination. Participants will review the informed consent and HIPAA information with study personnel. After providing consent, participants will complete clinical interviews and questionnaires, which may involve inquiry about personal information, including demographics, medical history, health behaviors, and current medications. These questions will ensure inclusion eligibility. Participants who meet eligibility criteria will be fitted with a Continuous Glucose and Ketone Monitor (CGM/CKM) and scheduled for their dietary and cognitive assessment appointment. MRI scanning will be an option for participants who are interested and eligible for MRI. Those interested in participating in the MRI sessions will complete the CCBBI MRI eligibility screening form and scheduled for MR imaging with study team. The schedule of study testing visits is shown in **Table 2.**

Table 2: Scheduled Study Visits

Week	Appointment #	Description	Expected Time Frame
Baseline	1	Determine potential participant interest in the study and go over pre-study eligibility form with CCS team member. A pamphlet describing the dietary protocol will be handed out at this time.	1 hr
Baseline	2a	Informed Consent Form & Structured Clinical Interview	90 min
If participant is ineligible or no longer interested, they are compensated, and study participation is terminated. If eligible and interested, participant continues in study as below:			
Baseline	2b	Mental Health Battery and Continuous Glucose Monitor / Continuous Ketone Monitor application	90 min
Baseline	3a	Weight, Hydration Status, Body Composition Testing, Survey/Side Effects, Venous Blood Draw, Body Composition, and Blood Pressure.	1 hr
Baseline	3b	Cognitive testing	1 hr
Baseline	3c	Dietary consult	45 min
Baseline	3d*	MR Testing	1 hr

5	4	Continuous Glucose Monitor / Continuous Ketone Monitor application	5 min
6	5	Weight, Hydration Status, Body Composition Testing, Survey/Side Effects, Venous Blood Draw, and Blood Pressure.	1hr
11	6	Continuous Glucose Monitor / Continuous Ketone Monitor application	5 min
12	7a	Cognitive Tests	1 hr
12	7b	Weight, Hydration Status, Body Composition Testing, Survey/Side Effects, Venous Blood Draw, and Blood Pressure.	1 hr
12	7c*	MR Testing	1 hr

Testing Visits. As detailed in Tables 1 and 2, PHQ-9 data will be collected at baseline and bi-weekly by means of an internet-based survey and questionnaire administration program (REDCap / Qualtrics). HRSD data will be collected in-person or virtually by study assessors at baseline, 6- and 12-weeks. As part of their standard counseling protocol, counselors will also administer the CCAPS-34 to assess global mental health at baseline and 3-wk intervals. Other outcomes will be assessed at baseline, 6- and 12-weeks at a single visit in the PAES Building centrally located on the OSU campus (see **Fig 1**).

For testing at the PAES (**Fig 2**), subjects will arrive to the lab in the morning after an overnight fast. We will test for hydration, measure height and body mass, and then have participants complete surveys followed by resting blood pressure. A phlebotomist will obtain blood samples from a forearm vein in subjects after sitting for 10-min. Appropriate sample tubes will be used for EDTA, sodium heparin, or serum for different analytes. A serum tube will be sent to Quest Diagnostics to assess standard chemistry panel (liver enzymes, kidney function, lipids, etc.).

Serum and plasma will be immediately centrifuged and aliquoted into tubes and stored at -80°C until subsequent analyses. Samples will be thawed only once for analysis and assayed in duplicate for ketones, glucose, and insulin, which will be used to calculate an index of insulin resistance, and HbA1c. Extra serum and plasma will be archived for future analysis of biomarkers that may provide insight into novel associations with depression. We will determine body composition from a single whole-body scan using dual-energy x-ray absorptiometry (iDXA, Lunar Corporation, Madison, WI). Finally, subjects will complete a battery of computerized cognitive tests. Total time for this visit will be less than 2-hours.

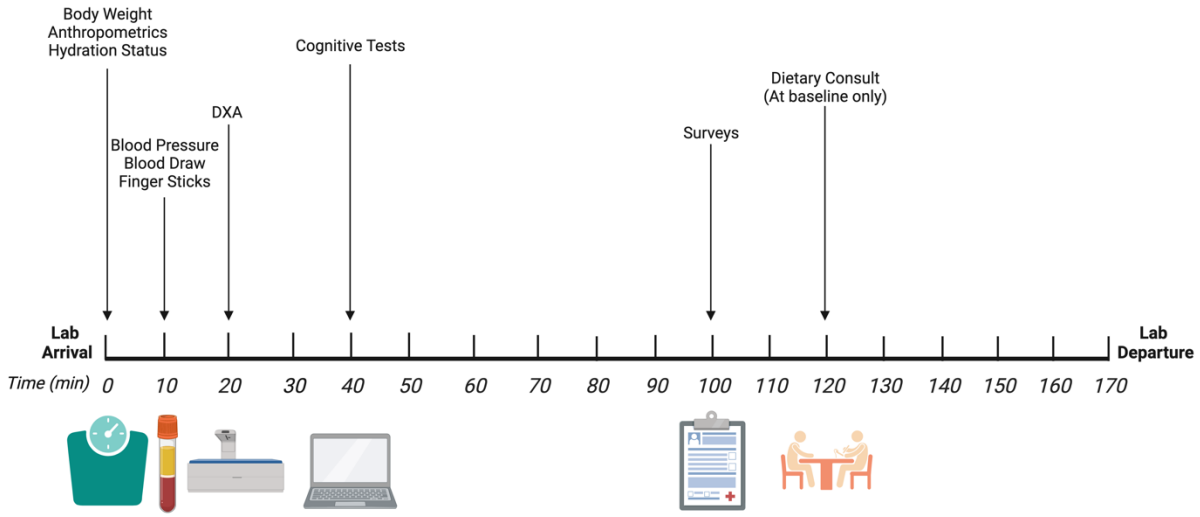
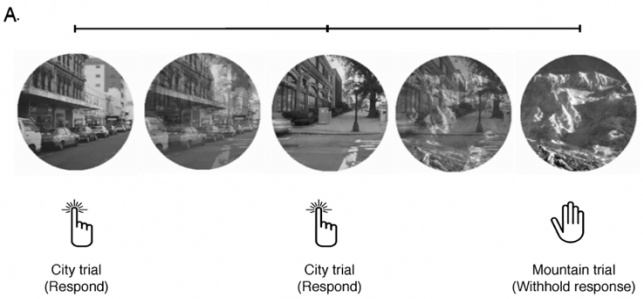


Fig. 2 test day timeline. Created with BioRender.com

Neurocognitive test materials and procedure. Testing sessions will be administered by trained lab staff. All participants will complete an assessment of cognitive function with the NIH Toolbox (IPAD-based assessments that examines cognitive function) and standardized neuropsychological testing (such as sub-tests from the Delis-Kaplan Executive Function System, Stroop Color Word Test, and Wechsler Memory Scale). Computer-based testing of memory (pictures and words) and executive function (attending to visually presented stimuli, such as scenes) may also be administered.

The gradCPT contains grayscale photographs of mountain scenes and city scenes. Scene images gradually transition from one image to the next [31,32];). Participants are instructed to press the space bar on the keyboard for each city scene, and to withhold responses for mountain scenes. Practice trials will be given prior to the start of the task with feedback for each trial response to ensure that the task instructions were understood. The actual task lasts approximately 4 minutes and feedback is not provided during the task.



A. Illustration of gradCPT. Scenes gradually transition from one image to the next image. Participants are instructed to respond to city scenes and withhold for mountain scenes (Esterman et al., 2012).

MRI Image Acquisition (approximately 60 min)**.** Participants who are MRI-eligible may volunteer for pre- and post-intervention MRI. We have the resources to complete pre- and post- intervention

MRI on approximately 15 volunteers, possibly more depending on availability of funding. Images will be collected on a 3T Siemens Prisma scanner at the Center for Cognitive and Behavioral Brain Imaging (CCBBI) located in the OSU Psychology building (1835 Neil Ave.). A contrast agent will not be used. Participants will enter the scanner room, lay supine on the MRI table, will be fitted with ear plugs (noise reduction), and will have their heads stabilized with cushions (to reduce head motion). The participants will be moved into the bore of the scanner, and localizer, structural, resting- and task-related functional images will be collected. Subjects will be screened for contraindications to MRI using the CCBBI screening form (i.e., for metal implants and other magnetic material that will interfere will MRI).

To optimize semi-automated tissue and neuroanatomical classification, a whole-brain T1-weighted sequence and a T2-weighted sequence will be acquired. Cortical reconstruction and volumetric segmentation will be performed, and these data will be used to optimize registration and normalization of functional brain volumes.

Resting-state fMRI: Whole brain echo-planar imaging (EPI) volumes sensitive to the BOLD signal will be acquired. Images will be re-aligned, un-warped, and normalized. Confounding effects of white matter, CSF signal, and head motion will be regressed from the functional time series, followed by bandpass filtering, linear detrending and smoothing, and whole brain resting state networks will be identified (e.g., default mode network, salience network, etc).

Task-fMRI: During whole brain EPI data acquisition, participants will be presented with words and pictures and asked to make judgements about the stimuli, such as indicating whether a particular stimulus (e.g., face-name association, word, number, or letter) has been previously presented, if a presented stimulus is a city or mountain scene, the direction an arrow is pointing (left or right), if a pair of stimuli match (e.g., faces with neutral or emotional expressions; word with a face). Behavioral responses will be recorded with an MRI compatible button box.

DIETARY INTERVENTION

The diet intervention will start after all baseline testing is complete. Participants will receive extensive education and ongoing support from the dietetic team to achieve the nutritional goals of a well-formulated KD. Each participant may require slightly different levels of coaching depending on their baseline knowledge and individual situation. Thus, the intensity of engagement may vary across participants. We plan to provide a portion of their caloric intake in the form of staple food items in order to offset participant food costs, ensure nutrient quality, and facilitate adherence.

The KD will follow general principles as we have described[30] with the aim to achieve blood ketones >0.5 mM, which will require most participants to consume <50 g/day carbohydrate and ~1.5 g/kg reference weight protein. Fat will comprise the remaining calories with an emphasis on monounsaturated and saturated sources from whole foods. A wide range of foods will be incorporated including non-starchy vegetables, fruits (berries, olives, tomatoes, lemons/limes), meats (beef, chicken, pork, fish, lamb), nuts and seeds, oils (olive, canola, coconut), cheese, butter,

cream, eggs, and fatty fish (salmon, sardines). Nutritional ketosis is associated with natriuresis that will lead to sodium and fluid loss if the extra sodium excreted is not compensated by individualized intakes. If untreated, the resultant hypovolemia can manifest in side effects and adrenal stress (often mis-characterized as 'keto-flu') that disrupts body fluid, electrolyte, and mineral status. Thus, slightly higher sodium and potassium intakes are required to offset the natriuresis, which will be achieved through the provision of broth/LMNT electrolyte packs and appropriate food sources and cooking methods. In addition, neuro-muscular irritability characterized by muscle cramping will be addressed with individualized supplementation with oral magnesium and calcium. Shelf stable items such as high-quality fats/salad dressings, salmon & sardine packets, jerky, cheese whisps, nuts and seeds, will be included in the starter and replenishing kits.

DATA ANALYSIS AND STATISTICAL METHODS

Patient demographic and characteristics information, pre- and post-intervention depression scores and other outcomes will be summarized for the KD group at every time point. Considering this is a pilot feasibility study, we will focus on calculating effect sizes. Changes in depression scores within the KD group will also be evaluated using a linear mixed model for repeated measures, with the baseline score potentially included as a covariate to control for baseline variability. The linear mixed models (Multi-level Model, MLM) will allow us to easily handle missing data (assuming Missing-at-random) and estimate within group effects from the same model. These models can also easily handle co-variates and are robust to violations of normality. Normality and heteroscedasticity will be checked using residual plots. All data that are non-normal may be either suitably transformed (e.g., log, Box-Cox) or analyzed using non-parametric methods (Kruskal-Wallis test).

Incidental Findings

There may be incidental findings observed on MRI, cognitive, and fitness assessments. For each type of assessment, the participant's primary care physician will be contacted within 30 days of incidental finding detection. Each participant will provide contact information for their healthcare provider at entry of the study.

STUDY MONITOTRING

Concomitant Medication/Supplements and Treatment

All concomitant medications/supplements used 1 month prior to Screening Visit and during the study will be reported to the study personnel for assessment and recorded in the participant's study documents.

CONDUCT OF THE STUDY

1. **Ethics and Regulatory Considerations**

This study will be conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2004) and United State Code of Federal Regulation Title 21. Signed written informed consent for participation in the study will be obtained from all participants before protocol-specific procedures are carried out. Participants will be informed of their right to withdraw from the study at any time. Participants will be informed that their participation in the study is completely voluntary, personal information will be both de-identified to preserve anonymity.

2. **Institutional Review Board**

The Investigator will ensure that an appropriately constituted IRB, in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study. Before the study is started, the Investigator will forward copies of the protocol and consent form for this study to the IRB for review and approval. IRB approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review. The IRB must be informed of all subsequent protocol amendments. No alterations, modifications to IRB-approved documents, including the protocol, protocol summary, consent form, recruitment materials and questionnaires will be allowed. The IRB must also be informed of all SAEs and of unexpected AEs as outlined in the IRB's SOPs (standard operating procedures) or reporting guidelines.

3. **Informed Consent and Protected Health Information**

The study will be explained verbally as well as on the informed consent document. Each participant will be given ample opportunity to inquire about details of the study and to read and understand the consent form before signing it. It will be made clear that participants can withdraw from the study at any time.

Each participant's signed informed consent document must be kept on file by the Investigator. The participant should receive a copy of the informed consent document. A participant may not be admitted to the study unless informed consent of the participant (or his/her legally authorized representative) has been obtained.

4. **Participant Confidentiality**

The Investigator is responsible for ensuring that participants' anonymity will be maintained. For all the data collected over the course of the study for each participant (i.e., records, biological samples and questionnaires) a unique subject identifier (i.e., a code) will be assigned and used instead of the subject's name. The code for each participant which links the subject name with their identifier will only be available to research personnel. Electronic CRFs or other documents will identify participants by initials, number, or code, and not by name. The Investigator will keep a separate log showing codes, names, and addresses. Any records that contain the subject's name and identifier will either be stored in the Clinical Psychology file storage room in a file cabinet (locked) 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 contain the

subject identifier only will also be kept in either a file cabinet in our locked file storage room or on a password protected computer. Biological samples collected from each participant will be kept in a storage freezer labelled only with the subject identifier. Subject names 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 ten years after the completion of the study. All records or biological data obtained after signing of the informed consent (including the screening visit, even for subjects that are not eligible for participation in the study) are treated with the same confidentiality safety measures as those subjects who qualify. Any information obtained during the prescreening for participants that were not eligible will be deleted. Any potential incidental findings from MRI, blood biomarkers, etc. will be shared with the participant. Incidental findings from the MRI imaging will be reported to the participants primary care physician within 30 days of finding. The remaining information (ie. Blood biomarkers) is non-diagnostic and will be provided so the participant may choose to share with their physician.

5. **Withdrawal of Participants from the Study**

Participants may be removed from the study for any of the following reasons:

- A participant requests discontinuation;
- The Investigator initiates removal for medical or compliance reasons;
- Occurrence of any AE or condition that could, in the Investigator's opinion, interfere with the evaluation of the effect of the study beverage or put the participant at undue risk.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable, therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. In the event that a participant is withdrawn from the study, the reason for the withdrawal will be documented.

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