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Effect of a non-energy restricted ketogenic diet on cognition in sedentary healthy young adults

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ABSTRACT

Background: Ketogenic diet (KD) is increasingly recognized as a strategy to combat obesity. However, its effects on cognition in sedentary healthy young adults remain underexplored. *Methods:* In a quasi-experimental design, 186 participants were screened, 78 excluded based on predefined criteria, leaving 108 healthy adults (age 25–45 years, BMI 18–29.9 kg m^{-2}, sedentary <5,000 steps/day) assigned to either KD group (<5% carbohydrates, 20–25% protein, 70–75% fat; $n = 54$) or control group (regular diet ~50–65% carbohydrates; $n = 54$). Participants underwent a 4 weeks' dietary intervention. Cognitive domains were assessed at baseline and post intervention using validated computer-based test battery. Pre, mid and post weight, BMI, blood ketones and fasting glucose were also measured. Forty-three participants in the KD group and 38 in the control group completed the trial. *Results:* Four weeks of non-energy restricted KD improved processing speed, semantic memory, working memory, episodic memory, fluid cognition, crystallized cognition and overall cognitive composite scores (all $P \leq 0.001$) versus controls. Attention and inhibitory control ($P = 0.46$) and cognitive flexibility ($P = 0.21$) showed no significant differences. Blood ketones increased (0.12–1.32 mmol L^{-1}, $P < 0.001$) in KD participants versus controls (0.118–0.105 mmol L^{-1}, $P = 0.94$). KD reduced weight ($P < 0.001$), BMI ($P < 0.001$) and fasting glucose ($P < 0.001$). Post intervention

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ketones predicted cognitive gain in most cognitive domains except attention & inhibitory control and cognitive flexibility. *Conclusion:* Short term KD intervention enhances memory, processing speed, fluid, crystallized and overall cognitive function composite scores in sedentary healthy adults.

KEYWORDS

ketogenic diet, cognition, ketosis, working memory, episodic memory, attention

INTRODUCTION

According to the World Obesity Federation's "World Obesity Atlas 2025", over one billion people are projected to be obese by 2030, mostly in low and middle income countries [1]. Various diets are used to address obesity, including the ketogenic diet (KD), which is high in fat and low in carbohydrates. It induces physiological ketosis, shifting metabolism from glucose to fat, and raises blood β-hydroxybutyrate (BHB) levels to ≥0.5 mM [2, 3]. BHB, acetoacetate (AcAc), and acetone collectively called ketone bodies (KBs); are mainly produced in the liver and rapidly taken up by extrahepatic tissues such as the heart, skeletal muscle and brain. In adults with normal BMI on a regular diet, blood KB levels are ≤0.3 mM [4]. However, ketogenic diets can raise plasma ketone levels to 0.5–5 mM [5].

KD and KBs have been linked to cognitive benefits in preclinical [6, 7] and clinical studies [8–12] likely via neuroprotection, reduced oxidative stress and enhanced synaptic plasticity. Cognition encompasses domains such as memory, attention, language, reasoning and decision making which can be affected by aging [11, 13], neurodevelopmental dysfunction, genetics, or environmental factors [14]. KD has also demonstrated neuroprotective effects in epilepsy [15], Parkinson's disease [16], Alzheimer's disease and mild cognitive impairment [17] and may improve memory and insulin sensitivity in older adults [18].

Based on the prior evidence, this study investigated the effects of a 4-week KD on all cognitive domains including memory, fluid cognition, crystallized cognition, and overall cognitive function and examined correlations with blood ketones, fasting blood glucose, weight, and BMI in sedentary healthy adults.

METHODS

This was a quasi-experimental design carried out from November 2021 to December 2023 at Institute of Basic Medical Sciences (IBMS), Khyber Medical University (KMU) Peshawar, Pakistan. Convenience sampling technique was employed for selection of the participants. The online Openepi sample size calculator version 3.01 was used to determine the sample size. From the literature, mean difference of ketogenic diet group ($\Delta = 10.2 \pm 8.48$) and mean difference of participants' choice diet group ($\Delta = 4.5 \pm 9.49$) [19, 20] for memory domain, were utilized for between group comparisons. Assuming $\alpha = 0.05$ (two-tailed), power of 80%, and group ratio of 1:1, the required sample size was 40 individuals per group. We enrolled 54 participants in each group (total $n = 108$), accounting for an expected 25–30% dropout rate due to the use of comprehensive cognitive battery.

Participants

A total of 186 individuals were initially enrolled in the study. Of these, 64 were excluded based on predefined eligibility criteria. Among the remaining 122 participants screened, 14 were excluded following biochemical assessments. The final sample of 108 healthy participants was assigned to either the ketogenic diet (KD) group ($n = 54$) or the control group ($n = 54$). (Flow diagram as Supplementary file 1).

Eligibility was determined based on age (25–45 years) and body mass index (BMI 18–29.9 kg m^{-2}). This age range captures adults with fully mature cognitive function and minimal age-related decline. The selected BMI range reflects a large, generally healthy segment of the population and allows examination of cognitive outcomes without obesity related effects, a group that remains under represented in cognitive research.

Sedentary status was verified prior to enrolment using a mobile pedometer. In accordance with established literature defining <5,000 steps/day as sedentary behaviour [21–23], participants provided two days of pedometer readings, and those averaging below this threshold were deemed eligible. All participants were instructed to maintain their usual activity levels, avoid any form of exercise during the 4-week trial and refrain from using nutritional supplements throughout the study period.

Participants with known allergies to ketogenic diet components, gastrointestinal disorders, diabetes, hypertension, cardiovascular disease, hepatic or renal impairment, as well as pregnant or lactating women, were excluded. Individuals following intermittent fasting or any other dietary regimen were also not included. Depression was screened using the Hamilton Depression Rating Scale (HAM-D); participants scoring >7 were excluded. Eligible participants underwent further screening for hypertension, HbA1c, lipid profile, liver and kidney function tests. All participants received detailed information about the study during a briefing session prior to initiation.

Written informed consent was obtained from all the participants. The study was conducted according to the guidelines provided in the Declaration of Helsinki and all procedures concerning human subjects were approved by the Ethics Committee of the Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan **KMU/IBMS/IREB/9th meeting/2021/295**).

Procedure

In this study, participants in the ketogenic diet (KD) group followed a non-energy restricted ketogenic diet consisting of ≤5% carbohydrates, 20–25% proteins and 70–75% fat for a duration of four weeks. With guidance from a dietitian and expert nutritionist, meal plans and recipes were developed using Windiet software (version 2005, Robert Gordon University, UK). All ingredients were carefully weighed and their macronutrient compositions were analysed using the same software. To ensure adherence to the prescribed macronutrient ratios, pre-portioned meal boxes containing breakfast, lunch, and dinner were prepared and provided to participants daily from Day 1 to Day 28 of the trial. Participants were instructed to report and return any leftover food, which was then weighed and recorded to assess actual consumption.

Meanwhile, the control group participants continued with their self-prepared regular diet (approximately 50–65% carbohydrates) and were asked to record their daily food intake

throughout the study period. Their dietary records were subsequently analysed using Windiet software (One-day Menu of ketogenic diet vs. regular diet) (Supplementary File 2).

On Day 0 (screening day), participants' presented following an overnight fast for blood collection and screening for biochemical assessments. Blood pressure, heart rate, respiratory rate and tremors were also noted. Participants completed a health screening questionnaire and provided 24-h dietary recall of two days. Their food preferences were noted. Hamilton depression rating scale (HAM-D) was also administered to rule out depression.

On Day 1 participants were called after an overnight fast; fasting blood ketone levels (mmol L^{-1}) and fasting glucose (mmol L^{-1}) were assessed in capillary blood using reagent strips and a monitoring device (Abbott Freestyle Optium Neo Blood Glucose/Ketone). Their height, weight and BMI were recorded. The participants than underwent comprehensive cognitive testing on I pad based software. On day 15 blood ketones, fasting glucose, weight and BMI were measured after an overnight fast. On day 29, the same protocol as on day 1 was followed.

Core cognitive measures

Cognition was analysed using NIH Toolbox cognition software on I-pad screen [24] on day 1 and day 29 of trial for both ketogenic and control groups. The automated protocol provided practice and demonstration prior to data collection for each test. It measures numerous aspects of cognitive functions for age 3–85 years, comprising of working memory, episodic memory, semantic memory, processing speed, attention and cognitive flexibility. Seven core cognitive measures and three NIH Toolbox composite scores are included in this study. Following cognitive measures were assessed in this study.

Working memory. List sort working memory test (List sort) was used to assess working memory. It necessitated the participants to immediately recall and rearrange a list of items presented to them visually as well as verbally. The test needed 7 min for completion and its scoring was calculated by summing the items correctly answered in two lists shown to them. The score ranges between 0 and 26.

Episodic memory (form B). The Picture Sequence Memory Test (PSMT) is a robust measure of fluid episodic memory. Participants viewed a series of 6–18 objects in a specific order and were then asked to recall and reorder them correctly. Each participant completed two trials. At post-intervention an alternate Form B of the NIH Episodic Memory test was used to minimize practice effects. The 7-min test measured change in performance by comparing uncorrected scores from baseline to post-intervention.

Processing speed. The Pattern Comparison Processing Speed Test (PCPST) measures processing speed by asking participants to quickly judge whether paired images are the same or different. Each participant had 85 s to respond to up to 130 pairs. The 3-min test used raw scores (0–130) to assess changes in performance over time.

Attention and inhibitory control. The Flanker Test assessed attention and inhibitory control by requiring participants to focus on target stimuli while ignoring distracters. The 3-min test included 20 trials, and final scores (0–10) were based on accuracy and response time.

Cognitive flexibility. Dimension Change Card Sort Test (DCCS) measured executive function, particularly cognitive flexibility. Participants sorted bivalent images by colour or shape, requiring flexible and timely responses. This four-minute test produced scores ranging from 0 to 10, with changes from baseline to post-test reflecting improvement or decline.

Fluid cognition composite score. Fluid cognition composite score was calculated by averaging the standardized scores of five tests: Flanker, DCCS, PSMT, List Sort, and PCPST. Fluid abilities, which support problem solving, quick thinking, memory encoding, and adapting to new situations are sensitive to aging and neurobiological changes. An increase in the composite score from baseline indicates improvement while decrease indicates decline.

Semantic memory was assessed using two tests:

a. **Picture vocabulary test (PVT)**

A computer adaptive test where participants' select an image matching a spoken word from the four given options. Each question adapts based on the previous response. The 4-min test used uncorrected standard scores, with higher scores indicating improved vocabulary.

b. **Oral reading recognition test (ORRT)**

Measures reading decoding by having participants read and pronounce words with responses marked correct or incorrect via keypad. Change from baseline is assessed using uncorrected standard scores.

Crystallized cognition composite score. This composite reflecting language and semantic memory, averages standard scores of PVT and ORRT. Crystallized abilities rely on experience, education, and cultural exposure. It remains relatively stable in adulthood and reflects verbal knowledge and skills.

Cognitive function composite score. The cognitive function composite score is calculated by averaging fluid and crystallized composite scores, providing a reliable overview of general cognitive performance. Higher scores indicate better function.

All the tests were performed in the same order and at the same time for all the participants.

Statistical analysis

IBM statistics SPSS version 26 was used. Data normality was checked and results are reported as mean ± SD. Baseline characteristics, metabolic and anthropometric variables were compared using Independent sample/paired *t* tests for normally distributed data and Mann Whitney *U*/Wilcoxon signed rank tests for non-normal data.

Linear mixed models assessed pre to post changes in cognitive outcomes between KD and Control groups. Each cognitive domain and composite score was analysed separately, with fixed effects for group, time, and their interaction and random intercepts for participants. Baseline BMI was used as covariate for all the tests and due to baseline differences in PVT, ORRT, crystallized cognition and cognitive function composite scores, their baseline scores were also included as covariates for analysis. Non-normal variables were reflected and log-transformed. Bonferroni corrections were applied; significance was set at $P < 0.05$.

Exploratory regressions examined metabolic predictors of cognitive change: Model 1: post intervention ketones, Model 2: ΔBMI, Model 3: Δ fasting glucose and Model 4: ketones, ΔBMI, Δ fasting glucose, group, gender, age (Δ = post-pre score).

RESULTS

Baseline characteristics

There were no significant differences between the groups at baseline (Table 1).

Metabolic markers

Figure 1a shows blood ketone concentration in KD group rose from baseline 0.12 to 0.89 mmol L^{-1} on day 15 to 1.32 mmol L^{-1} on day 29 of the trial whereas the control group remained near baseline throughout (0.11 mmol L^{-1}). Fasting blood glucose levels in the ketogenic diet group showed a consistent downward trend, decreasing from 5.09 mmol L^{-1} on day 1–4.75 mmol L^{-1} on day 15 and further to 4.71 mmol L^{-1} by day 29. In contrast, the control group displayed a different pattern: glucose levels initially decreased from 4.92 mmol L^{-1} on day 1–4.73 mmol L^{-1} on day 15, but then increased again to 5.01 mmol L^{-1} by day 29. This initial decline may reflect short term adjustments in eating patterns at the start of the study or variation in carbohydrate intake over the course of the study; however, because the participants continued consuming a diet with normal or high carbohydrate content, their fasting glucose levels rose again by Day 29 (Fig. 1b).

Anthropometric markers

Both weight and BMI showed a downward trend in the ketogenic diet group, indicating substantial weight loss over time. In contrast, the control group maintained relatively stable weight

Table 1. Baseline characteristics

	Ketogenic diet group (KD) $N = 43$		Control group (C) $N = 38$		
	Mean	SD	Mean	SD	*P* value
Gender females/males	26/17		19/19		0.377**
Age (years)	29.5	5.14	28.9	4.41	0.530*
Education (years)	15.16	2.10	14.7	1.16	0.613*
Mother's Education (years)	8.697	6.79	9.32	6.07	0.636*
Blood pressure (systolic) (mmHg)	116.93	10.35	113.16	7.39	0.068*
Blood pressure (diastolic) (mmHg)	78.88	7.93	76.18	7.11	0.062*
Hamilton depression scale (HAM-D)	2.39	1.79	2.58	1.55	0.599*
Height (m)	1.68	0.084	1.695	0.088	0.449***
Ketone levels (mmol L^{-1}) (baseline)	0.133	0.203	0.118	0.098	0.943*
Fasting glucose levels (mmol L^{-1}) (baseline)	5.09	0.46	4.96	0.37	0.07***

*Mann Whitney *U* test; **Chi square test; ***Independent samples *t*-test.

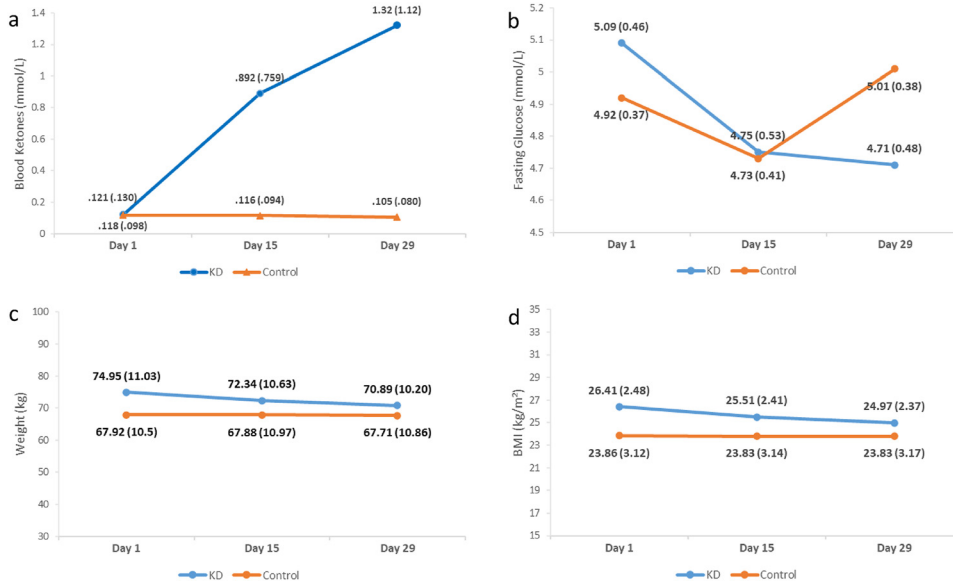

Fig. 1. Trajectories of metabolic and anthropometric indicators across baseline, mid and post intervention assessments

and BMI, with only negligible fluctuations (Fig. 1c and d). KD group participants lost a mean weight of 4.06 kg in 4 weeks Although there were baseline differences in weight and BMI between the two groups, this was statistically controlled by including baseline BMI as a covariate in the cognitive testing analyses. This adjustment helped ensure that any differences observed in cognitive outcomes were not attributable to initial BMI variation (Supplementary file 3).

These graphical metabolic and anthropometric indicators reflect a characteristic shift towards increased fat oxidation and reduced glycemic load in individuals following ketogenic diet comparative to controls.

Cognition domains

Linear mixed model analyses were performed to examine the effects of time and group and their interaction (time × group) on all the ten cognitive domains separately while controlling for baseline BMI and baseline cognitive performance to account for initial group differences.

Significant main effects of time were observed for all domains (P = 0.012 - <0.001) (Table 2) indicating overall improvement over time.

Significant group effect was observed in PVT (P = <0.001), list sort (P = <0.001), PSMT (P = 0.001), PCPST (P = 0.048), Flanker (P = 0.004) fluid cognition composite scores (P = <0.001), crystallized cognition composite scores (P = 0.02) and Cognitive function composite scores (P = <0.001) indicating KD group had higher overall cognitive domain scores than the control group, averaged across all time points whereas for ORRT (P = 0.20) and DCCS (P = 0.35) there was no difference in scores between KD and control groups indicating that the mean scores did not differ between the two groups when averaged across time points (Table 2).

Table 2. Comparison of cognition assessment scores at baseline and after 4 weeks between ketogenic diet & control group

Cognitive domains	KD group (43)		Control group (38)		Time *P*	Group *P*	Time × Group *P*
	Pre score	Post score	Pre score	Post score			
PVT	89.72 ± 6.54	98.79 ± 5.43	93.05 ± 6.10	93.03 ± 7.79	<0.001	<0.001	**<0.001**
ORRT	114.16 ± 7.5	121.67 ± 3.63	123.95 ± 4.6	126.3 ± 3.47	<0.001	0.20	**0.002**
CRSYT.COG.COMP.	101.67 ± 5.6	110.47 ± 3.46	109.05 ± 4.4	110.32 ± 5.14	<0.001	0.02	**<0.001**
FLANKER	7.93 ± 0.861	8.29 ± 0.787	8.07 ± 0.798	8.30 ± 0.87	0.001	0.004	0.46
DCCS	7.73 ± 0.971	8.15 ± 0.730	7.87 ± 0.89	8.00 ± 0.93	0.012	0.35	0.21
PCPST	44.47 ± 6.24	50.16 ± 6.24	45.03 ± 6.20	44.95 ± 8.50	0.001	0.048	**0.001**
LIST SORT	16.07 ± 1.88	21.7 ± 1.78	16.03 ± 1.89	16.21 ± 1.74	<0.001	<0.001	**<0.001**
PSMT	108.9 ± 12.1	127.14 ± 6.05	108.53 ± 14.2	114.1 ± 15.1	<0.001	0.011	**<0.001**
FLUID COG.COMP	99.93 ± 7.79	116.02 ± 7.23	100.95 ± 9.14	103.92 ± 9.5	<0.001	<0.001	**<0.001**
COGNITIVE FUNC.COMP.	100.3 ± 6.36	115.35 ± 5.28	105.29 ± 6.76	107.71 ± 7.7	<0.001	<0.001	**<0.001**

PVT: Picture vocabulary test, ORRT: Oral reading recognition test, CRYS.COG.COMP: Crystallized cognition composite score, FLANKER: Flanker inhibitory control & attention test, DCCS: Dimensional change card sort test, PCPST: Pattern comparison processing speed test, LIST SORT: List sorting working memory test, PSMT: Picture sequence memory test, FLUID COG.COMP: Fluid cognition composite score, COG.FUNC.COMP: Cognitive function composite score.

Continuous variables are shown as mean ± standard deviation. Linear mixed model analysis was carried out for all cognitive domains.

Note: Each model included group, time, group × time as fixed effect and baseline BMI as covariate. For ORRT, PVT, crystallized cognition composite and cognitive function composite scores due to baseline variation between the group scores, pre scores were also used as covariate. BMI as covariate was insignificant for all cognitive domains ($P > 0.05$) except fluid cognition composite score ($P = 0.03$).

A significant time × group interaction was found across most of the cognitive domains, indicating that changes from pre to post-test differed between groups. Specifically, ketogenic group showed greater improvement than the control group on vocabulary abilities, reading and decoding abilities, semantic memory, working memory, episodic memory, processing speed and the three composite scores.

Time × group interaction observed for PVT [$F(1,79) = 28.83$, $P = <0.001$)] indicated that ketogenic diet group showed greater improvement from pre to post intervention compared to control group. KD group's vocabulary scores increased by approximately 9.1 points than the control group following intervention after controlling for baseline score and BMI differences (Table 2).

Significant time × group interactions were observed for reflected square root transformed ORRT [$F(1,79) = 10.8$, $P = 0.002$; 0.53 higher scores], List Sort [$F(1,79) = 106.40$, $P = <0.001$; 5.44 points higher scores], PSMT [$F(1,79) = 15.05$, $P = <0.001$; 12.65 points higher scores], PCPST [$F(1,79) = 12.80$, $P = 0.001$; 5.82 point higher scores], crystallized cognition [$F(1,79) = 40.78$, $P = <0.001$; 7.53 points higher scores], fluid cognition [$F(1,79) = 50.01$, $P = <0.001$; 13.12 points higher scores], and overall cognitive function [$F(1,79) = 84.76$, $P = <0.001$; 12.63 points higher scores]. Across these domains, KD group showed greater improvement over time after controlling for BMI differences and baseline scores. No significant time × group interactions were found for cognitive flexibility (DCCS) or attention and inhibitory control (Flanker) ($P = >0.05$) (Table 2).

Exploratory regression analysis

Exploratory regressions tested whether changes in metabolic parameters predicted cognitive changes after ketogenic intervention. In Model 1, separate linear regressions were run for each cognitive outcome, with change in cognitive score as the dependent variable and post intervention ketone levels as the predictor. Post intervention ketone levels were significant predictors of working memory ($\beta = 0.54$, $P = <0.001$), episodic memory ($\beta = 5.6$, $P = 0.001$), processing speed ($\beta = 0.34$, $P = 0.002$), PVT ($\beta = 0.44$, $P = <0.001$), ORRT ($\beta = 0.26$, $P = 0.013$), fluid composite scores ($\beta = 0.54$, $P = <0.001$),crystallized composite scores ($\beta = 0.41$, $P = <0.001$) and cognitive function composite scores ($\beta = 0.58$, $P = <0.001$) indicating that higher ketone levels were associated with greater cognitive gains. In contrast, the model was not significant for Flanker ($P = 0.13$) and DCCS ($P = 0.27$) (Table 3).

Individual linear regression analyses were also done for change in cognitive domain scores and change in BMI (Model 2). BMI change was significant predictor of cognitive domains including working memory ($\beta = -0.55$, $P = <0.001$), episodic memory ($\beta = -0.33$, $P = 0.003$), processing speed ($\beta = -0.42$, $P = <0.001$), PVT ($\beta = -0.37$, $P = 0.001$), ORRT ($\beta = 0.29$, $P = 0.007$), fluid composite scores ($\beta = -0.59$, $P < 0.001$), crystallized composite scores ($\beta = -0.38$, $P = 0.001$) and cognitive function composite scores ($\beta = -0.59$, $P = <0.001$) indicating that weight loss was associated with greater cognitive gains in these domains (Table 3).

Moreover, individual linear regression analyses were carried out for cognitive score change and fasting glucose change (Model 3) (Table 3) Δ fasting glucose was significant predictor of working memory ($\beta = -0.29$, $P = 0.009$), episodic memory ($\beta = -0.29$, $P = 0.008$), fluid composite ($\beta = -0.38$, $P = <0.001$) and cognitive function composite scores ($\beta = -0.30$,

Table 3. Association of metabolic variables and anthropometric indicators with cognitive test scores

	PVT β (P)	ORRT β (P)	CRY.COG β (P)	PCPST β (P)	LIST SORT β (P)	PSMT β (P)	FLUID COG. β (P)	COG. FUNC. COMP. β (P)
Model 1								
Post ketone	**0.44 (<0.001)**	**0.26 (0.01)**	**0.41 (<0.001)**	**0.34 (0.002)**	**0.54 (<0.001)**	**0.38 (<0.001)**	**0.54 (<0.001)**	**0.58 (<0.001)**
Model 2								
ΔBMI	**−0.37 (0.001)**	**−0.29 (0.007)**	**−0.38 (0.001)**	**−0.42 (<0.001)**	**−0.55 (<0.001)**	**−0.33 (0.003)**	**−0.59 (<0.001)**	**−0.59 (<0.001)**
Model 3								
ΔFasting glucose	NS	NS	NS	NS	**−0.29 (0.009)**	**−0.29 (0.008)**	**−0.38 (<0.001)**	**−0.30 (0.007)**
Model 4								
Post ketones	0.**32** **(0.03)**	−0.12 (0.47)	0.14 (0.31)	0.04 (0.82)	0.05 (0.71)	0.17 (0.25)	0.09 (0.54)	0.13 (0.29)
ΔBMI	0.22 (0.18)	0.22 (0.23)	0.27 (0.09)	−0.28 (0.13)	0.19 (0.17)	0.13 (0.49)	−0.15 (0.34)	0.02 (0.89)
ΔFasting glucose	**−0.34 (0.003)**	0.10 (0.37)	0.**27** **(0.01)**	−0.002 (0.99)	0.05 (0.54)	−0.09 (0.46)	−0.08 (0.43)	0.07 (0.44)
Group	**0.63 (<0.001)**	**0.80 (<0.001)**	**0.84 (<0.001)**	0.14 (0.42)	**0.89 (<0.001)**	**0.39 (0.035)**	**0.42 (0.009)**	**0.69 (<0.001)**
Age	−0.07 (0.46)	0.03 (0.80)	−0.04 (0.67)	−0.05 (0.61)	0.009 (0.91)	−0.05 (0.63)	−0.10 (0.27)	−0.08 (0.29)
Gender	**0.22 (0.02)**	0.02 (0.81)	**0.17 (0.049)**	**0.26 (0.01)**	0.003 (0.97)	0.17 (0.11)	0.15 (0.09)	**0.18 (0.024)**

PVT: Picture vocabulary test, ORRT: Oral reading recognition test, CRYS.COG.: Crystallized cognition composite score, PCPST: Pattern comparison processing speed test, LIST SORT: List sorting working memory test, PSMT: Picture sequence memory test, FLUID COG. Fluid cognition composite score, COG.FUNC: Cognitive function composite score. Δ = post-score-pre-score. NS = model not significant. Univariate and multivariable linear regression analysis was performed. Models were not significant for DCCS and Flanker (not shown).

Table 3 shows the standardized beta coefficient and P values for predictors included in the regression models. Group (KD vs. Control), metabolic variables (ΔBMI, Δ Fasting glucose and. post ketones), age and gender were entered as predictors of cognitive change. Significant predictors (P = <0.05) are highlighted in bold.

Model 1: DV: Cognitive scores IV: Centered log transformed Post Ketone levels, **Model 2:** DV: Cognitive scores IV: ΔBMI, **Model 3:** DV: Cognitive scores IV: Δ Fasting glucose, **Model 4:** DV: Cognitive scores IV: Centered log transformed Post Ketone levels +Δ BMI+ Δ Fasting glucose + groups + Age + gender.

P = 0.007) indicating that greater reduction in fasting glucose was associated with greater improvement in cognitive outcome. Fasting glucose was not a significant predictor for processing speed (P = 0.054), ORRT (P = 0.37), PVT (P = 0.80) and crystallized composite scores (P = 0.61).

In model 4 group, age and gender were added in addition to post ketones, ΔBMI and Δ fasting glucose as predictors, the effect of all the metabolic markers became non-significant while

group remained a significant predictor for the domains including PVT ($\beta = 0.63$, $P = <0.001$), ORRT ($\beta = 0.80$, $P = <0.001$), crystallized composite scores ($\beta = 0.84$, $P = <0.001$), working memory ($\beta = 0.89$, $P = <0.001$), episodic memory ($\beta = 0.39$, $P = 0.035$), fluid composite score ($\beta = 0.42$, $P = 0.009$) and cognitive function composite scores ($\beta = 0.69$, $P = <0.001$) indicating that group was the strongest predictor, with the ketogenic group showing substantially greater improvement than the control group when holding all the other variables constant. For processing speed ($P = 0.42$), group was not a significant predictor.

For PVT, fasting glucose ($\beta = -0.34$, $P = 0.003$) and group were significant predictors, with each unit decrease in glucose associated with 30-point rise in PVT scores. Ketones also predicted vocabulary abilities ($\beta = 0.32$, $P = 0.03$), suggesting higher post ketone levels relate to better vocabulary performance. Gender predicted vocabulary as well, with males scoring 3.91 points higher ($\beta = 0.22$, $P = 0.02$).

For crystallized cognition, fasting glucose ($\beta = 0.27$, $P = 0.01$) predicted a 19-point increase per unit of change in glucose and gender remained significant ($\beta = 0.17$, $P = 0.049$), with males scoring 2.26 points higher.

Gender was again a significant predictor for cognition function composite score ($\beta = 0.18$, $P = 0.024$; males +12.1 points) and processing speed ($\beta = 0.26$, $P = 0.01$; males +4.09 points).

DISCUSSION

In the present study, healthy adults aged 25–45 years with BMI 18–29.9 kg m^{-2} demonstrated significant improvements across most cognitive domains and in the three cognitive composite scores following four weeks of non-energy restricted ketogenic diet intake. However, attention and inhibitory control and cognitive flexibility did not reach significance. These effects coincided with significant weight loss, reduced fasting glucose and elevated blood ketones suggesting a shift towards greater metabolic efficiency and flexibility.

The observed cognitive enhancement can be attributed to multiple converging mechanisms like improved neuronal energy metabolism through utilization of blood ketones as an alternate and more efficient cerebral fuel [25], reduced systemic inflammation accompanying weight loss [26], improved insulin sensitivity [27] due to decrease in fasting glucose. Notably the participants' habitual diet prior to the intervention was high in refined carbohydrates [28, 29] which has likely magnified the metabolic transition on commencing a low carbohydrate KD regimen, producing rapid improvements in glycemic stability and brain energy availability. The resulting combination of elevated ketones supply, lower glycemic variability and improved insulin sensitivity may explain the broad enhancement observed across cognitive domains even within a relatively short intervention period.

It has been stated that 0.1 mM boost in plasma ketones is typically associated with a 1.0–1.2% increase in proportion of ketones' contribution to total brain energy metabolism [30]. In the present study, mean blood ketones increased from 0.12 ± 0.13 mmol L^{-1} at baseline to 1.32 ± 1.12 mmol L^{-1} after four weeks in KD group, confirming induction of nutritional ketosis. According to existing literature circulating ketones between 0.5 and 3.0 mmol L^{-1} reflect a metabolic state in which ketones becomes a significant alternative cerebral fuel [31]. This enhancement indicates a pronounced metabolic shift from predominant glucose utilization towards increased fatty acid oxidation, reflecting improved metabolic flexibility. Circulating

ketones exerts neuroprotective and signalling effect which likely attributed to cognitive benefits. Additionally, sustained ketosis observed in our participants therefore reflects both successful and meaningful physiological adaptation which together may explain broad cognitive gains, weight reduction and improved glycemic control during the intervention.

Although the distribution of weight categories differed between the intervention and control groups (12 normal weight and 31 overweight participants in KD group vs 23 normal weight and 15 overweight participants in control group), baseline BMI was used as a covariate in the analyses to control for its potential confounding effects. After adjusting for BMI, the group effect on most of the cognitive domains remained significant, suggesting ketogenic diet improved cognitive performance regardless of weight status of the participants. Baseline BMI showed negative association only with fluid composite scores. It was observed that for one-unit increase in baseline BMI, fluid cognition composite scores decreased by about 0.65 points indicating participants with higher baseline BMI demonstrated lower fluid scores. However, it should be considered that while BMI reflects overall body weight relative to height, it overlooks subtle differences in body composition which may differentially influence cognition.

Analysis of our results suggest that individual metabolic changes such as change in BMI, blood ketone levels and reduction in fasting glucose were associated with improvements in cognitive performance when considered separately. However, when included together in multivariable model, none of the predictors remained statistically significant, indicating that these metabolic markers share overlapping variance. It may also suggest that these metabolic indicators may be interrelated and contribute collectively rather than independently to the cognitive gains. The interdependence among the said variables is biologically plausible as reduction in BMI and fasting glucose and elevation in blood ketones are parallel outcomes of improved metabolic flexibility during ketogenic adaptation. Elevated ketones can enhance neuronal energy efficiency while reduced BMI and glucose reflects better insulin sensitivity and vascular health. Each outcome support cognition through shared physiological mechanisms such as improved mitochondrial function, reduced oxidative stress [27] and enhanced cerebral metabolism [32]. It is probable that these markers influence cognitive outcomes by acting synergistically rather than independently. Conversely, the findings may suggest that other underlying mechanisms contribute to cognitive gains. Multivariate analysis also showed that after controlling for metabolic, anthropometric factors and group; gender remained a significant predictor of PVT, processing speed, crystallized cognition and cognitive function composite scores, with males scoring higher than females probably indicating sex related physiological or hormonal influences on cognition.

The existing literature has largely focused on selective cognitive measures, with limited studies evaluating the full spectrum of cognitive domains. Mohorko et al. reported improvements in working memory and processing speed following ketogenic diet (KD) in obese adults after 12 weeks of KD [33]. Though their study included sedentary participants, it allowed up to 10% carbohydrates, relied on self-reported intake and had higher baseline ketones (0.5 mmol L^{-1} vs 0.11 mmol L^{-1} in our study). Unlike their selective testing, we assessed all major cognitive domains and included a control group. In contrast, Iacovides et al. observed no cognitive benefits after three weeks of KD in healthy, normal-weight (21–38 yrs) recreationally active adults [34]. Differences from our results may relate to their small sample ($n = 11$), gender imbalance, KD composition, restricted BMI range and differing cognitive tests.

Studies in older or cognitively impaired individuals also show mixed outcomes. Krikorian et al. reported improved verbal memory but not executive function or working memory in adults >70 years with early memory decline [12]. Fortier et al. found improvements in processing speed, episodic memory, language, and executive function after six months of KD drink intake in adults ≥55 yrs [8]. Ota et al. reported similar benefits in Alzheimer's patients receiving MCT-based ketogenic formula [10]. However, differences in duration and participant characteristics limit direct comparison.

An important consideration when interpreting the present cognitive findings is the potential influence of practice effects associated with repeated administration of the computerized testing platform. The use of computer based cognition battery though include adaptive algorithms and randomized item sets designed to minimize learning effects, some degree of practice related improvement between pre and post assessments cannot be entirely excluded. However, because both intervention and control groups were exposed to identical testing procedures, any residual systematic bias in observed group differences is minimized.

Key strengths of this study include provision of a prepared diet, inclusion of healthy participants and comprehensive cognitive assessment. The present study has several limitations. The short intervention period, inability to conduct daily ketone measurements because of financial limitations and absence of follow-up assessments may restrict both the generalizability and the long-term interpretation of the results. Additionally, although we assessed metabolic variables such as BMI, fasting blood glucose and ketones; other potential mediators of cognitive change like insulin resistance indices and inflammatory markers were not measured in this study. Future studies incorporating these variables would help clarify the mechanistic pathways linking ketogenic diet interventions to cognitive outcomes.

Future research should stratify participants by body weight to explore differential cognitive responses to ketogenic diet or focus on specific weight groups to clarify targeted effects on cognitive domains. Ensuring balanced sample size across weight categories will improves statistical power to detect potential moderating effects of BMI.

In conclusion, a four-week non energy restricted ketogenic diet improved multiple domains of cognition in healthy adults, including working memory, episodic memory, semantic memory, processing speed, fluid cognition, crystallized cognition and the overall cognitive function composite scores compared with the control group. However, no improvements were observed in attention and inhibitory control and cognitive flexibility.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2060.2025.00743.

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