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REGULAR ARTICLE

Metabolic Improvements with a Ketogenic Diet Correlate with Symptom Improvement in Psychosis: A Randomized Controlled Trial

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Background and Hypothesis: **Psychiatric medications contribute to high rates of metabolic dysfunction in psychotic disorders. Ketogenic diets reduce metabolic syndrome, have anticonvulsant effects in epilepsy, and may improve symptoms of schizophrenia and bipolar disorder. We report the first randomized controlled trial to assess effects of ketogenic diets on metabolism, psychiatric symptoms, and cognition in people with schizophrenia-spectrum and bipolar-1 disorders.**

Study Methods: **Participants were randomized to a ketogenic diet (KETO; $n = 28$) or diet-as-usual (DAU; $n = 30$) for 1 month. Partway through the trial, a KETO extension was offered to both groups, resulting in a subgroup who completed the diet for 4 months ($n = 25$). We assessed changes in metabolic health, clinical symptoms, and cognition after 1 month (KETO versus DAU) and after 4 months (KETO versus baseline).**

Study Results: **KETO participants' daily ketone levels surpassed the standard ketosis threshold. Relative to DAU, KETO participants showed reductions in weight ($P_{adj} < .001$), hemoglobin A1c ($P_{adj} = .05$), and insulin resistance ($P_{adj} = .05$). Clinical symptoms (positive, negative, depression) and cognitive performance improved after 4 months on the KETO (all *P*-values $< .001$). Increased blood ketone levels in KETO participants correlated with improvements in pre-diabetic markers and depressive symptoms (all *P*-values $< .001$). Reduced weight following the KETO was unrelated to metabolic and symptom improvements.**

Conclusions: **We demonstrate feasibility of administering a KETO in outpatients with schizophrenia and bipolar-1 disorder. Participants showed improvement in metabolic health, cognitive performance, and clinical symptoms. Improvement in depressive symptoms was associated with ketosis rather than weight loss, implicating ketosis as the therapeutic mechanism.**

Key words: schizophrenia; bipolar disorder; randomized controlled trial; ketogenic diet; metabolism; neuropsychological testing; psychosis symptoms; depressive symptoms.

Introduction

Psychotic disorders are associated with impaired cognition and real-world functioning, thereby placing a large burden on affected individuals and their families. Current antipsychotic medications fail to address cognitive deficits and negative symptoms and may worsen both.[1–3] Second generation antipsychotics commonly induce weight gain, glucose dysregulation, and hyperlipidemia, and contribute to high rates of metabolic syndrome in patients with schizophrenia-spectrum and bipolar-1 disorders.[1–4] The ketogenic diet as a therapeutic intervention could address incomplete treatment response to antipsychotic medications and compromised metabolic health. Single-arm and uncontrolled studies suggest ketogenic diets can alleviate metabolic syndrome and clinical symptoms in psychiatric disorders (see review[5]; pilot study[6]; case studies[7,8]). We present data from the first randomized control trial of a ketogenic diet in people with psychosis.

The American College of Cardiology defines metabolic syndrome as the presence of 3 of 5 risk factors: increased waist circumference, elevated serum triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glucose.[9] Metabolic syndrome is associated with poor quality of life, more severe psychiatric symptoms, impaired cognition, and reduced lifespans.[1,3,10–14] Metabolic

disorders precede the onset of psychotic disorders and were linked with schizophrenia before the introduction of antipsychotic medications, implicating metabolic dysfunction in the pathophysiology of schizophrenia.[15] In support of this notion, a meta-analysis reports disrupted glucose metabolism and insulin resistance in medication-naïve first-episode schizophrenia patients.[16] One longitudinal study followed patients for 20 years after their first hospital admission for psychosis and found that 50% of bipolar and 67% of schizophrenia patients had become obese.[17]

Diet plays a large role in metabolic syndrome onset.[18,19] Poor diet and reduced exercise are common consequences of avolition and functional impairment in schizophrenia.[20,21] Although weight loss improves metabolic health, the ketogenic diet benefits both metabolism and brain function, including cognition[22] and amelioration of epilepsy.[23] The ketogenic diet is a normo-caloric diet composed of high-fat (70%), low-carbohydrate (10%), and adequate protein (20%) that induces the breakdown of fat, increasing production of ketone bodies.

Mitochondrial metabolism of ketone bodies yields 27% more ATP than glycolysis. Prioritizing ketone body metabolism over glycolysis could counteract dysfunctional glucose metabolism observed in schizophrenia.[16,24,25] Ketones have demonstrated extensive neuronal benefits including reducing inflammation,[26] increasing expression of genes related to neural plasticity,[27] and suppressing excitotoxic glutamatergic signaling,[28–31] all of which are mechanisms implicated in the pathology of schizophrenia.[32–34]

Uncontrolled studies and case reports suggest the ketogenic diet may improve clinical symptoms and metabolic health in several psychiatric disorders.[6,32,33] Danan et al.[34] described outcomes of inpatients with serious mental illness (ie, major depressive disorder, bipolar disorder, schizoaffective disorder) who followed a ketogenic diet for 6-248 days. The diet was feasible, well-tolerated, and associated with substantial improvements in depressive symptoms, psychosis, and metabolic health. Case studies showed improved metabolic health and psychotic symptoms in 4 individuals with psychotic diagnoses.[7,8] A more recent randomized controlled trial (RCT) described outcomes in patients with treatment resistant depression who were randomized to a 6-week ketogenic diet or an active control diet.[35] Depression severity markedly decreased in both groups, with slightly more reduction in the ketogenic diet group; although this difference was not sustained 6 weeks after meal delivery stopped.

We report outcomes from the first RCT in people with schizophrenia-spectrum and bipolar-1 disorders on a ketogenic diet. Outcome variables include markers of metabolic health, cognition, and clinical symptoms. Our study included 2 phases; in a 1-month RCT, participants were randomized to a ketogenic diet (KETO) or a diet-as-usual (DAU). In a subsequent 4-month extension study, DAU participants were enrolled in a 4-month ketogenic diet and KETO participants were offered an additional 3 months, that is, all extension study participants underwent the ketogenic diet for the same length of time. We expected KETO participants to show greater improvements in (1) metabolic health, (2) psychiatric symptoms, and (3) cognitive performance, when compared to DAU. We also expected ketogenic-diet gains to be larger after 4-months on the diet. To assess whether ketosis or weight loss was the therapeutic mechanism underlying improvements following a ketogenic diet, improvements were correlated with individual differences in ketone levels, proportion of time spent in ketosis, and weight change.

Methods

Participants

We collected data from 49 participants who met criteria for either schizophrenia/schizoaffective disorder (SZ, $n = 30$) or bipolar disorder with psychotic features ($n = 19$). Data from 2 participants were not included in the RCT analyses (explained in section Statistical Analyses). Table S1 contains participant demographic details. There were no significant differences between DAU and KETO groups in demographics, psychiatric symptoms, and metabolic measures at baseline. Diagnosis was determined using the Structured Clinical Interview for DSM-IV (SCID)[36] conducted by clinical psychologists (trainee or licensed). Exclusion criteria included any substance use disorder in the past 6 months; current cancer diagnosis; pregnancy, breastfeeding, or planned pregnancy within 1 month; current diagnosis of type 1 diabetes; glucose-lowering drugs (other than metformin) or weight loss medications; history of gastric bypass surgery or any weight loss surgery; history of significant medical or neurological illness; a previous head injury that resulted in loss of consciousness; experience with the ketogenic diet less than 6 months before their start date; and changes in medication less than 2 weeks before their start date. Participants were excluded for taking GLP-1 agonists but not metformin; of the 5 participants taking metformin, 3 were in the DAU group and 2 were in the KETO group. The study was approved by the institutional review board of UCSF, and all participants provided written informed consent.

Diet Intervention

One-Month Intervention Study (RCT). After completing eligibility screening, 58 participants were randomly assigned to a KETO group, or a DAU group (Figure 1). KETO participants were asked to follow a ketogenic diet for 1 month. Before starting the diet, participants were given a coaching session to understand the structure of the diet. They received 18 microwavable ketogenic meals each week by a study-contracted meal delivery service. Participants were allowed to eat food aside from the meals provided by the study, but they were instructed to eat at least 2 prepared meals per day and aim for a diet composed of 70%-80% fat, 10%-20% protein, and no more than 10% carbohydrates. DAU

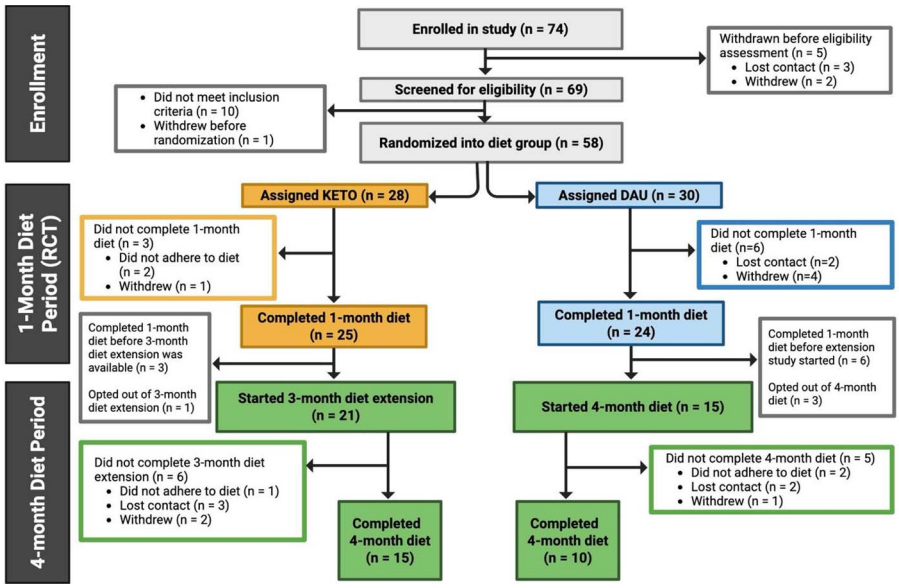

Figure 1. Study Enrollment Process and Participant Retention.

participants were asked to continue eating their typical diet for 1 month and were not provided with meals. A licensed dietitian or a research assistant contacted KETO and DAU participants weekly to check on their progress and answer questions. Appointments with a study-affiliated psychiatrist were available for all participants. Except for the reporting of ketone levels to study staff, DAU and KETO groups had the same level of interaction with study staff, including weekly calls from the dietician regardless of the diet they were following.

Four-Month Extension Study. When additional funding became available, all participants who completed the 1-month intervention study were invited to join an extended ketogenic diet study. Participants originally in the KETO group followed the ketogenic diet for 3 additional months; participants originally in the DAU group followed the ketogenic diet for 4 months. Ketogenic meals were delivered as in the 1-month study. All participants in the extension study received 4 months of ketogenic meals.

Feasibility and Tolerability. No serious adverse events occurred in study participants, but minor events, like headaches, resolved with increased fluid intake and electrolytes. Primary reasons cited for withdrawing from the KETO group included difficulty adhering to the diet and disinterest in completing research assessments.

Data Acquisition

Data were collected during remote and in-person visits to the San Francisco VA Medical Center. At baseline, 1-month, and 4-month appointments, participants completed various assessments, including a blood draw.

Clinical Assessments. The MATRICS Consensus Cognitive Battery (MCCB) evaluated cognitive domains that are commonly impaired in psychotic disorders[37]; we used the MCCB Overall Composite score for analysis. Positive and negative schizophrenia symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS)[38] and the Scale for the Assessment of Negative Symptoms (SANS)[39]; we used SAPS and SANS total scores for analysis. To capture depression symptoms, participants self-administered the Patient Health Questionnaire (PHQ-9).[40] All cognitive tests and symptom assessments were administered by clinical psychologists or trained research assistants.

Physiological/Metabolic Assessments. Height, weight, waist circumference, blood pressure, and heart rate were measured with lab equipment. Blood samples were drawn by phlebotomists at the San Francisco VA Medical Center at each in-person visit, that is, baseline, at 1-month, and at end of the last-month for people in the extension study. Samples were analyzed to measure glucose, hemoglobin A1C (HbA1c), insulin, C-reactive protein (CRP), and β-hydroxybutyrate (BHB). Using the results of the blood tests, we assessed insulin resistance using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; blood glucose (units) × insulin (units)/405). Height and weight were used to calculate Body Mass Index (BMI; weight (kg)/height $(m)^2$). Blood levels of BHB collected at the post-diet session confirmed participants' adherence to the ketogenic diet (based on a threshold of 0.5 mmol/L).

KETO participants (1-month intervention and 4-month extension study) were asked to take daily measurements of their blood pressure and heart rate. The ability to measure daily ketone levels became available part-way through the study; consequently, only a subsample of participants reported these values (18 in the 1-month and 18 in the 4-month trial).

Statistical Analyses

Analyses were performed in R. One participant in the DAU group was excluded from analyses because their BHB level at their post-diet visit was well above the ketosis threshold, indicating a deviation from study protocol. Data collected from one participant in the KETO group were also excluded because the participant reported at their post-diet visit that they had not followed the ketogenic diet.

Primary Analyses. Our primary analyses examined changes in physiological/metabolic (BHB, BMI, HbA1c, HOMA-IR, and CRP) and clinical/cognitive variables (PHQ-9, SAPS, SANS, MCCB). Between-group effects of the 1-month intervention study were analyzed using *t*-tests on the post-diet change scores (i.e., 1-month minus baseline) for DAU versus KETO. Follow-up regression models controlling for baseline scores confirmed that observed diet-related changes were not attributable to differences between participants at baseline. Effects of the 4-month KETO extension study were analyzed using paired t-tests comparing post-diet scores to baseline. Cohen's *d* quantified effect sizes. We corrected for multiple comparisons for groups of similar tests using the false discovery rate (FDR) method, that is, 5 physiological/metabolic tests and 4 clinical/cognitive tests, as groups of similar variables that could be expected to covary.

Secondary Analyses. We also explored whether significant gains from the ketogenic diet were related to individual differences in achieved ketosis versus the degree of weight loss. Here we used linear regressions to evaluate relations of post-diet BHB and weight (BMI) change scores with variables that changed at 1-month (KETO group only) or 4-months (from the primary analyses). These models controlled for baseline scores given that baseline and change scores were often correlated.[41] For any significant associations with post-diet BHB change scores, we produced follow-up models that added BMI change scores; this allowed us to test whether ketosis-related changes could be similarly explained by weight loss. Additional exploratory analyses considered whether time spent in ketosis (using the available at-home measurements) were similarly correlated with ketogenic diet gains. We did not evaluate DAU participants for these analyses given a lack of variance in BHB change scores.

Results

Ketosis Was Achieved and Sustained

As evidence of the diet's feasibility in our study participants, their daily ketone levels reached and surpassed the standard ketosis threshold of 0.5 mmol/L within 1 week of starting the diet (Figure 2; Table S2). In the last 2 weeks of the 1-month KETO diet, participants' ketone levels averaged 1.28 mmol/L (±0.79). In the last month of the 4-month KETO diet, participant's ketone levels averaged 1.26 mmol/L (±0.73). Three out of 18 participants in the 1-month KETO group reported average ketone levels below the ketosis threshold. Only one out of 18 participants in the 4-month KETO group measured average ketone levels below the ketosis threshold, reporting average ketone levels of 0.47 mmol/L during the last month of their participation.

Ketogenic Diet Improved Metabolic Markers

Participants in both the 1- and 4-month KETO groups showed improvements in several metabolic markers (Table S3).

As expected, BHB (Figure 3A) increased more in the 1-month KETO group than in the DAU group based on a between-group *t*-test of the post-diet change scores ($t_{44} = 4.87$, $P < .001$, $P_{adj} < .001$, $d = 1.44$). Follow-up tests revealed a significant increase in BHB levels for KETO compared to baseline ($t_{22} = 5.03$, $P < .001$, $P_{adj} < .001$, $d = 1.05$), but not DAU compared to baseline ($P = .91$). BHB also increased in the 4-month KETO group ($t_{23} = 4.21$, $P < .001$, $P_{adj} = .001$, $d = 0.86$).

BMI (Figure 3B) decreased more in the 1-month KETO group than in the DAU group ($t_{46} = -5.78$, $P < .001$, $P_{adj} < .001$, $d = -1.69$). Follow-up tests revealed a significant decline in BMI from baseline among KETO ($t_{23} = -6.68$, $P < .001$, $P_{adj} < .001$, $d = -1.36$), but not DAU participants ($P = .31$). Reduced BMI was also evident in the 4-month KETO group ($t_{24} = -5.81$, $P < .001$, $P_{adj} < .001$, $d = -1.16$).

HbA1c (Figure 3C) decreased more in the 1-month KETO group than in the DAU group, ($t_{41} = -2.11$, $P = .041$, $P_{adj} = .05$, $d = -0.64$). Follow-up tests revealed a decrease in HbA1c in the KETO group ($t_{20} = -2.45$, $P = .024$, $P_{adj} = .04$, $d = -0.53$), but not in the DAU group ($P = .91$). HbA1c also decreased in the 4-month KETO group ($t_{20} = -2.99$, $P = .007$, $P_{adj} = .011$, $d = -0.61$).

HOMA-IR (Figure 3D) decreased more in the 1-month KETO group than in the DAU group ($t_{40} = -2.15$, $P = .037$, $P_{adj} = .05$, $d = -0.67$). Follow-up tests revealed a trend-level decrease in HOMA-IR in the KETO group ($t_{22} = -1.99$, $P = .058$, $P_{adj} = .073$, $d = -0.42$), but no change in the DAU group ($P = .24$). There was a trend-level reduction in HOMA-IR in the 4-month KETO group ($t_{21} = -1.84$, $P = .081$, $P_{adj} = .1$, $d = -0.39$).

CRP (Figure 3E) did not significantly decrease between the 1-month KETO and DAU groups ($t_{45} = -0.984$, $P = .331$), and although there was a numerical increase in CRP in the 4-month KETO group, it was not significant ($t_{21} = 1.12$, $P = .27$).

Ketogenic Diet Improved Psychiatric Symptoms and Cognitive Function

Participants in the 4-month KETO group showed improvements in psychiatric symptoms and cognitive performance relative to baseline (Table S3).

There was a trend-level difference in PHQ-9 change scores between KETO and DAU participants, but this became insignificant after correction for multiple comparisons (Figure 4A; $t_{32} = -1.91$, $P = .065$, $P_{adj} = .26$, $d = -0.66$); this

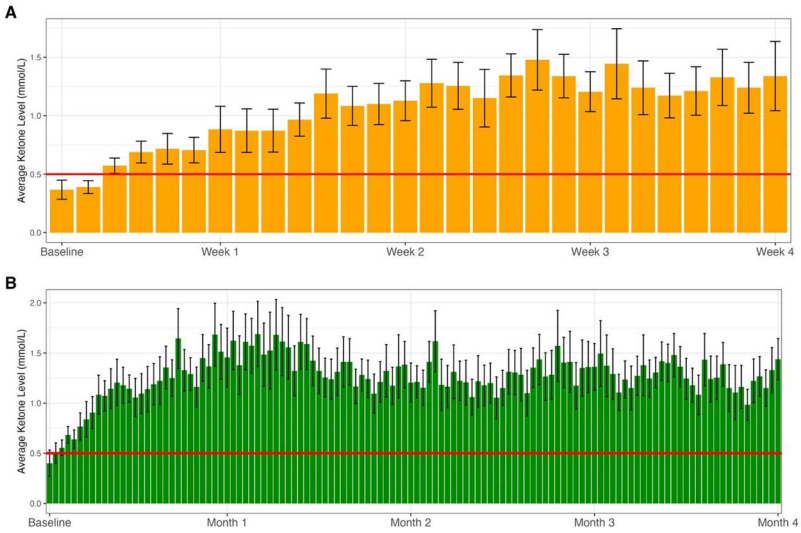

Figure 2. Average Daily Ketone Levels Reported by Participants Following the 1-Month (A) and 4-Month (B) Ketogenic Diet Protocols. Horizontal line at 0.5 mmol/L indicates the ketosis threshold.

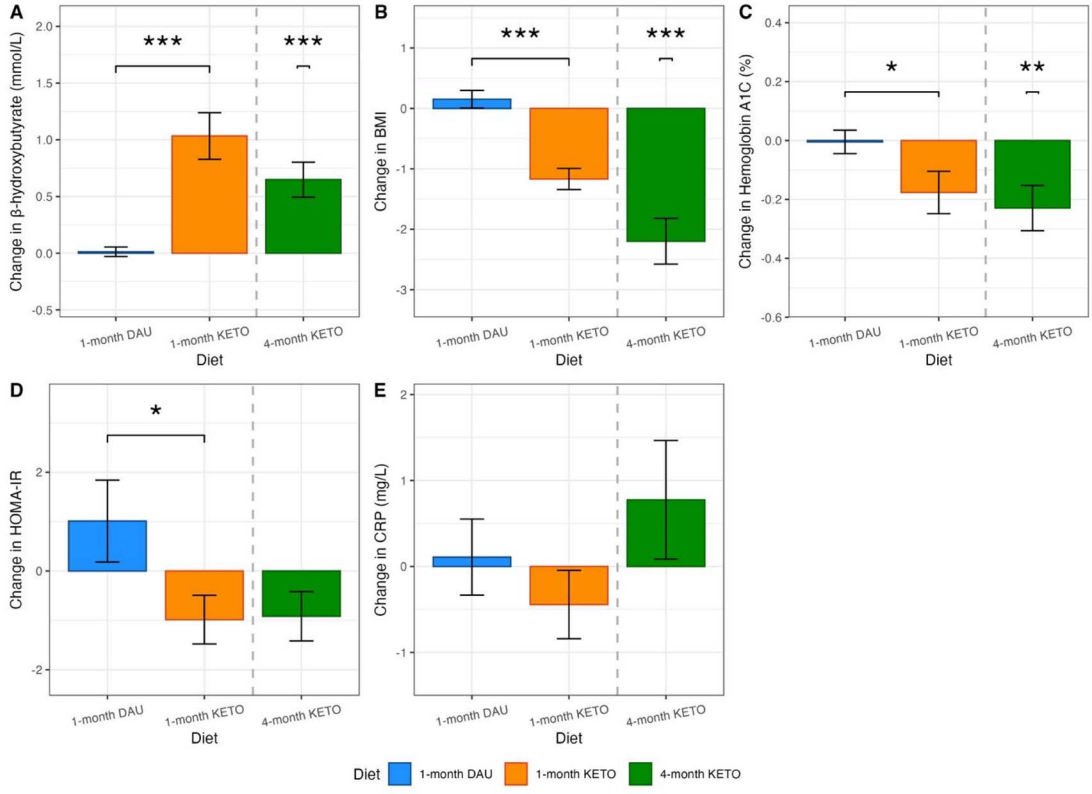

Figure 3. Change in BHB (A), BMI (B), HbA1c (C), HOMA-IR (D), and CRP (E) for Participants in the 1-Month DAU, 1-Month KETO, and 4-Month KETO Diet Groups. $^{*}P \leq .05$, $^{***}P < .001$.

effect became significant based on a paired *t*-test of PHQ-9 scores in the 4-month KETO group ($t_{24} = -4.53$, $P < .001$, $P_{adj} < .001$, $d = -0.91$).

Based on a between-group *t*-test of the post-diet change scores, SAPS scores did not differ between the 1-month KETO and DAU groups ($P = .31$; Figure 4B). SAPS scores did decrease in the 4-month KETO group ($t_{23} = -3.75$, $P = .001$, $P_{adj} = .001$, $d = -0.77$).

Similarly, SANS scores did not differ between the 1-month KETO and DAU groups ($P = .42$; Figure 4C) but did decrease in the 4-month KETO group ($t_{23} = -3.27$, $P = .003$, $P_{adj} = .003$, $d = -0.67$).

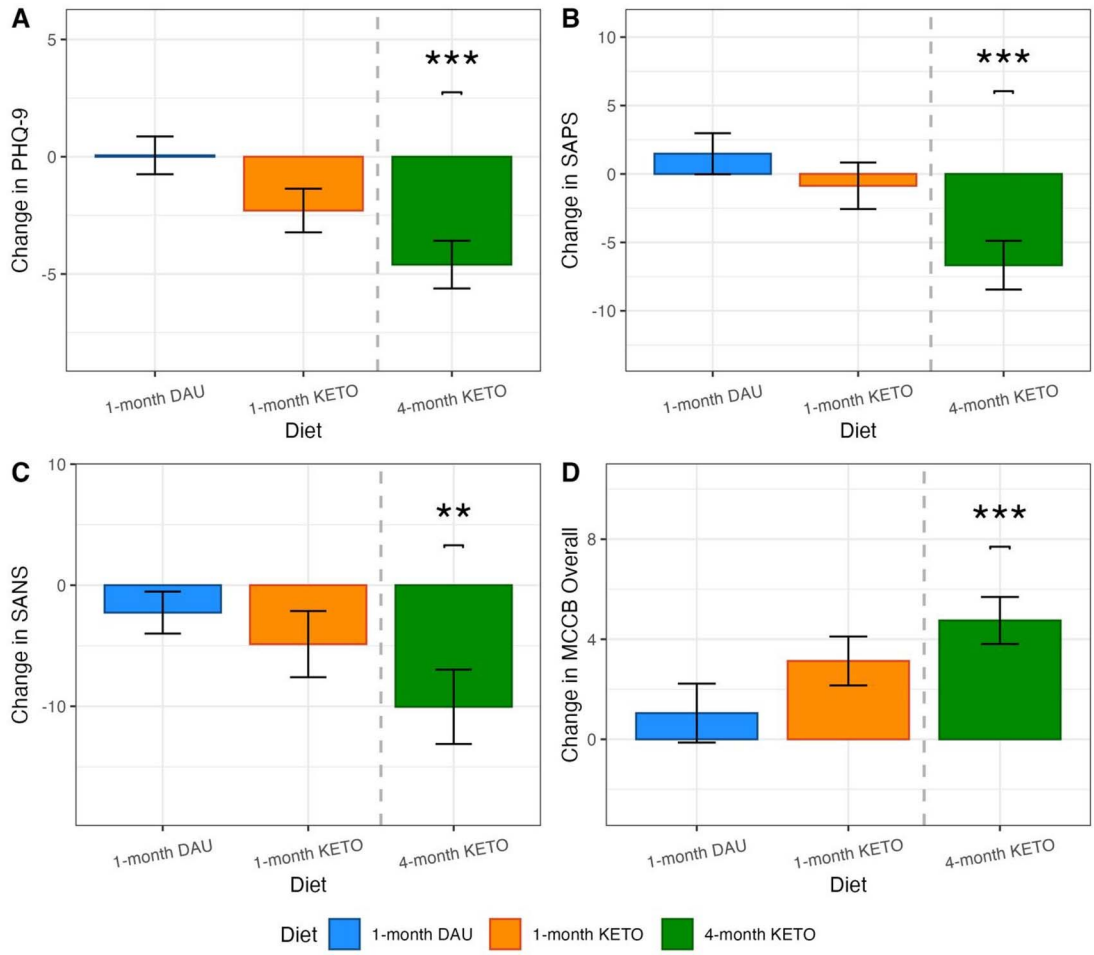

Figure 4. Change in PHQ-9 (A), MCCB (B), SAPS (C), and SANS (D) Scores for Participants in the 1-Month DAU, 1-Month KETO, and 4-Month KETO Diet Groups. $^{**}P < .01$, $^{***}P < .001$.

MCCB Overall Composite post-diet change scores (Figure 4D) did not differ between the 1-month KETO and DAU groups ($P = .18$). MCCB Overall Domain scores did increase in the 4-month KETO group ($t_{23} = 5.05$, $P < .001$, $P_{adj} < .001$, $d = 1.03$).

Increased Ketone Bodies Correlate with Metabolic and Psychiatric Symptom Improvement

As a final consideration, we explored whether any significant or trend-level changes observed in the 1-month KETO group were directly related to increases in ketone bodies (based on in-laboratory measurements of BHB) or reduced weight (BMI) using post-diet change scores. Standardized betas and *P*-values are found in Table S4. Significant results did not change when the change in BHB was replaced by the raw BHB values at the post-diet timepoint, indicating that baseline variance did not account for the significant results.

Increases in BHB inversely correlated with decreases in HbA1c ($\beta_{18} = -0.46$; $P < .001$; Figure 5C); in other words, people who showed greater increases in ketone bodies showed larger drops in HbA1c. A similar inverse correlation was observed for average daily ketone levels and HbA1c changes ($\beta_{12} = -0.4$; $P = .01$). Greater increases in BHB also correlated with greater PHQ-9 reductions ($\beta_{13} = -0.61$, $P < .001$; Figure 5D). We observed non-significant relationships between BHB increases with BMI ($P = .55$; Figure 5A) and HOMA-IR changes ($\beta_{19} = -0.14$; $P = .06$; Figure 5B), although the latter was trending in the expected direction. A comparable association was seen when correlating change in PHQ-9 scores with the proportion of time in ketosis based on daily at-home measurements (Figure S1).

None of the aforementioned post-diet change scores showed significant associations with BMI reductions (Table S4). Furthermore, when included in the same model, greater increases in BHB were still associated with reductions in HbA1c and PHQ-9 (Table S5).

Correlation analyses in the 4-month extension study showed a significant association between BHB increases and HbA1c decreases ($P < .001$). Relations between BHB changes and changes in BMI, HOMA-IR, and PHQ-9 were not significant but trended in the same direction as the 1-month effects (Figure S2).

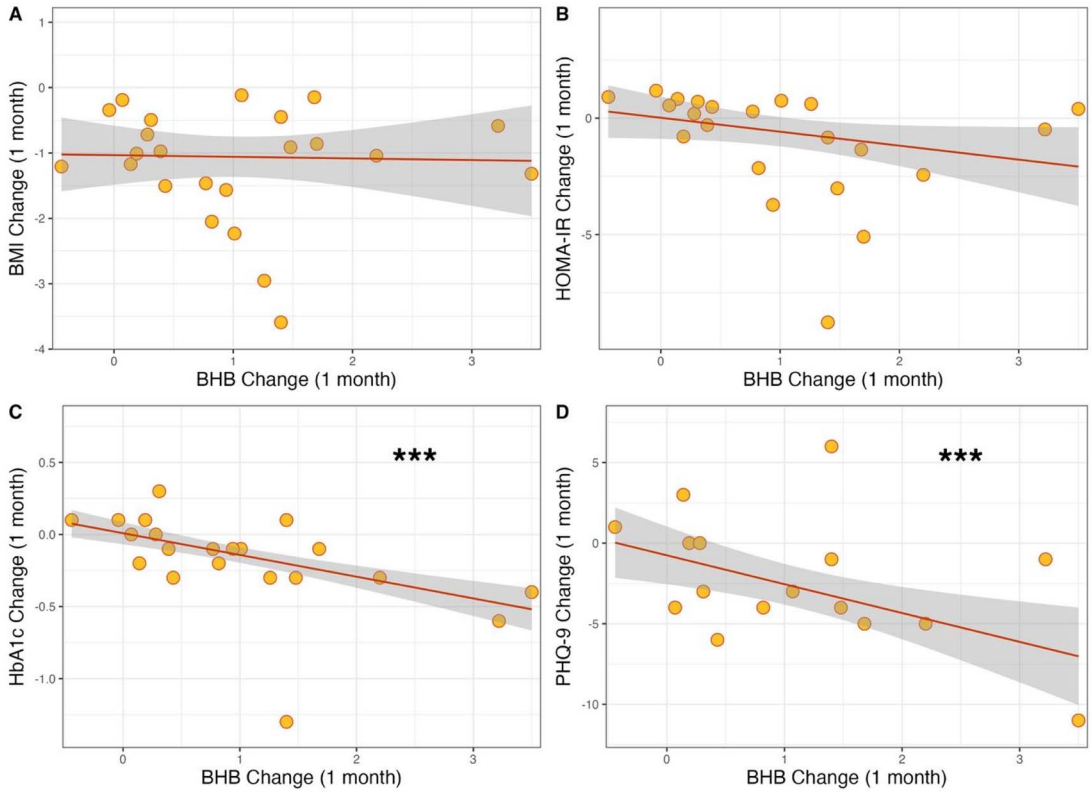

Figure 5. Linear Relationships between Change in BHB and BMI (A), HOMA-IR (B), Glucose (C), and PHQ-9 (D) after the 1-Month KETO Diet Intervention. No relationships were significant after the 1-month DAU intervention (not shown). $^{***}P < .001$.

Discussion

This is the first randomized control trial to investigate the effects of the ketogenic diet in participants with schizophrenia-spectrum and bipolar-1 disorders. Our results demonstrate both favorable outcomes and feasibility of people with serious mental illness adhering to a ketogenic diet. Compared to a diet-as-usual group, people who followed a 1-month ketogenic diet saw metabolic improvements. Among participants who completed the 4-month ketogenic diet extension study, trend-level improvements in metabolic markers and depressive symptoms became significant. We also observed broader improvements in psychiatric symptoms and cognitive functioning after 4 months on a ketogenic diet. This suggests that a 1-month intervention is not long enough to see the benefits that can be seen after 4 months. The downward trends can be seen in Figures S3 and S4. Increased production of ketone bodies and maintenance of ketosis (not weight loss alone) correlated with improvements in depressive symptoms and metabolic health, indicating that individual variation in ketogenic-diet adherence may influence clinical gains. In conclusion, it was primarily metabolic markers that improved in the RCT, with psychiatric symptoms showing group-level improvements in the single arm phase.

Based on at-home ketone level measurements, participants assigned to the ketogenic diet successfully achieved and maintained ketone levels above the established ketosis threshold of 0.5 mmol/L. This confirmed participants' adherence to the diet protocol, allowing us to infer that the changes in the ketogenic diet groups may be related to the induction of ketosis. This confirmation of subject adherence undermines concerns about the palatability of the diet and provides encouraging evidence for future research. While a previous study in an inpatient setting showed a majority of participants were able to adhere to the ketogenic diet, an outpatient study that did not provide meals saw lower adherence rates.[33,34] In our study, 25 of 28 participants assigned to the KETO arm completed the 1-month study. The diet may therefore be feasible in an outpatient psychiatric population with adequate support.

After 1 month on a ketogenic diet, people with psychosis exhibited decreased BMI and a trend-level reduction in HbA1c. These changes were characterized by small-to-moderate effect sizes. The trend-level improvement in HbA1c became significant among participants who completed the 4-month diet extension study (reflected by medium-to-large effect sizes). Reduced BMI and HbA1c are common results from a ketogenic diet,[42] likely due to its effectiveness in reducing body fat. HbA1c is a type of protein in the blood that measures the average glucose level over the past 2-3 months and is used to diagnose diabetes and pre-diabetes. Elevated HbA1c is linked with impaired cognition in some people with schizophrenia.[43,44]

Participants who followed the ketogenic diet for 1 month demonstrated numerical, but non-significant, improvements in cognitive performance, depressive symptoms, and positive symptoms of psychosis compared to those following their usual diet. However, after 4-months on the diet, significant improvements were found for all clinical measures of cognition and psychiatric symptoms of depression and psychosis. Previous studies observed cognitive benefits in children with treatment-resistant epilepsy and adults with mild cognitive impairment who followed a ketogenic diet.[22,45] Existing literature also shows reduced psychiatric symptoms from a ketogenic diet in people with major depression[35,46] and psychotic-spectrum disorders.[6] Depressive symptoms commonly co-occur in psychotic disorders and have a major impact on real-world functioning.[47] We observed a trend-level reduction in PHQ-9 after 1 month on the ketogenic diet compared to the DAU group that did not survive multiple comparison correction. Because this was not a primarily depressed sample, one possibility is that heterogeneity of depressive symptoms across our participants dampened this group-level effect.

An important consideration in a ketogenic diet study is the fact that blood measures of ketosis can be impacted by brief fluctuations in diet adherence. Measurements on a single day may not accurately represent adherence to the diet over time. Repeated measurements always provide a better estimate of true variance. This is particularly important when examining individual differences based on metrics collected at a small number of timepoints (eg, 2).[48] Our daily ketone-level estimates are a meaningful addition with better temporal resolution for accurately measuring sustained ketosis. The in-laboratory blood test results for some participants in the KETO group showed BHB values below the ketosis threshold; however, the at-home, average daily ketone levels for all but one participant were above the ketosis threshold of 0.5 mmol/L, so we did not consider those participants to be non-adherent. Higher levels of ketone bodies, reflected by both in-lab blood tests and daily at-home measurements, were linked to greater drops in depressive symptoms and HbA1c. Exploratory analyses showed that the proportion of days spent in ketosis also correlated with depressive symptom reductions. Together these findings support our exploratory hypothesis that clinical benefits would be related to a more maintained state of ketosis. We also highlight that our correlation results were reliable across separate measures of ketogenic diet adherence.

We suspect that the underlying mechanism driving depression symptom reductions is based on the presence of ketone bodies, and not simply due to weight loss. Unlike ketone levels, decreased BMI did not explain improvements in depressive symptoms. This suggests that simply losing weight may not reap the same benefits as being in ketosis. Psychiatric improvements might therefore follow improved metabolic function. In support of this notion, metabolic markers significantly improved at 1 month, and those initial gains correlated with depression symptom improvement (while symptoms only showed significant group-level improvements after 4 months on the diet). Of the 80% of participants who demonstrated a reduction in depressive symptoms after a 1-month KETO diet, 62% saw further improvement after completing the 4-month KETO diet (Figure S4). The same trend of progressive improvement was seen in cognitive performance and negative symptoms, suggesting that the duration of a ketogenic diet may play an important part in clinical outcomes.

The metabolic psychiatry field often attempts to separate weight loss from the effects of a ketogenic diet. However, weight loss, independent of increased ketones, may still be an important part of the ketogenic mechanism as it is one of the primary metabolic improvements seen in this study. Following the trend of continued improvement in psychiatric symptoms and cognitive performance, 87% of all KETO participants saw continuous reduction in BMI with an extended ketogenic diet (Figure S3). Our findings suggest that maintenance of ketosis may confer greater metabolic benefits over time. Future studies with larger samples can help clarify the extent to which positive ketogenic impacts of psychiatric function are beyond what is seen with a typical diet or other non-pharmacological treatments. Studies with longer diet periods and more data collection timepoints could provide more information about benefits of the ketogenic diet over time and how improvements in metabolic and psychiatric health are related.

Like us, Sethi et al.[6] did not find a decrease in the CRP measure of inflammation after 4 months on the keto diet and, instead, saw a non-significant numerical increase. This conflicts with evidence that ketone bodies have anti-inflammatory effects.[49,50] While following the ketogenic diet necessitates increased fat intake, saturated fats are associated with increased inflammation, and we did not attempt to reduce the saturated/unsaturated ratio in the food we supplied. A finer tuned diet, focused on increasing intake of unsaturated fats, may mitigate the increase in inflammatory markers.

Limitations

Several limitations of this study should be acknowledged. Due to limited funding, participants in the diet-as-usual group did not receive a controlled diet delivered to their homes. Participants in the ketogenic diet group therefore had inherent advantages in that they received easily prepared meals at no cost and followed a diet containing fresh vegetables, meat, and fish. We cannot rule out expectancy effects among ketogenic-diet participants when compared to diet-as-usual. However, even within the ketogenic-diet group, participants who more effectively and consistently adhered to the diet also obtained greater benefits. This highlights meaningful variation related to ketosis among participants with access to the same resources. We also note that some changes were only observed in the 4-month diet group, and we did not have a 4-month control group for comparison;

although, as in the 1-month study, improvements in HbA1c and depressive symptoms correlated with individual differences in sustained ketosis. Our sample was relatively small and thus precluded us from testing more complex models to examine the interplay among our metrics of interest and from performing diagnostic subgroup analyses. Our blood tests did not assess biomarkers that might provide a more comprehensive understanding of participants' metabolic functioning, such as cholesterol, low-density lipoprotein, and electrolytes. These measures would be important to include in future studies to evaluate risk factors of cardiovascular disease.[51] In addition, the ketogenic diet can potentially induce mild abnormalities in electrolyte levels, and this could be linked to increased risk for kidney stones.[52] Blood marker values were missing for some participants due to errors at the testing laboratory. Medication changes were not tracked by the study team. We also began the at-home measurements part-way through the study.

Future Directions and Conclusions

Our RCT shows promise for employing a ketogenic diet in people with psychosis, and helps motivate future controlled trials for serious mental illness, some of which recently launched[53] or completed.[35] Outpatient studies commonly include less symptomatic participants with stable resources. Not only were some of the participants severely affected by their illness, but some did not have stable housing. We also want to note that certain psychiatric comorbidities may increase the likelihood of patients adopting unhealthy restrictive eating habits. Clinicians and researchers should consider histories of eating disorder or obsessive-compulsive tendencies when determining whether the strict methods used for monitoring diet adherence are contraindicated for a given individual. To this end, future studies might evaluate whether less intensive alternatives, like exogenous ketone drinks, can augment the benefits of a ketogenic diet.

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Author Contributions

S.V. Abram and J.M. Kyner are co-first authors.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin.

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Conflicts of Interest

The authors have no relevant financial interests to report. S.V.A., J.M.K., A.V., M.S.J., S.L.F., D.H.M., and J.M.F. are U.S. Government employees. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the views of the Department of Veterans Affairs.

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