

# An Experimental Ketogenic Diet for Alzheimer Disease Was Nutritionally Dense and Rich in Vegetables and Avocado

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## ABSTRACT

**Background:** The ketogenic diet (KD) has gained interest as a potential therapy for numerous conditions; however, studies rarely report the food and micronutrient profile of the diet.

**Objective:** The aim of this study was to report changes in food selection and nutritional quality from the baseline diet (BD) to a KD therapy in participants with Alzheimer disease (AD).

**Methods:** Fifteen AD patients participated in a single-arm clinical trial to assess the feasibility of a 3-mo KD intervention. A registered dietitian instructed participant study partners to assist participants with a self-selected, nutritionally dense KD. We collected food and nutrient intake via monthly 3-d food records. Serum  $\beta$ -hydroxybutyrate was measured within 48 h of each 3-d food record to assess ketosis status. Food records before KD initiation characterized the BD. Food records during the intervention coincident with the most robust ketosis characterized the KD. Principal components analysis identified foods affiliated with the BD and KD. Mean food and nutrient intake change was tested by the Kruskal–Wallis test for variance with significance set at  $P \leq 0.025$ .

**Results:** Ten participants adhered to the KD. Study partners provided complete food records for 6 KD-adherent individuals. The KD was characterized by increased medium-chain triglyceride (MCT) oil, nonstarchy vegetables, butter, eggs, olive oil, avocados, and nuts and seeds with practical elimination of potatoes, grains, red meat, sugar-sweetened beverages, and desserts. Fruit intake, including avocado, was similar between diets. Nonstarchy vegetable intake increased from 1.2 servings/d to 4.3 servings/d ( $P < 0.01$ ) on the KD. Micronutrient intake was similar between diets, meeting Dietary Reference Intakes for most nutrients. Between diets, the KD was associated with increased intake of choline and vitamin K and decreased intake of manganese and fiber.

**Conclusion:** As a potential therapy in AD, the KD can be nutritionally dense with high intake of vegetables and substantial variety. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) as NCT03690193. *Curr Dev Nutr* 2019;3:nzz003.

## Introduction

The ketogenic diet (KD) is a very high-fat, low-carbohydrate diet that restricts carbohydrate to  $\leq 10\%$  of consumed energy, starkly different from the 50–65% of energy from carbohydrate of the typical American diet. This macronutrient profile promotes a systemic shift from glucose metabolism toward conversion of fatty acids to ketone bodies as a substrate for energy. With a long history in the treatment of refractory childhood epilepsy (1), the KD has recently experienced a surge in mainstream popularity (2) as a diet for weight loss (3), athletic performance in competitive athletes (4), and perceived general health (5). Its utilization as a potential therapy for multiple neurological and metabolic conditions has piqued the interest of researchers and



**Keywords:** ketogenic diet, Alzheimer disease, fruits, vegetables, principal components analysis

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Manuscript received October 4, 2018. Initial review completed December 10, 2018. Revision accepted January 3, 2019. Published online February 20, 2019. Supported by University of Kansas Alzheimer's Disease Center grant P30AG035982 (to RHS and JMB), the University of Kansas Heartland Institute for Clinical and Translational Science Award Center, the University of Kansas Department of Dietetics and Nutrition, and the Stop Alzheimer's Now Foundation.

Author disclosures: MKT and DKS, no conflicts of interest. JMB receives or has received research support in the last 2 y for clinical trials from Lilly, Avid Radiopharmaceuticals, Toyama Chemical Company, Merck, and Biogen. RHS within the last 2 y has received an honorarium from Accera and clinical trial support from Ausio Pharmaceuticals, LLC and the Alzheimer's Association.

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Abbreviations used: AD, Alzheimer disease; AI, Adequate Intake; BD, baseline diet; BHB,  $\beta$ -hydroxybutyrate; CDR, clinical dementia rating; EAR, Estimated Average Requirement; KD, ketogenic diet; MCT, medium-chain TG; PCA, principal components analysis; RD, registered dietitian.

clinicians alike (6–11). Our recent publication suggests that the KD is feasible and may hold therapeutic efficacy in a population of patients with Alzheimer disease (AD) (12).

In the past decade, there have been a growing number of human trials involving the KD; however, these trials were generally most focused on achievement of a ketogenic macronutrient profile. Recently, nutrition experts have advocated for the application of “healthy” or “well-formulated” ketogenic diets (8, 13). Thus far, studies have described KD education principles, meal plans, and related biomarker outcomes well but often lacked reports of actual dietary intake (14–16). Ketone status measurement (i.e., blood or urine concentration) is a good indicator of adherence to the KD by definition, but these markers are ignorant of KD food group and micronutrient composition. Whether patients closely adhere to “healthy” prescribed dietary protocols is unknown. Absent this important information, many among the health care and scientific communities remain hesitant, believing the KD to be an unfeasible or merely short-term nutritional approach because of either long-term health concerns or perceptions that the KD is unpalatable and lacks variety (17).

The primary aim of this study was to describe the KD education principles and assess the dietary changes associated with KD adherence from the University of Kansas Ketogenic Diet Retention and Feasibility Trial (KDRAFT), a trial to assess the feasibility of the KD in patients with AD (12).

## Methods

### Study design

We examined the difference in dietary intake between the baseline diet (BD) and KD intervention from a single-arm, clinical trial (NCT03690193) involving patients diagnosed with AD.

### Participants

Fifteen older adults meeting the McKhann et al. criteria (18) for AD were enrolled in the trial as described previously (12). Individuals were eligible to participate in the study if they had a clinical dementia rating (CDR) (19) of very mild AD (CDR 0.5), mild AD (CDR 1), or moderate AD (CDR 2); had an active study partner; BMI  $\geq 21$  kg/m<sup>2</sup>; normal electrolytes and liver function; and spoke English. Exclusion criteria included type 1 diabetes, ongoing or recent cancer, cardiac event in the past year, or other serious medical risks identified by research physicians. The study protocol was approved by the Institutional Review Board at the University of Kansas Medical Center. Informed consent was obtained from all study participants and study partners per institutional guidelines.

### KD intervention and counseling

A registered dietitian (RD) counseled the study partners of each participant to assist in implementation of a self-selected, nutritionally dense KD at the baseline study visit. Participants were instructed to consume a 1:1 KD (ratio of lipid in grams to nonlipid in grams) or better, which was approximately comprised of 70% fat, 20% protein, and  $\leq 10\%$  carbohydrate as energy. The Mifflin-St Jeor equation (20) was used to estimate daily energy needs and target medium-chain TG (MCT) oil (Now Foods) dosage. Participants aimed for an MCT

dosage of 40% of total targeted fat intake, starting at 1 tablespoon/d and adding  $\frac{1}{2}$  tablespoon on a weekly basis until the target daily dosage or maximum tolerance was met. Daily multivitamin, vitamin D, calcium, and phosphorus supplements were also provided to alleviate concerns of potential micronutrient deficiency. A 3-d example KD menu was provided at the beginning of the study as an aid for initiating the KD. After initiation of the KD, the RD made weekly phone calls to study partners to encourage compliance and address KD-related questions. Achievement of a ketosis-inducing macronutrient intake was the primary goal of the nutritional counsel, yet **Table 1** describes additional key nutrition messages that were discussed with participants.

### Dietary intake

Dietary intake was measured via multiple self-reported 3-d food records completed by participant study partners at home, in real time. The RD provided study partners with written and verbal diet record instruction and reviewed recently completed records with study partners for detail and completeness upon their return at study visits. Records were collected at baseline, month 1, and month 2. Each record consisted of 3 consecutive days including 2 weekdays and 1 weekend day. Baseline records reflected intake before the initiation of the diet intervention. Records at months 1 and 2 reflected intake while following the KD. Food record data were entered into the Nutrition Data System for Research (version 2016) to quantify food and nutrient intake. To characterize intake that was truly ketogenic, dietary data that corresponded with a participant’s most robust serum  $\beta$ -hydroxybutyrate (BHB) concentration were selected for presentation. All micronutrient intake was converted to percentage intake of RDA and Adequate Intake (AI). Estimated Average Requirement (EAR) is commonly used to assess group nutrient intake, but we elected to present RDA and AI based on the small sample size and our interest in the KD’s ability to meet individual needs. We did calculate percentage intake of EAR for nutrient intake that fell below the RDA or AI. All dietary data represent intake from food, excluding micronutrient supplementation.

### Ketone status

Ketone status was monitored via 2 measurement methods. Firstly, participants self-monitored urine ketones each evening using urine acetoacetate test strips (Ketostix, Bayer). Measurements were recorded as negative, trace (5–14.9 mg/dL), small (15–39.9 mg/dL), moderate (40–79.9 mg/dL), or large ( $\geq 80$  mg/dL) in a provided diary. Daily ketone status served as immediate feedback to inform participants of their adherence to the KD. Negative to trace urine ketone status was used as an indication to decrease carbohydrate and increase fat intake as needed. Secondly, BHB was collected and measured after a 12-h fast within 48 h of the final day recorded in the 3-d food record for that study time point. Nursing staff at the KU Clinical and Translational Science Unit collected serum samples and BHB was analyzed in the KU Hospital Clinical Laboratory.

### Principal components analysis

We used the [psych] statistical package written for R statistical software to perform principal components analysis (PCA). The object of this analysis was to identify a single dietary pattern characterized by food groups with the greatest variability of intake between the BD and KD. To do this, Nutrition Data System for Research output of food

**TABLE 1** KDRAFT ketogenic diet education principles<sup>1</sup>

Component	Guidelines
Macronutrient	
Fat	Consume $\geq 70\%$ as energy Focus: extra virgin olive oil, avocado, olives, nuts and seeds Moderate: nut and seed butters, butter, bacon
Carbohydrate	Restrict to $\leq 10\%$ of energy Vegetables and small amount of fruit as primary source
Protein	Not to exceed 100 g for most individuals Focus: fatty fish, eggs, dark meat poultry, unprocessed red meat Limit: processed meat
Food groups	
MCT oil	Titrate dosage weekly by 7.5 mL starting at 15 mL/d Original aim: 40% of total energy as fat or until tolerance reached Feasible aim: 15–30 mL daily, as tolerated Best tolerated in coffee and blended with additional long-chain fat source
Vegetables	Unlimited intake of nonstarchy vegetables Eliminate starchy vegetables Use vegetable intake as opportunity for additional fat
Fruit	Restrict to $\frac{1}{2}$ cup of berries per day Unlimited avocado intake
Dairy	Use heavy cream as an additive to coffee or tea 1–2 servings of full-fat cheese allowable Limit unsweetened, full-fat milk or yogurt to no more than $\frac{1}{2}$ cup/d
Grains	Eliminate refined and whole grains Replace grain flours with almond or coconut flour Small amount of resistant starch may help MCT tolerance
Sweetener	Eliminate sugar intake Use sweeteners sparingly, primarily Stevia or Truvia
Water	Drink $\geq 64$ fluid ounces (1.89 L) of water daily
General	
Supplementation	Multivitamin, vitamin D, potassium, phosphorus (not included in this analysis)
Urinary ketones	Measure and record urinary ketones daily If not producing ketones, reduce carbohydrate and increase fat

<sup>1</sup>KDRAFT, Ketogenic Diet Retention and Feasibility Trial; MCT, medium-chain TG.

group variables was consolidated into 33 food groups, centered and standardized, and entered into the PCA. Dietary intake data from all participants at both time points (BD and KD) were included together in a single PCA, resulting in a diet factor identifiable by opposing ends of a spectrum. The food items with large positive loading coefficients best described foods with the greatest change toward the KD, whereas foods with large negative loading coefficients best described intake of food items on the BD. Participant adherence to this dietary pattern was calculated for each time point by multiplying the standardized intake of each food group at that time point by its respective loading factor and summing all 33 of these values.

### Statistical analyses

The primary aim of this research was to characterize the changes in food group and nutrient intake of the KD from the BD. Continuous variables were expressed as mean  $\pm$  SD. ANOVA models utilized the nonparametric Kruskal–Wallis test for variance owing to small sample

size, lack of normality through visualization of Q-Q plots, and no missing dietary data from each of the 6 individuals included in this analysis. Individual change in PCA diet pattern adherence and select food group intake changes are also presented. Statistical analyses were performed using R (version 3.4.3; R Foundation). To further account for the small sample size of this study, statistical tests were 2-tailed with significance set at  $P < 0.025$ .

### Results

Ten of the 15 enrolled AD participants successfully adhered to the KD, evidenced by multiple days of urine ketone production and serum BHB elevated  $>0.3$  mmol/L at  $\geq 1$  lab collection time point (12). Data from 6 KD-adherent participants who provided complete 3-d food records 1) at baseline and 2) during the KD therapy coincident with the most robust serum BHB were included in the analysis. Reported challenges to completeness of 3-d food records primarily involved

**TABLE 2** Participant characteristics and intake of food and nutrients without DRIs<sup>1</sup>

	Overall (n = 6)	Baseline diet (n = 6)	Ketogenic diet (n = 6)	P
Sex (F/M)	3/3			
Age, y	71.7 ± 8.5			
Serum BHB, mmol/L		0.1 ± 0.0	0.8 ± 0.5	<0.01
Macronutrient intake				
Energy, kcal		1950 ± 295	1860 ± 205	0.52
Fat, g		91 ± 11	151 ± 20	<0.01
Carbohydrate, g		210 ± 57	46 ± 20	<0.01
Protein, g		81 ± 11	88 ± 11	0.26
Fatty acid intake				
MCT oil, mL		0.0 ± 0.0	19.2 ± 3.0	<0.001
SFAs, g		30 ± 5	69 ± 18	<0.01
MUFAs, g		34 ± 4	50 ± 6	<0.01
PUFAs, g		20 ± 7	21 ± 7	0.87
Trans fatty acids, g		2.6 ± 0.6	2.9 ± 1.0	0.42
ω-3 fatty acids, g		2.2 ± 0.8	2.3 ± 0.6	0.87
Cholesterol, g		264 ± 85	729 ± 155	<0.01
Carbohydrate intake				
Sugar, g		84 ± 33	25 ± 11	<0.01
Glycemic load, glucose reference		118 ± 33	18 ± 9	<0.01
Fruits and vegetables <sup>2</sup>				
Fruit		0.8 ± 0.7	0.2 ± 0.4	0.10
Avocado		0.0 ± 0.0	0.4 ± 0.6	0.16
Nonstarchy vegetables		1.2 ± 0.9	4.3 ± 2.1	<0.01

<sup>1</sup>Values are means ± SDs unless indicated otherwise. Group differences were assessed by the Kruskal–Wallis test for variance. Significance was set at  $P \leq 0.025$ . All dietary data derived by 3-d food record at each time point. For both diets, nutrient data were derived by food only. BHB,  $\beta$ -hydroxybutyrate; DRI, Dietary Reference Intake; MCT, medium-chain TG.

<sup>2</sup>Fruit and vegetable intake reported as ½-cup (118 mL) raw servings and 1-cup (237 mL) cooked servings.

caregiver burden associated with AD care responsibilities. Participant characteristics, cognition, and ketone production data for the entire study sample have been previously reported (12). The mean serum BHB of the 6 participants included in this analysis increased from 0.1 to 0.8 mmol/L, with a range of 0.3–1.4 mmol/L. Participant characteristics, macronutrient composition, and intake of nutrients or foods without DRI values of this analysis are reported in Table 2.

The PCA dietary pattern was distinguishable by food group loadings on opposite ends of the pattern's spectrum (Figure 1). Foods that loaded toward the positive end characterized the foods with the largest change in intake toward the KD, foods that loaded in the middle of the figure indicated foods that had little change from the BD to the KD, and foods that loaded toward the negative end indicated foods that were commonly consumed in the BD but not in the KD. Adherence to the KD was associated with increased intake of MCT oil, nonstarchy vegetables, butter, eggs, olive oil, cured meat, cream, poultry, avocados, nuts and seeds, and fresh fish and seafood. In addition, adherence to the KD essentially eliminated intake of potatoes, grains, red meat, desserts, fried foods, and sugar-sweetened beverages. Individual adherence to the PCA diet pattern at both time points is presented in Figure 2.

Daily nonstarchy vegetable intake increased by 3.1 servings on the KD (mean ± SD: 1.2 ± 0.9 compared with 4.3 ± 2.1 servings). Fruit servings on the KD decreased by 0.6 servings (mean ± SD: 0.8 ± 0.7 compared with 0.2 ± 0.4 servings), although nonsignificantly. Avocado servings increased nonsignificantly from BD to KD (mean ± SD: 0.0 ± 0.0 compared with 0.4 ± 0.6 servings). Considering intake of both fruits (including avocado) and nonstarchy vegetables, intake significantly increased from BD to KD (mean ± SD: 2.0 ± 1.3 compared with 5.0 ± 2.3 servings). Individual change in intake of fruits and vegetables is presented in Figure 3.

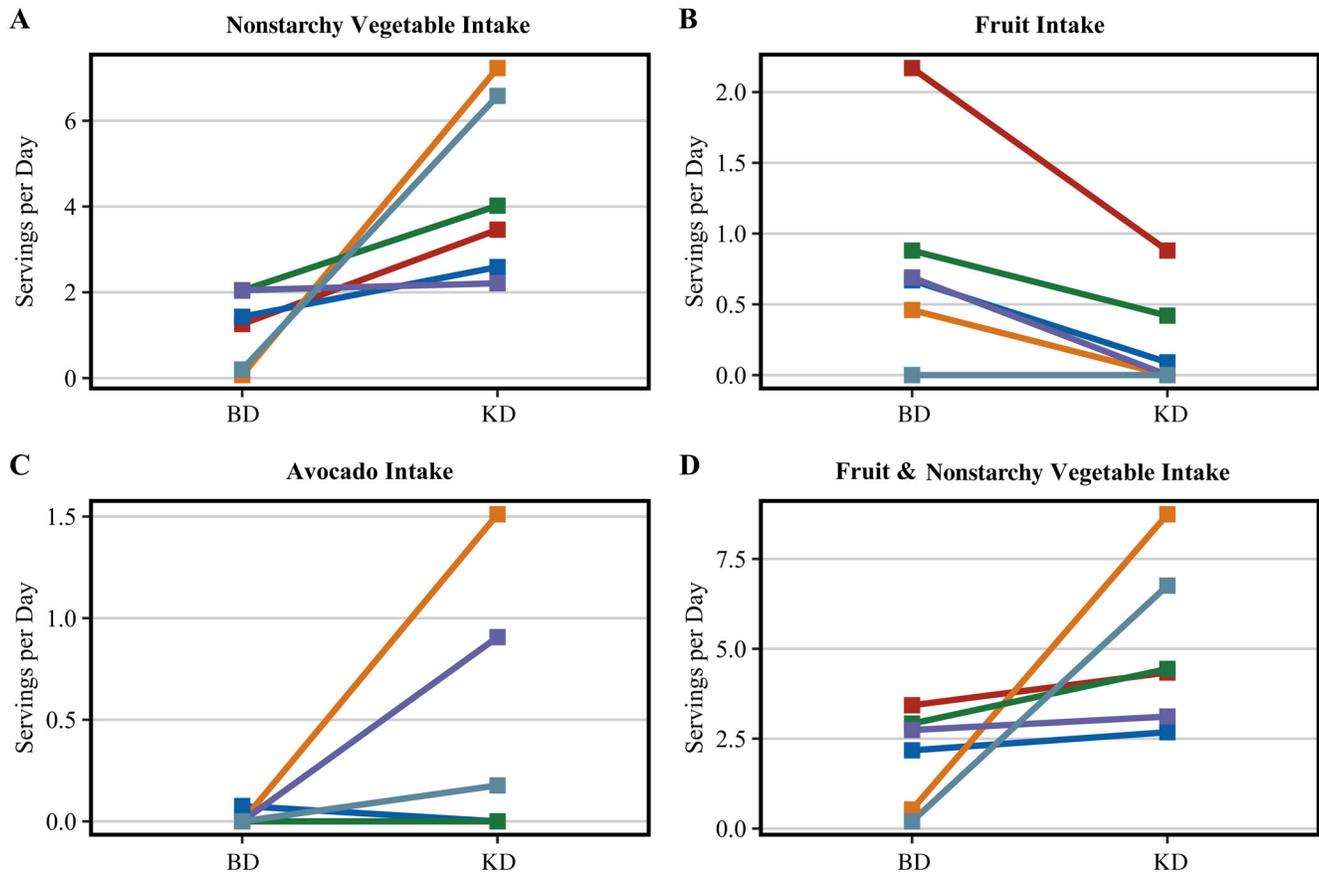
Figure 4 depicts the mean intake change for nutrients with established RDA and AI values. Both diets met the RDAs or AIs for  $\alpha$ -linolenic acid, iron, niacin, pantothenic acid, phosphorus, riboflavin, selenium, vitamin B-12, vitamin B-6, and zinc. The KD also met the RDAs or AIs for choline, vitamin A, vitamin C, and vitamin K. The KD failed to meet the RDA or AI for calcium, folate, magnesium, manganese, potassium, thiamin, vitamin D, and vitamin E. On the KD, fiber intake was significantly lower ( $P = 0.025$ ), whereas intakes of vitamin K ( $P = 0.025$ ) and choline ( $P = 0.01$ ) significantly increased.

## Discussion

The findings of this study provide evidence that consumption of a nutrient-dense KD is attainable. Selection of 3-d food records at time points that coincide with robust serum ketone measures is justification that these data accurately represent ketosis-inducing dietary intake. We acknowledge that like any dietary approach focused on macronutrient parameters, KDs can have varying nutrient profiles; however, these data demonstrate that with appropriate messaging and adherence, the concerns regarding micronutrient deficiency with KDs may be unwarranted (21).

The PCA was intended to demonstrate the robust change in food group consumption by following the KD. This particular analysis was possible owing to the fundamental difference in food choices between a regular diet and KD, including practical elimination of specific food items. Because this particular analysis highlighted foods with contrasting intake variability dependent upon specific diet adherence, many of the food loadings were anticipated, yet there were unanticipated results. Toward the KD end, we expected MCT oil to





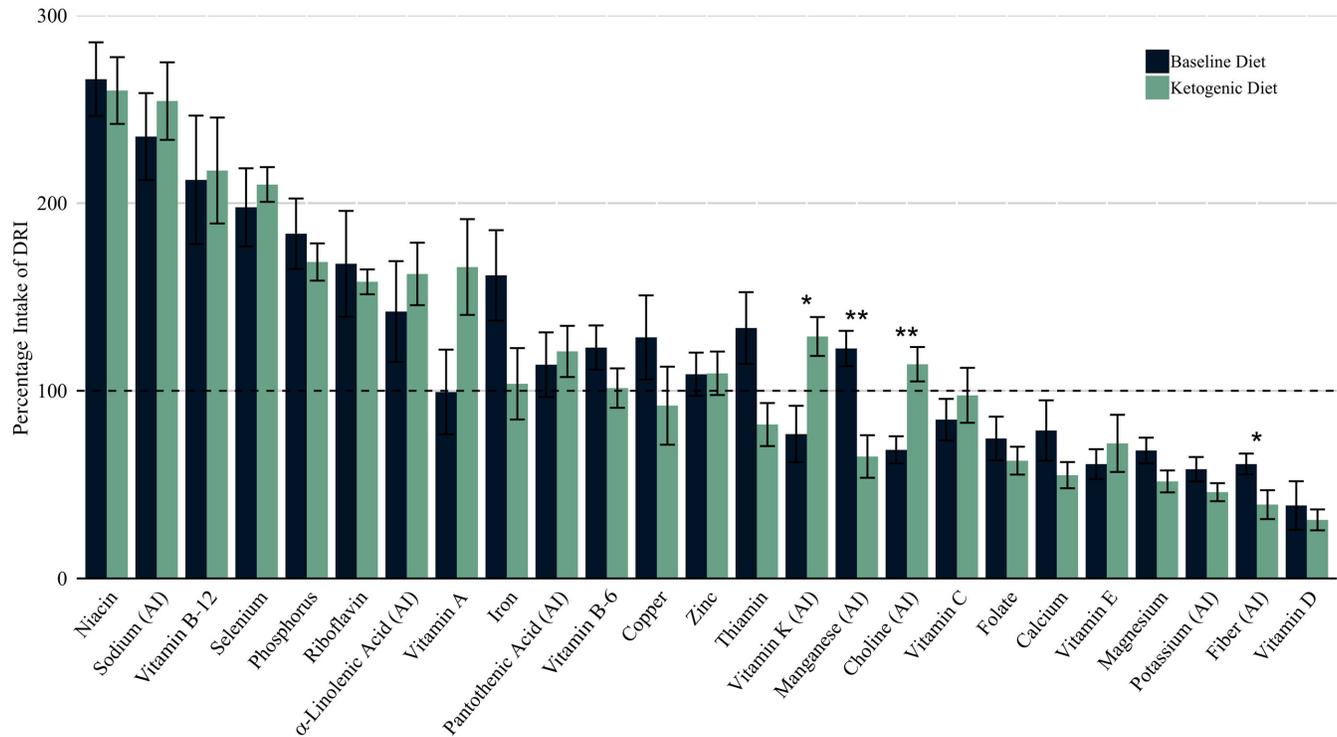
**FIGURE 3** Individual change in fruit and vegetable intake between the BD and KD. The lines indicate the individual change in standard USDA food group serving intake between diets ( $n = 6$ ). (A) Change in nonstarchy vegetable intake from BD to KD. (B) Change in fruit intake (excludes avocado) from BD to KD. This was of interest owing to the message to limit fruit to  $\frac{1}{2}$  cup of berries per day. (C) Change in avocado intake from BD to KD. Two participants have overlapping lines as they did not consume avocados at either time point. (D) Change in total fruit (includes avocado) and nonstarchy vegetable intake from BD to KD. BD, baseline diet; KD, ketogenic diet.

Fatty acids from MCT are easily shunted into hepatic mitochondria where they are  $\beta$ -oxidized and the resultant acetyl-CoA is converted to ketone bodies for nonhepatic energetics (26, 27). In a ketotic state, fat metabolism is the primary energy mechanism, indicating that SFA may be primarily destined for energy production, a contrasting metabolic fate to that in a glucose-rich state (28, 29). Even within KDs that double SFA intake, little change in circulating SFA has been observed (29). In this study, SFA accounted for 45% of total fat intake with negligible effect on cholesterol (12), considerably less than a SFA-centric KD found to have more detrimental effects on lipid status over the short term (30). Indeed, such high SFA intake may be of valid concern (31); however, we again assert that comprehensive reporting of food and nutrient intake on the KD has been mostly neglected in human trials. It is yet to be determined how KDs formulated with known protective foods (i.e., vegetables and avocado) may influence health outcomes. In addition, because the nutrigenetics of lipid metabolism are complex (32), there is evidence that genotype may be pertinent when considering KD applicability (33).

MUFAs coming from olive oil, avocados, and nuts and seeds also increased on the KD. MUFAs are considered vital fatty acids consistently linked to multiple improved health outcomes (34, 35), particularly those from plant sources (36), the primary source of MUFAs in this analysis.

No change occurred in PUFAs, including anti-inflammatory omega-3 fatty acids. It should be noted that participants were already meeting recommendations for  $\omega$ -3 as  $\alpha$ -linolenic acid before the initiation of the KD intervention (37). Long-chain  $\omega$ -3 intake, specifically DHA (22:6n-3) and EPA (20:5n-3), was low in the diet at baseline and KD. Within the context of a KD, increases in SFAs and MUFAs with no change in PUFAs may be a positive finding because PUFAs are anecdotally thought to have lower tolerance in high quantity on the KD and  $\omega$ -6 PUFAs could have more proinflammatory properties than MUFAs, SFAs, and  $\omega$ -3 PUFAs (38). In future studies,  $\omega$ -3 intake could potentially be optimized with greater emphasis upon fatty fish, chia seed, and walnut consumption.

Although the KD was quite nutrient dense, some of the micronutrients that have previously been identified as nutrients of concern among older adults (39) fell below the RDA and AI. We calculated percentage intake of EAR for these nutrients. The KD met the following percentage intake of EAR: 90% vitamin E, 78% folate, 67% calcium, 62% magnesium, and 55% vitamin D. Supplement intake was not included in this analysis, but participants were provided and instructed to take multivitamin, vitamin D, calcium, phosphorus, and magnesium supplements while following the KD. This report suggests that, while following a KD, these may be nutrients to address from a food or



**FIGURE 4** Comparison of mean nutrient intake with DRI values on the baseline and ketogenic diets. Nutrients are RDAs unless noted as AI. Intake is presented as percentage of the specified DRI. Mean differences were tested by the Kruskal–Wallis test for variance.  $n = 6$ . \*,\*\*Significant intake change: \* $P < 0.025$ , \*\* $P < 0.01$ . AI, Adequate Intake; DRI, Dietary Reference Intake.

supplementation perspective. It is noteworthy that the nutrients with low intake in the KD were also similarly low in the BD.

There are limitations to this study that should be discussed. Of the original 15 participants enrolled in the study, 5 participants withdrew within weeks of the start of the KD intervention. Completeness of the dietary intake information was also a factor that limited this analysis to a small sample of 6 participants. Discussed in our previous publication, the responsibility of the caregiver (study partner in our case) vastly increases as the patient's level of dementia also increases (40). Thus, caregiver burden was an obstacle to the collection of complete, informative 3-d food records from 4 of the study participants. Although one of our goals was to characterize patient intake on the KD, the primary feasibility aim was assessable through ketone production biomarkers, a much simpler measurement for study partners to collect. Three-day food records are commonly used as the "gold standard" in dietary assessment validation studies, yet they require high participant motivation and may have limitations related to self-report.

As KD research continues to grow, it will be inevitable that the nutrition field will embrace its practical use if it is found to benefit specific conditions. Going forward, it will be important to consider KD diet quality. Although the primary goal of the KD is to produce ketones, thought to have powerful messaging and potential therapeutic roles, it should be recognized that nutrient-dense versions of the diet may synergistically improve the efficacy, tolerability, and time capacity of KD therapies. Numerous diet quality indexes have been constructed to objectively differentiate nutritional quality between individuals

(41–44). These indexes are inherently incapable of sensitively measuring the diet quality of the KD because they do not encompass foundational KD principles, primarily the expected significant increase in fatty acid consumption. We advocate for the formation of a hierarchical KD quality index that encompasses concepts such as KD ratio, nutrient-rich food intake, and optimal fatty acid profile/ratio that can be applied to future KD research.

In conclusion, the KD can be a diverse, nutrient-dense diet rich in nonstarchy vegetables and avocados.

### Acknowledgments

The authors' responsibilities were as follows—MKT: collected the data, was responsible for data analysis, and was the primary contributor of manuscript content; RHS, JMB, and DKS: oversaw data collection, and contributed content and edits to the manuscript; and all authors: were involved in study design, had full access to the data, and read and approved the final manuscript.

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