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A pilot study examining a ketogenic diet as an adjunct therapy in college students with major depressive disorder

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A ketogenic diet (KD) has shown promise as an adjunctive therapy for neurological and neuropsychiatric disorders, including bipolar disorder and major depressive disorder (MDD). We examined tolerance for a KD in young adults with MDD and assessed symptoms of depression and metabolic health. Students ($n = 24$) with a confirmed diagnosis of MDD at baseline receiving standard of care counseling and/or medication treatment were enrolled in a 10–12 week KD intervention that included partial provision of ketogenic-appropriate food items, frequent dietary counseling, and daily morning tracking of capillary *R*-beta-hydroxybutyrate (*R*-BHB). Primary outcome measures for mood symptoms included the Patient Health Questionnaire (PHQ-9) and Hamilton Rating Scale for Depression (HRSD). Additional outcomes included body composition, neurocognitive function, and blood hormonal and inflammatory markers. Sixteen students (10 women, 6 men, mean age 24 yr) completed the intervention. Nutritional ketosis (*R*-BHB > 0.5 mM) was achieved 73% of the time. Depressive symptoms decreased by 69% (PHQ-9) and 71% (HRSD) post-intervention ($p < 0.001$), with improvement occurring within 2–6 weeks. Global well-being increased nearly 3-fold ($p < 0.001$). Participants lost body mass (−6.2%; $p = 0.002$) and fat mass (−13.0%; $p < 0.001$). Serum leptin decreased (−52%; $p = 0.009$) and brain-derived neurotropic factor increased (+32%; $p = 0.029$). Performance improved on several cognitive tasks. In students with mild to moderate depression based on PHQ-9 and HRSD, implementation of a WFKD for 10–12 weeks is a feasible adjunctive therapy and may be associated with improvements in depression symptoms, well-being, body composition, and cognition.

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INTRODUCTION

Major depression is a substantial and costly disorder that affects over five percent of adults worldwide [1]. From the second quarter of 2019 to June of 2020 corresponding to the onset of the COVID pandemic, the prevalence of depression spiked from 6.5–24.3% [2]. Major depression has increased markedly within college campuses and has been identified as one of the most prevalent mental health disorders in young adults [3]. Current psychotherapy interventions, such as behavioral activation, cognitive behavioral therapy, and interpersonal psychotherapy, can be implemented individually or in conjunction with one another and are associated with clinically significant improvements in depression [4, 5]. Depression can also be managed pharmacologically, either alone or in combination with behavioral interventions. However, pharmacological intervention may be accompanied by anxiety, decreased libido, nausea, insomnia, and decreased metabolic health [6, 7], which may exacerbate depressive symptoms [6].

Although psychotherapy and pharmacological intervention are effective in many cases, they do not address potential impaired metabolic contributions to the pathophysiology of depression. Increasing evidence suggests that poor metabolic health, including insulin resistance and/or metabolic syndrome, may increase the risk of depression [8]. People with excess adiposity are more likely to meet the criteria for and report symptoms of depression [9]. The correlation between obesity, insulin resistance, and depression may be partially mediated by alterations in inflammatory pathways that manifest in higher levels of various immune/inflammatory mediators, such as TNF-alpha, IL-1beta, and IL-6 [10]. Given the likelihood that dysregulated metabolic function may be a modulator exacerbating depression, nutrition-focused interventions may augment the effects of psychotherapy and pharmacological interventions for depression [11].

One dietary pattern that consistently improves metabolic health, especially for obese and/or insulin resistant individuals, is a very low-carbohydrate well formulated ketogenic diet (WFKD) in which carbohydrates are restricted to <50 g/day, protein is consumed in moderation (~1.5 g/kg/day), and fat is consumed ad libitum to satiety [12–19]. The WFKD promotes a natural metabolic state of nutritional ketosis, where fatty acids and ketone bodies become the dominant energy substrates. In addition to its established role as a treatment for refractory epilepsy [20, 21], it has been hypothesized that a WFKD could successfully treat mood disorders including depression [22–25]. A few human case studies

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in individuals with depression ($n = 34$) point to a WFKD as a potentially effective adjunct therapy for mood disorders [26, 27]. Furthermore, there is also evidence that higher ketone levels are associated with decreased depression symptoms in people with type 2 diabetes [28].

In the context of Major Depressive Disorder (MDD), a WFKD may achieve symptom reduction through pleiotropic mechanisms. Potential pathways include decreased inflammation [13, 15, 29–31], increased brain-derived neurotrophic factor (BDNF) [32], improved body composition, and neuroprotective effects in the hippocampus [33–36]. Ketosis is associated with more stable brain networks as observed in functional MRI studies [37–39].

Given the prevalence of MDD among university students [40], and the potential for a WFKD to positively impact both metabolic and mental health, the primary purpose of this study was to test the feasibility of implementing a WFKD as an adjunct therapy in college students with MDD undergoing counseling and/or medication treatment. Our hypothesis was that the WFKD would be feasible in most participants and associated with improvement in measures of depression and metabolic health. Rigorous diagnostic assessments of mental health and dietary adherence were implemented. Additional assessments of body composition, neurocognitive function, and blood hormonal and inflammatory markers were conducted to inform future investigations.

METHODS

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Ohio State University—Department of Human Sciences (IRB number 2022H0271), in accordance with the latest version of the Declaration of Helsinki (2013). All participants were informed of the experimental procedures, potential risks and the purpose of the study prior to enrolment and before obtaining their written and informed consent. No identifiable images of participants are included in this publication.

Overview

This was a single arm prospective study that involved a WFKD intervention that lasted 10–12 weeks depending on participant availability. Changes in variables were analyzed pre- and post-intervention. In addition, PHQ-9 and WHO-5 surveys were also assessed bi-weekly, and the HRSD, body composition, and blood markers were assessed at week 6 (i.e., mid-point). For lab-based visits, subjects arrived in the morning after an overnight fast followed by assessments for hydration, height, body mass, body composition, surveys, resting blood pressure, cognitive performance, and a blood draw.

Participants

Students enrolled at The Ohio State University (OSU) were recruited between Jan 2023 and April 2024. Students with depression who were currently engaged in counseling treatment provided through campus and community psychiatric treatment providers were made aware of the study during their therapy sessions. Interested individuals completed a pre-screening checklist by the study clinician, which included a summary of the study and a series of inclusion/exclusion criteria to which they answered 'yes' or 'no.' Individuals meeting screening criteria were then scheduled to meet with study staff to discuss the study in greater detail and sign an informed consent document approved by the IRB before participating in the study.

A total of 36 students met preliminary inclusion criteria and completed a 2–3 h baseline SCID-5 interview by a Master's level Psychology doctoral student to further determine eligibility. Participants had to be: (1) students registered at OSU (age 18–30 yr at the time of enrollment) with confirmed MDD as determined by a clinical interview and SCID-5 diagnosis conducted by a member of the study team, (2) currently engaged in counseling and/or medication treatment for depression and available for at least a 10-wk period, and (3) willing to eat a WFKD eating pattern as prescribed. Exclusion criteria included: (1) disordered eating (anorexia nervosa, bulimia nervosa, binge eating disorder, other specified/ unspecified eating disorder, avoidant restrictive eating disorder), (2) a substantial imminent risk of suicide, (3) body mass index (BMI) < 20 kg/m^2, (4) habitual consumption of a low-carbohydrate diet in the last 6 months, (5) gastrointestinal disorders or allergies that would prevent adherence to prescribed diets, (6) alcohol consumption more than 3 drinks daily or 14 drinks weekly, (7) diagnosed diabetes, liver, kidney, or other metabolic or endocrine dysfunction, or use of diabetic medications other than metformin, (8) an inability to access or prepare appropriate KD foods/ meals, (9) pregnant, lactating, or planning on becoming pregnant during the study, or (10) unwilling to perform finger-stick blood testing.

Of the 36 participants who completed the SCID-5, 12 were excluded, and 24 completed baseline testing. A total of 16 participants completed the entire study. A CONSORT diagram is shown in Fig. 1. Baseline characteristics of the 16 participants who completed the study are shown in Table 1. Seven participants were prescribed medications including norepinephrine dopamine reuptake inhibitors (NDRI; n = 2), serotonin aganoist and reuptake inhibitor (SARI; n = 1), selective serotonin reuptake inhibitors (SSRI; n = 1), atypical antipsychotics (n = 1), tiazine anticonvusant (n = 1), and a combination of drug classes previously mentioned (n = 1).

Dietay intervention

Prior to baseline testing (BL), a dietary education session was provided to ensure participants understood the guiding principles to a WFKD and were comfortable with adhering to the diet for 10–12 weeks. The diet intervention began after the baseline testing visit. Participants received extensive personalized education and ongoing support from the dietetic team to achieve the nutritional goals of a WFKD. The intensity of coaching varied across participants depending on their baseline knowledge and individual situation. We utilized a HIPAA-compliant messaging app (Healthie, New York, NY, USA) that allowed the participant to communicate with dietetic staff throughout the intervention. We provided staple ketogenic-friendly food items to partially offset participant food costs, ensure nutrient quality, and facilitate adherence. Ten pre-packaged ketogenic meals (Factor 75, Aurora, IL, USA) were provided to each participant at baseline to provide a visual guide of how a balanced WFKD meal should be composed for the duration of the study when participants implemented the diet thereafter at home. Subsequently, participants chose food and meals on their own with the exception that we provided a few shelf-stable items such as high-quality fats (e.g., olive oil), salad dressings, salmon & sardine packets, beef jerky, Whisps cheese crips, nuts and seeds, and an oatmeal alternative.

The WFKD followed general principles with the aim to achieve blood *R*-BHB > 0.5 mM, which required most participants to consume < 50 g/day of carbohydrate and ~1.5 g/kg reference weight protein [41]. Fat comprised the remaining calories with an emphasis on monounsaturated and saturated sources from whole foods. A wide range of foods were encouraged including non-starchy vegetables, low glycemic fruits (berries, olives, tomatoes, lemons/limes), meats (beef, chicken, pork, fish, lamb), nuts and seeds, oils (olive, avocado, coconut), cheese, butter, cream, eggs, and fatty fish (salmon, sardines). Since a KD is associated with an enhanced natriuretic effect that may often lead to sodium and fluid losses, colloquially referred to as 'keto-flu'[42, 43], participants were provided broth/LMNT electrolyte packs (Naples, FL, USA). Consumption of magnesium and calcium rich foods were encouraged if symptoms of muscle cramping were reported.

Surveys

The PHQ-9 was used to assess self-reported depressive symptoms [44] and the WHO-5 to assess global mental health data [45] using an internet-based survey and questionnaire administration program (Qualtrics, Seattle, WA, USA). The Hamilton Rating Scale of Depression (HRSD) [46] was administered by a qualified member of the study team either in-person or virtually.

Body composition

Body mass was measured with an electronically-calibrated scale to the nearest ± 0.1 kg (SECA 305, Hamburg, Germany) and body composition was estimated from a single whole-body scan using dual-energy x-ray absorptiometry (iDXA, Lunar Corporation, Madison, WI, USA).

Blood collection and analysis

Each day of the intervention, participants recorded fasting capillary *R*-BHB and glucose from a fingerstick using reagent strips and a monitoring

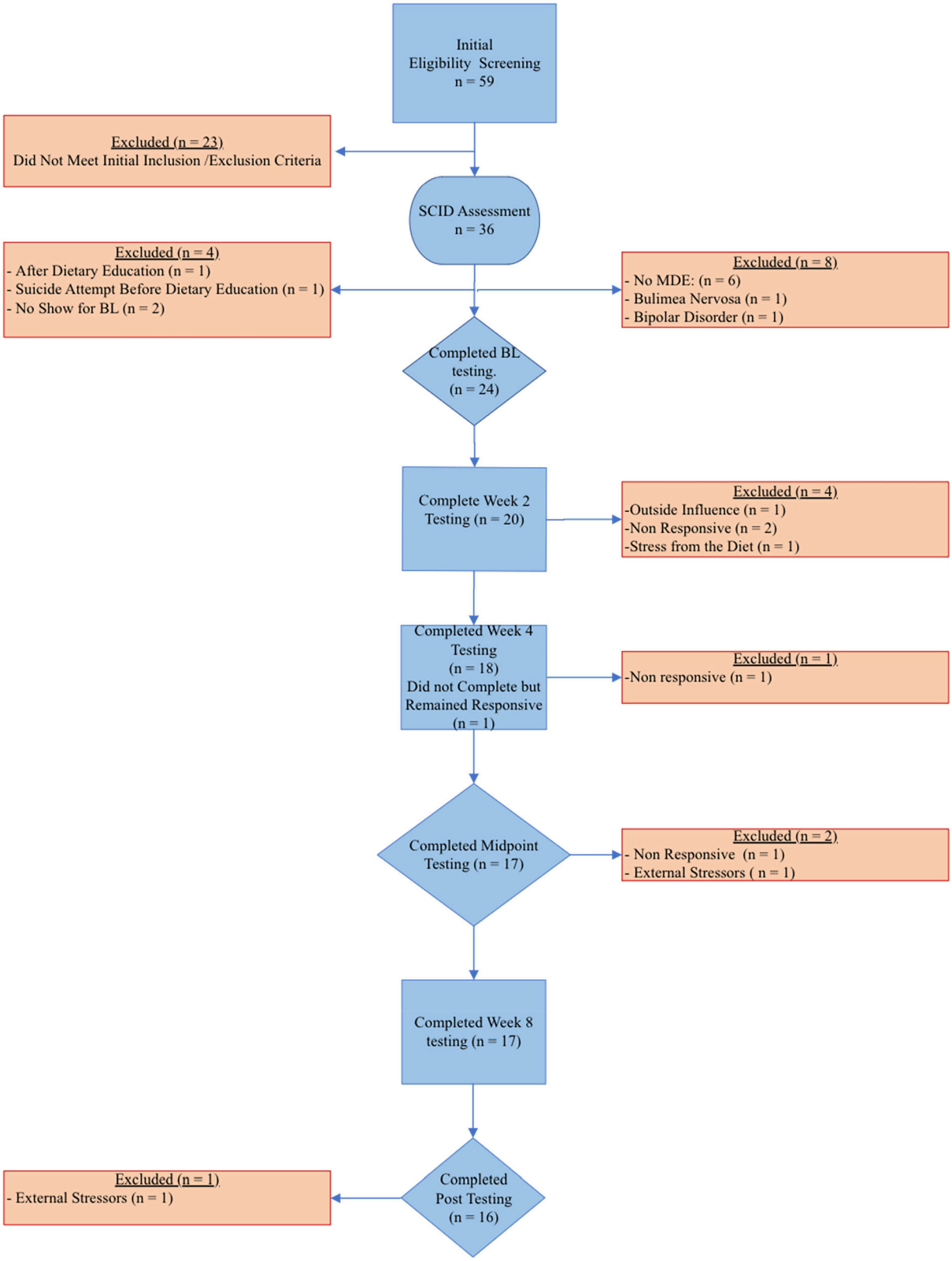


Fig. 1 Consort Diagram.

device (KetoMojo, Napa, CA, USA) in the morning before eating their first meal of the day. At study visits, participants rested in a seated position for 10 min before a phlebotomist obtained blood from a forearm vein into serum tubes. One tube was sent to a certified laboratory (Quest Diagnostics) to perform a standard chemistry panel. The remaining serum tubes were centrifuged, aliquoted into cryovial tubes, and stored at −80 °C until subsequent analyses. Fasted adipokines (BDNF, IL-1β, IL-6, IL-8, IL-10, Insulin, Leptin, MCP-1, TNF-α, β-NGF) were assessed using Meso Scale Discovery's (MSD) U-Plex Human adipokine panel (Meso Scale Discovery, Rockville, MD). Samples were run in duplicates and analyzed using MSD's

Table 1. Baseline descriptives of study completers ($n = 16$).

	Mean	(SD)
Participants (female/male)	10/6	
Age (yrs)	24	3
Height (cm)	169.2	9.7
Body Mass (kg)	73.1	27.0
Body Mass Index (BMI: kg/m^2)	25.2	7.7
Body Fat Percentage (%)	31.8	10.1
Fat Mass (kg)	24.5	18.7
Lean Body Mass (kg)	45.7	11.6
HRSD	13.9	4.5
PHQ-9 Score	15.3	4.9
Fasting Capillary R-BHB (mM)	0.4	0.4
Fasting Capillary Glucose (mg/dL)	85	12

Values are means and standard deviations unless otherwise indicated.

Workbench 4.0 software. Calculations were run using a 4-parameter logistic with 1/y2 weighting, and intra-assay CVs for the standard and samples was 3.6%. A measure of insulin resistance (HOMA-IR) was determined from fasting serum glucose and insulin [47].

Cognitive tests

Cognitive function was assessed using the NIH Toolbox (NIH-TB) Cognition Battery (version 2) [48] on an iPad. The following tests were administered:

Auditory verbal learning test (episodic memory). Fifteen words were presented orally over three consecutive learning trials. After each trial, participants were asked to recall as many words as possible. The outcome variable was the sum of the number of words recalled across all trials.

Picture sequence memory test (episodic memory). Pictures of activities were presented in a specified order in different locations on the iPad screen with an audio recording that simultaneously described each picture. Participants were asked to place the pictures in the correct location on the screen. The outcome variable was the number of pictures that were correctly placed.

Oral symbol digit test (processing speed). Participants were asked to orally indicate the number that was paired with an abstract symbol based on a coding key. The outcome variable was the number of correct answers provided in 120 s.

Pattern comparison processing speed test (processing speed). Participants were asked to identity whether two pictures were the same ("yes" button) or not the same ("no" button) as quickly as possible. The outcome variable was the number of correct items (out of 130) completed in 90 s.

Dimensional change card sort test (executive functions and set-shifting). In this task, a target visual stimulus must be matched to one of two choice stimuli according to either shape or color. The outcome variable were percent correct and response time (seconds).

Flanker inhibitory control and attention test (attention and inhibitory control). Participants were instructed to choose the direction of the central stimulus while inhibiting stimuli on the right and left of the central stimulus. On congruent trials, all stimuli faced the same direction. On incongruent trials, the central stimulus faced the opposite direction. Response time (seconds) for congruent and incongruent trials were obtained.

List sorting working memory test (working memory). A series of stimuli were presented visually and orally one at a time. In the first condition, participants were instructed to sequence the stimuli in size order, from smallest to biggest. In the second condition, participants were asked to sequence the stimuli from one category (food) in size order and then stimuli from the second category (animals) in size order. The outcome measure was the total number of items recalled in the correct order.

Statistical analysis

Participant characteristics and outcome variables were summarized for completers ($n = 16$). The normality of continuous variables was assessed using the Shapiro-Wilk test. For variables that demonstrated normal distribution at baseline, we used a 1 (condition) x 3 (time) repeated-measures mixed-effects analysis of variance (RM ANOVA). If a significant main effect was detected, Bonferroni post-hoc corrections automatically adjusted for multiplicity were used to analyze pairwise comparisons. For variables that did not meet normality assumptions at baseline, the non-parametric Friedman test with Dunn's correction for multiple comparisons was employed. Changes in depression scores in completers were evaluated using an analysis of covariance (ANCOVA), with the baseline score included as a covariate to control for baseline variability between participants. An intent to treat (ITT) analysis was conducted on participants who completed baseline testing and at least one additional PHQ-9 assessment using a Last Observation Carried Forward to minimize bias by including all participant regardless of adherence and to provide a more generalizable estimate of the interventions effect on depression scores. To explore associations between depression scores and weight loss and ketones, we performed simple regression using Pearson correlation coefficients. The significance level for all tests was set at $\alpha \leq 0.05$.

RESULTS

Adherence

Subjects who completed all aspects of the dietary intervention ($n = 16$) made dietary choices compatible with WFKD guidelines throughout the study. Seven of the eight participants who dropped at varying time points after baseline testing reported reasons that were unrelated to the WFKD (Fig. 1). One participant who dropped out before week 2 testing reported that they felt stress associated with attempting to adhere to the WFKD. Completers successfully reported capillary *R*-BHB and glucose values 77% of the days of the intervention. *R*-BHB concentrations varied among individuals (Fig. 2A). Of days reported, participants maintained *R*-BHB levels greater than or equal to 0.5 mM 73% of the time, with an average *R*-BHB of 0.7 mM over the study duration(Fig. 2B). There were no significant changes in fasting capillary glucose over time, with weekly averages falling within the normal fasting glucose range of 70 – 100 mg/dL.

Among participants undergoing pharmacotherapy for MDD at baseline, one participant reduced their SSRI dosage from 100 mg/day sertraline to 5 mg/day escitalopram, while their NDRI dosage increased from 150–300 mg/day, and gabapentin was introduced at the midpoint and continued thereafter. Another participant switched from an NDRI to a stable dose of an SNRI medication during week one. No other medication or dosing changes occurred during the intervention. A 2-way repeated measures ANOVA showed no significant interaction between time and medication status ($p = 0.60$), indicating that changes in depression scores over time did not differ significantly between the medicated and unmedicated groups.

Surveys

In study completers, there was a 37% decrease in PHQ-9 scores at week 2 ($p = 0.013$) that decreased further reaching a 69% improvement at week 10–12 ($p < 0.001$) (Fig. 3A) compared to baseline. The ITT analysis in 24 subjects closely mirrored the completer ($n = 16$) responses with a 65% improvement in PHQ-9. Depression symptom severity varied widely among participants at baseline (8–25 points), but irrespective of starting scores, everyone reported a decrease in PHQ-9 score, with no one exhibiting a relapse or significant worsening of depression symptoms over time (Fig. 3B).

Observer-rated HRSD scores at week 6 and week 10–12 decreased by 59 and 71%, respectively ($p < 0.001$) (Fig. 3C). Every

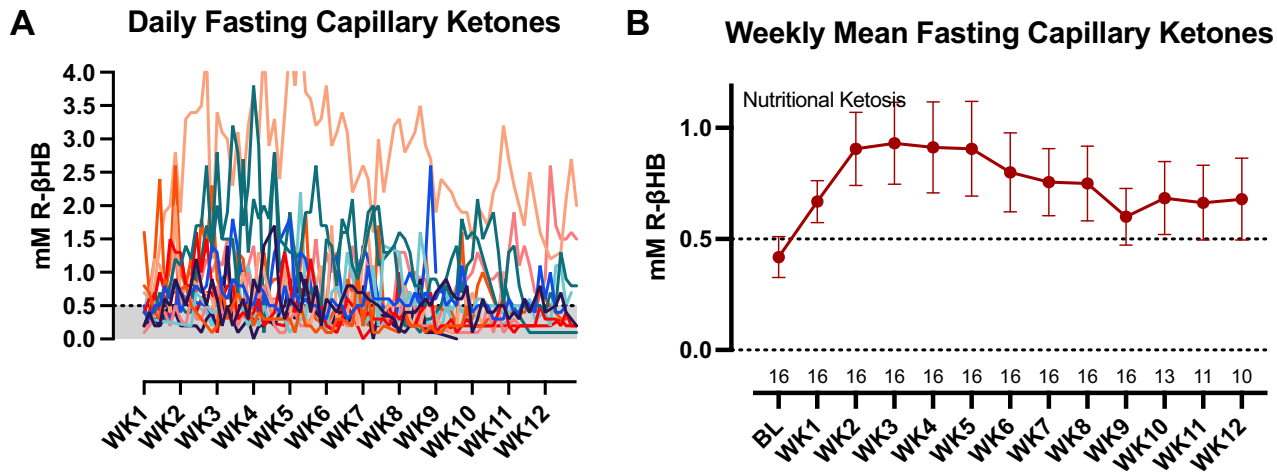


Fig. 2 Ketone Responses. Individual variability in daily morning fasted capillary (**A**) R- BHB and 7-day moving average of R-BHB (**B**). Values ≥ 0.5 mM denote ketosis. The numbers below the dotted line reflect the n- size. All values are mean ± SEM.

participant had lower HRSD depression ratings at week 6, with scores in all individuals being lower than 10 by week 10–12 (Fig. 3D), indicating no participant had moderate or severe depression at that point.

By week 2 of the intervention, there was nearly a 2-fold increase in perceived ratings of global wellness, which improved nearly 3-fold at post testing ($p < 0.001$) (Fig. 3E). No individual had a decrease in WHO-5 score (Fig. 3F).

Safety and adverse events

Subjective reports of adverse effects were voluntarily communicated via Healthie or during in-person visits. Two participants reported experiencing headaches accompanied by muscle cramping during the first week of dietary transition; both cases were resolved with electrolyte replenishment, and no further symptoms were reported. Additionally, three participants experienced flu-like symptoms unrelated to the diet, as indicated by non-adherence during these episodes.

Body mass and composition

Participants who completed the study lost an average of 5.0 kg total body mass from pre-post intervention, fifteen achieving the threshold of clinically significant weight-loss (−6.2%, $p < 0.001$) (Fig. 4). The significant body mass changes scaled favorably with body fat percentage (−2.4%, $p < 0.001$), FM (3.3 kg, $p < 0.001$) and LBM (1.1 kg, $p = 0.035$) -- a 3:1 FM:LBM body recomposition change.

Exploratory regression analysis

Ketones and depression. The marked improvement in MDD symptoms coincided with the onset of nutritional ketosis although correlational analyses between *R*-BHB and changes in depression symptoms were not significant. A trend was observed between *R*-BHB at week 4 and change in PHQ-9 score in study completers from baseline ($r = -0.46$, $p = 0.084$). No significant correlation was observed between changes in symptoms of depression and the weekly average of ketones during week 4 of testing ($r = -0.38$, $p = 0.19$). Week 4 was selected for statistical analysis as this was the timepoint at which the greatest change in PHQ-9 scores between subsequent test days was observed and because it coincided with some of the highest ketone values. Additionally, observer-rated HRSD scores at weeks 6 and 12 showed no significant association with daily morning *R*-BHB values (week 6: $r = 0.30$, $p = 0.26$; week 12: $r = 0.04$, $p = 0.89$).

Weight loss and depression. To evaluate whether weight loss influenced depression scores independently of ketosis, regression analyses were conducted. Change in PHQ-9 scores from baseline to midpoint and post-testing were not significantly correlated with changes in body weight (midpoint: $r = 0.24$, $p = 0.38$; post-test: $r = 0.33$, $p = 0.21$).

Biochemical markers

There were no significant changes in cholesterol, triglycerides or any other parameters assessed in the chemistry panel, except an increase in serum calcium (3%; $p = 0.003$), blood urea nitrogen (14%; $p = 0.029$), and a decrease in alanine transaminase (−27%; $p = 0.028$). Among the ten serum adipokines assessed (BDNF, IL-1β, IL-6, IL-8, IL-10, Insulin, Leptin, MCP-1, TNF-α, β-NGF), only leptin (−52%) and BDNF (+32%) showed significant changes over time (Table 2). Notably, post-intervention BDNF levels showed greater variability than the baseline (range: 1068–7093 vs. 156–5144 pg/dL). There was no significant change in HOMA-IR (−28%; $p = 0.151$).

Cognitive performance

Significant improvements were observed in cognitive tasks of episodic memory, processing speed, and executive functions. Specifically, participants demonstrated improved Auditory Verbal Learning (10%; $p = 0.032$), reflecting more recalled words from the episodic memory test across three trials. Participants also demonstrated improved Oral Symbol Digit Test (5%; $p = 0.046$) and Pattern Comparison Test (4%; $p = 0.021$), indicating faster processing speed at post-intervention. Post-intervention raw scores for the Dimensional Card Sort Test approached significance (−2%; $p = 0.057$), indicating a trend for improved cognitive flexibility and accuracy as well as faster response times. No significant differences for Picture Sequence Memory Test, Dimensional Change Card Sort Test, List Sorting Working Memory Test, or Flanker Inhibitory Control and Attention reaction times were observed.

DISCUSSION

The cluster of burgeoning MDD symptoms that emerge during young adulthood warrant the discovery of novel treatment options to address its complex pathophysiology. One such approach that has received considerable attention recently is "metabolic psychiatry". This field has primarily focused on ketogenic therapies with a growing evidence base indicating its potential for attenuation of mental health symptoms [26, 28, 49, 50]. This pilot study provides preliminary evidence that a WFKD is a feasible and synergistic strategy adjunctive to a

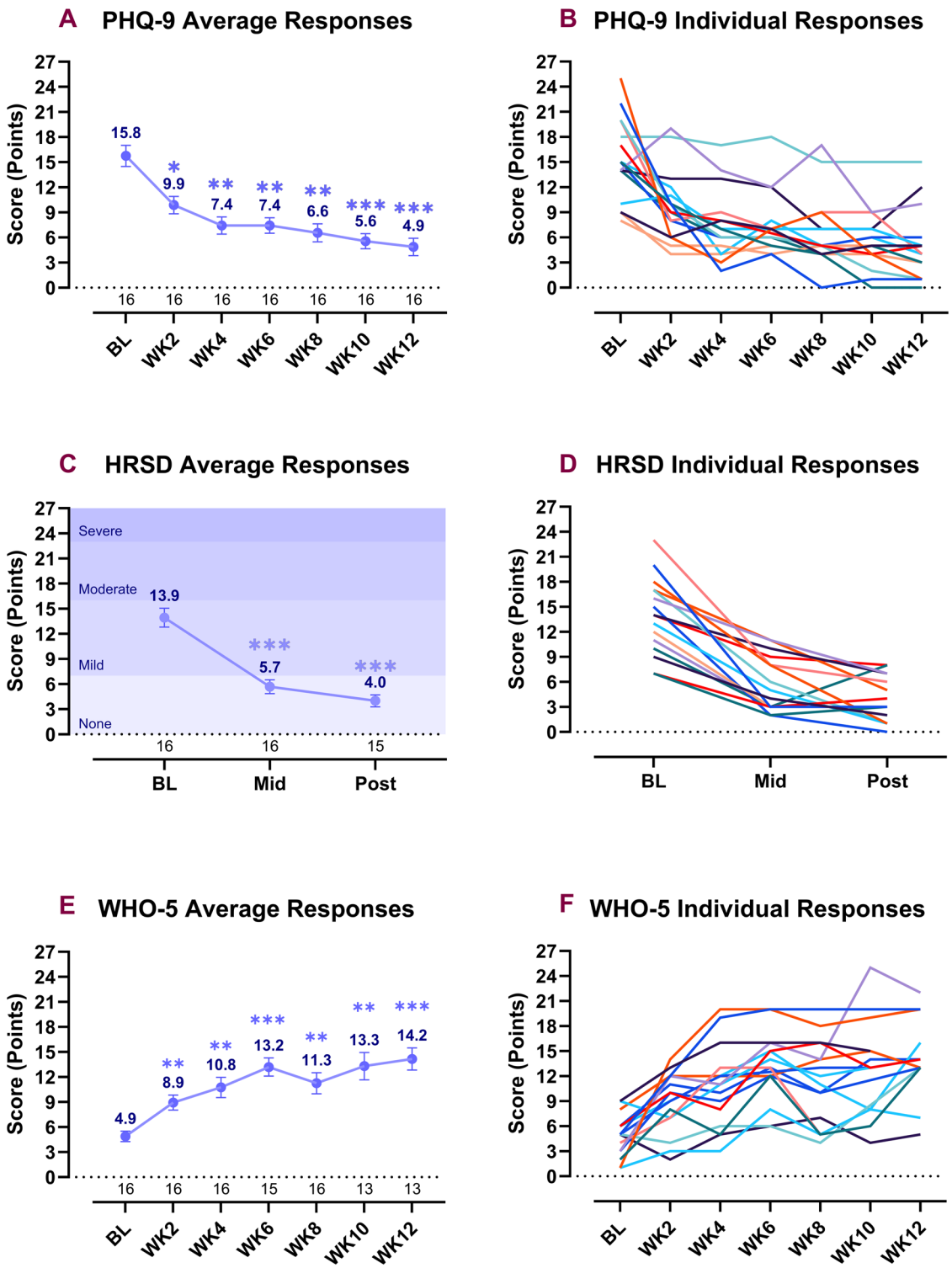


Fig. 3 Survey Responses. Mean and individual survey responses for PHQ-9 (**A**), (**B**), HRSD (**C**), (**D**), and WHO-5 (**E**), (**F**). Lower scores denote improvement in PHQ-9 and HRSD. The numbers below the dotted line reflect the n-size. The HRSD scale is divided into quadrants indicating no depression (0–7), mild depression (8–16), moderate depression (17–24), and severe (>25). All values are mean ± SEM. * = $p < 0.05$ compared to baseline. ** = $p < 0.01$ compared to baseline. *** = $p < 0.001$ compared to baseline.

counseling and consultation treatment program for young adults with MDD. Students diagnosed with MDD, as determined from a SCID-5, who chose to enroll in the study demonstrated compliance to the WFKD as evidenced by achieving a metabolic state of nutritional ketosis. The combined intervention resulted in clinically meaningful improvements in symptoms of depression, body composition, psychological wellbeing, and cognitive performance.

Patient population and generalizability

While this study focuses on a college student population, it is important to consider the challenges in scaling this intervention to

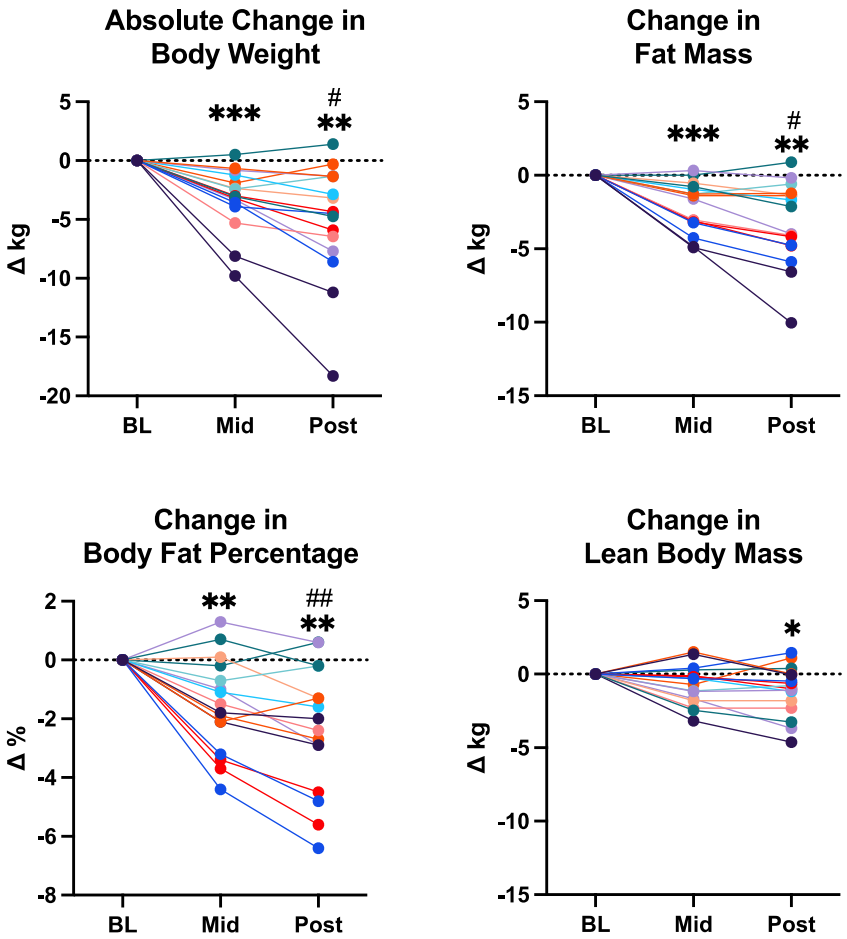


Fig. 4 Individual body weight and body composition responses. * = $p < 0.05$ compared to baseline. ** = $p < 0.01$ compared to baseline. *** = $p < 0.001$ compared to baseline. # = $p < 0.05$ compared to midpoint ## = $p < 0.01$ compared to midpoint.

Table 2. Serum adipokine panel.

Adipokine Biomarker	Baseline	Mid-Point	Post	One Way ANOVA (*p*-Value)
β-NGF	2.179 ± 0.225	2.219 ± 0.154	2.118 ± 0.782	0.843
BDNF	2920 ± 383	3335 ± 430	3861 ± 392[a]	0.029
IL-10	1.628 ± 0.393	1.775 ± 0.409	1.727 ± 0.459	0.908
IL-1β	0.8809 ± 0.152	1.043 ± 0.169	0.9960 ± 0.126	0.232
IL-6	2.343 ± 0.317	2.578 ± 0.259	2.577 ± 0.250	0.415
IL-8	10.49 ± 1.09	11.57 ± 0.816	12.30 ± 1.20	0.156
Leptin	2614 ± 830	1283 ± 522[a]	1242 ± 516[a]	0.009
Insulin	18.85 ± 2.57	16.31 ± 2.72	14.39 ± 1.50	0.135
MCP-1	231.0 ± 29.2	216.3 ± 21.0	244.9 ± 30.1	0.262
TNF-α	2.407 ± 0.270	2.367 ± 0.258	2.361 ± 0.180	0.945

All values are mean ± SEM in pg/mL except for insulin units as μIU/mL.
[a]Significantly different from baseline ($p < 0.05$).

a broader, more diverse population. College students may have specific advantages in terms of adherence, such as greater access to resources and support, but they also face unique stressors related to academic life that could affect their ability to engage consistently with the treatment. The generalizability of this intervention to individuals outside of this demographic is an important consideration. Challenges in applying this treatment to a broader population may include differing levels of health literacy, financial constraints, and the availability of specialized dietary counseling. Additionally, scaling the implementation of dietary counseling in community psychiatry clinics may be hindered by limited access to trained dietitians and the time-intensive nature of individualized dietary planning. Future research should examine how this intervention can be adapted to meet the needs of more diverse populations, including those with limited access to healthcare resources.

Adherence

The subjects who completed the study (n = 16) were in nutritional ketosis (>0.5 mM R-BHB) 73% of the time throughout the intervention. We attribute this to ability to achieve and maintain nutritional ketosis without side effects to the careful attention to fundamental principles of a WFKD including decreasing carbohydrate intake to <50 g/day, consuming quality fat sources, adequate mineral consumption, and an adequate but not excessive protein intake [41]. The extensive diet coaching and education before starting the diet, attention to individual food preferences, and access to study dietitians through a secure messaging app were also likely important components.

Although dietary compliance was high, the attrition rate (33%) in our study was higher than the 10% reported by Danan et al [26] in subjects with various forms of mental illness prescribed a ketogenic diet and the 25% in young adults with depression prescribed a non-ketogenic diet intervention [51]. One possible explanation for the higher attrition in this study compared to Danan et al. may be that this was not an inpatient study. Although participants in this study received support through a messaging app, some supplementary food items, and a baseline dietary consultation, they did not have the intensive, continuous supervision and structured environment provided in the inpatient study by Danan et al. Another reason for the attrition rate may be the younger age of the college students enrolled in the current study and unique circumstances associated with their semester course schedule, which made it challenging to fit the 12-week intervention into a single semester. Future studies could include post-intervention surveys or interviews to gain a fuller understanding of retention in this population. However, we noted that seven of the eight participants who dropped out at varying time points after baseline testing did so for reasons unrelated to the diet.

Depression symptoms

Significant improvements in symptoms of depression were observed, as evidenced by a 69% reduction in PHQ-9 and a 71% reduction in HRSD at post-testing, demonstrating concordance between self-reported and clinician-rated depression scores. These relatively large reductions in depression symptoms are consistent with prior case studies that have employed ketogenic diets in depressed cohorts [26, 27]. Significant decreases in PHQ-9 scores were evident by the second week of the intervention, with most scores falling below the PHQ-9 threshold for a diagnosis of MDD. The magnitude of the PHQ-9 response in completers at week 2 and the end of the intervention (−5.9 and −10.9 points, respectively represent clinically meaningful improvements in depression (i.e., ≥5 point reduction) [52]. This improvement in depression symptoms coincides with the onset of nutritional ketosis, typically achieved by participants around day 7 of the intervention [53].

Moreover, the improvement in depression scores was sustained for all subjects throughout the duration of the study suggesting at least some durability of the response. The improvement in depression occurred without any increase in medication prescriptions. The intervention was not designed to test whether reduced depression could be maintained without medication and was too short to assess remission of depression, which should be addressed in future work.

Weight loss, BDNF, leptin, and insulin

We observed clinically significant weight loss and improvements in body composition despite not providing explicit instruction to reduce energy intake. We attribute this effect to the ketogenic diet since medication and counseling would not be expected to elicit such effects. The magnitude of weight loss and changes in body composition were consistent with other ketogenic diet studies [36, 54, 55] including a recent study in a similarly aged university population [16]. Individuals with greater adiposity lost more body mass and body fat. Prior research has shown an association between obesity and an increased risk of depression, with higher body fat positively correlated with depressive symptoms [56, 57]. Thus, weight and fat loss noted in this study could support mood improvement or reduction in depressive symptoms, especially for individuals with comorbid obesity, although we did not detect a significant association between weight loss and improvement in depression.

In our investigation, we observed a 32% increase in BDNF which may suggest a potential neurobiological mechanism underlying an antidepressant effect. Given that MDD is associated with reduced BDNF levels in the hippocampus and prefrontal cortex [58], and that β-hydroxybutyrate has been shown to enhance BDNF expression [32], it is possible that WFKDs contribute to structural and functional improvements in these brain regions.

Leptin levels are known to be positively correlated with adiposity [59] and thus the significantly lower leptin (−52%) is consistent with an improved leptin sensitivity associated with weight and fat loss, and may be important as this adipose-derived hormone is considered an important link between metabolic health, cognitive function and inflammation [60, 61]. Participants had stable, normal glucose levels throughout the intervention, but their insulin and HOMA-IR values indicated more variability in insulin resistance. Insulin is associated with depression [62]. HOMA-IR was reduced by 28% but failed to reach significance. A WFKD consistently improves insulin resistance in individuals with higher levels of HOMA-IR [12, 18, 41], however, as the cohort studied here was relatively young and metabolically healthy from the perspective of glucose tolerance, HOMA-IR levels were likely to fall within the range of normal metabolic function.

Mechanistically, a WFKD may exert antidepressant effects through multiple pathways, including increases in brain derived neurotropic factors (BDNF) [32] and decreases in inflammation [13, 15, 29] which may reduce MDD severity, as elevations in inflammatory mediators and decreases in BDNF have been associated with severity of depression [30, 31, 54]. Other potential pathways through which WFKDs may impact depression symptoms include weight loss and improved body composition or through direct neuroprotective effects in the hippocampus, an important neural area related to cognitive function and mental health [33–36]. Ketogenic interventions, including both a WFKD and exogenous ketone supplements, are associated with more stable brain networks assessed with functional magnetic resonance imaging (fMRI) [37–39].

Cognitive performance

Performance improvements were observed in episodic memory, processing speed, and executive functions, which tend to show deficits in MDD. Previous work has reported positive or null effects of a KD on cognitive outcomes in healthy adults. A systematic review in healthy adults across the lifespan found that all but a few of the 27 studies reported a favorable effect of a KD intervention on cognition [63] with a minority reporting no effect [64]. In individuals with Alzheimer's disease [65], a positive effect of a ketogenic diet on verbal memory and processing speed was reported. We extend previous findings in healthy and pathological aging cohorts by demonstrating improvement in multiple cognitive domains, especially speeded tasks, in adults with MDD. Impairments in processing speed in MDD may be driven by deficits in attentional capacity or slowing of psychomotor speed [66, 67]. We did not observe any declines in mean cognitive performance.

Practice effects, referring to improvements in cognitive scores due to repeated administration of the same tests, may limit the interpretation of our results. Sources of practice effects include incidental learning, shift in strategy, or increased familiarity with the test-taking environment [68] and have been reported in nutrition studies [69]. Susceptibility to practice effects may vary by

cognitive domain. [68, 70]. Other studies examining practice effects on the NIH-TB battery reported significant practice effects for Dimensional Change Card Sort Test and Flanker Test [71] and the Pattern Comparison Processing Speed Test over 2-weeks [72]. Future work that includes a control group will allow for clarity to more clearly distinguish the role of ketogenic diet versus practice effects on cognitive performance.

Limitations

This study utilized a single-arm design without a control or dietary comparison group. Thus, it is not possible to isolate the effects of the WFKD from counseling and/or medication or to know how time alone would alter depression symptoms or cognitive performance. Therefore, conclusions regarding the efficacy of the WFKD alone to improve depression or cognitive function remain speculative. The cohort volunteered to enroll in the dietary intervention, which introduces the possibility of selection bias. Additionally, participants may have been influenced by demand characteristics, as their awareness of the study's purpose could have affected self-reported outcomes. Participants received treatment for MDD from a variety of providers within a 30-mile radius of campus, and we did not capture information regarding the specific type or frequency of counseling for depression.

Summary

This study is the first to demonstrate the feasibility of a WFKD as an adjunct therapy for college-aged students with MDD undergoing counseling and/or medication treatment. Results indicate robust and sustained decreases in depression symptoms over 10–12 weeks, which were accompanied by improvements in global well-being, body fat, and cognitive performance. Our results indicated that WKFD is a potentially beneficial adjunctive option to traditional therapies for MDD in college students, highlighting the need for replicating the findings herein in larger, randomized controlled trials.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are stored in Prism GraphPad format and are available from the corresponding author upon reasonable request. There are no restrictions on data availability.

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AUTHOR CONTRIBUTIONS

JV designed the experiment, conducted data analysis, and contributed to writing the manuscript. DD contributed to overall study coordination, including recruitment, study design, data collection, data analysis, and manuscript writing. RP contributed to study recruitment, data collection, and manuscript writing. JC contributed to study design and manuscript writing. SH assisted with cognitive testing, study design, and manuscript writing. WW managed recruitment, administered HRSD assessments, and contributed to editing. AL oversaw fMRI and cognitive testing, and assisted in editing. AB and BR contributed to data analysis and editing. CC, JS, and AC assisted in editing the manuscript. MK contributed to data collection, data analysis, and manuscript writing. TS assisted with dietary consultations, data collection, data analysis, and manuscript writing.

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COMPETING INTERESTS

JSV is a co-founder and shareholder of Virta Health, and has authored books that recommend a ketogenic diet. All other authors declare no conflicts of interest.

ADDITIONAL INFORMATION

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