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RESEARCH ARTICLE

Creatine monohydrate pilot in Alzheimer's: Feasibility, brain creatine, and cognition

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Abstract

BACKGROUND: Preclinical studies suggest that creatine monohydrate (CrM) improves cognition and Alzheimer's disease (AD) biomarkers. However, there is currently no clinical evidence demonstrating the effects of CrM in patients with AD.

METHODS: In this single-arm pilot trial, we investigated the feasibility of 20 g/day CrM for 8 weeks in 20 patients with AD. We measured compliance throughout; serum creatine at baseline, 4 weeks, and 8 weeks; and brain total creatine (tCr) and cognition (National Institutes of Health [NIH] Toolbox, Mini-Mental State Examination [MMSE]) at baseline and 8 weeks.

RESULTS: Nineteen participants achieved the target of ≥80% compliance with the CrM intervention. Serum Cr was elevated at 4 and 8 weeks ($p < .001$) and brain tCr increased by 11% ($p < .001$). Cognition improved on global ($p = .02$) and fluid ($p = .004$) composites, List Sorting ($p = .001$), Oral Reading ($p < .001$), and Flanker ($p = .05$) tests.

DISCUSSION: Our data suggest that CrM supplementation is feasible in AD and provides preliminary evidence for future efficacy and mechanism studies.

Trial Registration: ClinicalTrials.gov, NCT05383833, registered on May 20, 2022.

KEYWORDS
Alzheimer's disease, bioenergetics, brain creatine, cognition, creatine monohydrate, magnetic resonance spectroscopy, pilot trial

Highlights

- Creatine monohydrate supplementation was feasible in patients with Alzheimer's disease.
- Creatine monohydrate was associated with increased brain total creatine.
- Creatine monohydrate was associated with improvements in cognition.
- Efficacy of creatine monohydrate in Alzheimer's disease should be studied further.

1 | BACKGROUND

Impaired brain energy metabolism, including dysfunction in the creatine (Cr)[1] system, may contribute to the development and progression of Alzheimer's disease (AD),[2,3] making it a compelling therapeutic target. Cr, an organic molecule found throughout the body,[4] is critical in supplying energy to the brain and other high energy-demand organs.[5] Within cells, free Cr transports high-energy phosphates from the mitochondrial membrane to the cytosol, where it forms phosphorylated creatine (PCr),[4] which in turn replenishes adenosine triphosphate (ATP). To enhance intracellular Cr stores, supplementation with creatine monohydrate (CrM) effectively increases both total and PCr levels in skeletal muscle[6] and in the brain.[7] CrM supplementation may offer a cost-effective therapeutic strategy for improving brain energy metabolism in AD by targeting the brain Cr system.

CrM supplementation has been shown to increase brain Cr[7] and has promising preliminary evidence for enhancing cognitive function across diverse populations.[8–10] In AD mouse models, CrM supplementation improved cognitive function and brain energy metabolism and reduced pathological biomarkers such as amyloid beta (Aβ) and phosphorylated tau.[11–13] Despite the critical role of Cr in sustaining brain energy and these encouraging preclinical findings, no clinical trials have investigated CrM as an adjuvant therapy for patients with AD. Thus it is yet to be determined whether CrM is a feasible non-pharmacological intervention in patients with AD and whether it is associated with cognitive improvements and favorable changes in AD pathophysiology.

Here we report the feasibility, brain Cr, and cognitive outcomes data from our single-arm pilot trial investigating the feasibility and preliminary efficacy of 20 g/day CrM supplementation for 8 weeks in patients with AD.[14] We hypothesized that CrM supplementation would be feasible, increase brain Cr levels, and improve cognitive performance.

2 | METHODS

The Creatine to Augment Bioenergetics in Alzheimer's (CABA) trial was an 8-week, single-arm pilot trial testing the feasibility of 20 g/day of CrM in patients with AD. The University of Kansas Medical Center Institutional Review Board approved the study protocol. All participants provided written informed consent in compliance with institutional guidelines.

2.1 | Participants

Participants were recruited through the University of Kansas Alzheimer's Disease Research Center's (KU ADRC) Outreach, Recruitment, and Engagement Core. Eligible participants were 60–90 years of age and met the McKhann criteria for dementia due to AD.[15] Although it was not part of the eligibility criteria, we also measured plasma phosphorylated tau-217 (p-tau217) to characterize participants with a high likelihood of AD pathology (described later). Before joining the study, participants had to be taking a stable dose of AD-related medications, such as donepezil or memantine, for at least 30 days. In addition, participants required a study partner—a spouse, family member, or close friend—to support them throughout the intervention. Additional inclusion criteria included English as the primary language, a Mini-Mental State Examination (MMSE) score $\geq$17, and the ability to perform leg strength testing. Exclusion criteria included insulin-requiring diabetes, chemotherapy or radiation within the past 5 years, a cardiac event in the past year, other neurodegenerative disease, inability to undergo magnetic resonance imaging (MRI), and participation in a clinical trial or investigational drug or therapy within 30 days of screening.

2.2 | CrM Intervention

Participants consumed 20 g of CrM (Life Extension Inc., USA) daily for 8 weeks, split into two 10-g doses. Participants could stir the CrM powder into beverages of their choosing. A trained research dietitian provided oral and written education to participants and study partners on taking the CrM and called the study partner weekly to encourage compliance with the intervention.

2.3 | Anthropometrics

Height and weight were measured using a calibrated stadiometer and a calibrated standard digital scale. Body mass index (BMI) was calculated by dividing total body mass (kg) by the square of height (m). Waist circumference was measured by trained personnel using a standard tape measure as described by Norgan.[16]

RESEARCH IN CONTEXT

1. **Systematic review:** We conducted an extensive literature search using standard databases like PubMed. Preclinical studies indicate that creatine monohydrate (CrM) supplementation enhances cognition and reduces pathological biomarkers in mouse models of Alzheimer's disease (AD). However, no human trials have investigated CrM as a therapeutic option for patients with AD.
2. **Interpretation:** This pilot study demonstrated that CrM supplementation is feasible in AD and is associated with increased brain total Cr levels and improved cognition, suggesting that Cr may offer bioenergetic and cognitive benefits in AD.
3. **Future Directions:** Larger efficacy trials are needed to investigate CrM supplementation as a potential therapy in AD and to determine the optimal dose.

2.4 | Compliance measures and safety labs

Study participants and their partners were given CrM compliance trackers to record their daily supplement intake, which had two boxes to be checked each day, corresponding with the two daily doses of CrM. Study partners returned the compliance trackers at the 8-week visit (end of study). Participants who reported ≥80% compliance with their daily supplement intake were considered protocol compliant. In addition, the study dietitian monitored adverse events during weekly telephone calls with study partners.

Blood was drawn at baseline, 4 weeks, and 8 weeks to measure serum Cr levels via enzymatic assay (Quest Diagnostics). Serum Cr was used as an objective biomarker of compliance. Two participants did not have baseline serum Cr values, and an additional two were missing 4-week serum Cr values. A comprehensive metabolic panel was obtained at baseline to confirm eligibility and at the 8-week visit (Quest Diagnostics) to monitor the safety of CrM supplementation.

2.5 | Apolipoprotein E (*APOE*) genotype

Apolipoprotein E (*APOE*) genotype was determined at baseline using the TaqMan single nucleotide polymorphism (SNP) allelic discrimination assay (Thermo Fisher Scientific) to genotype the two *APOE*-defining SNPs, rs429358 and rs7412, thereby distinguishing among *APOE* ε2, *APOE* ε3, and *APOE* ε4 alleles. Participants with at least one *APOE* ε4 allele were considered to be "*APOE ε4* carriers."

2.6 | Plasma phosphorylated tau-217 (p-tau217) assay

Plasma p-tau217 assays were performed on 19 of 20 participants at baseline and 8 weeks using the ALZpath pTau217[17] assay on the Simoa HD-X (Quanterix, Lexington, MA) platform. Baseline plasma p-tau217 level was used to characterize brain amyloid pathology,[17] helping to distinguish between a high likelihood or the absence of AD pathology.[18] Participants who had p-tau concentrations ≥0.4 pg/mL were considered Aβ positive.[17]

2.7 | Cognitive measures

The MMSE, a 30-item cognitive test that can reliably indicate cognitive impairment,[19] was administered at baseline and 8 weeks. At baseline, the MMSE was used as part of our inclusion criteria (≥17). The National Institutes of Health (NIH) Toolbox Cognition Battery,[20] validated for use in patients with cognitive impairment,[21] was administered by trained personnel at baseline and 8 weeks using an iPad. The NIH ToolBox assesses the cognitive domains of attention, category switching, episodic memory, working memory, speed of processing, written language, and auditory language. The NIH Toolbox returns scores for each individual domain and composite scores for fluid, crystallized, and total cognition. Due to the single-arm, pre-post design of the CABA trial, we used unadjusted cognition scores in our analyses.

2.8 | Brain Cr measures and quantification using ^{1}H MRS

^{1}H magnetic resonance spectroscopic imaging (MRSI) scans were performed on a 3T MR system (Skyra, Siemens, Erlangen, Germany) using a 20-channel receiver radiofrequency coil. Each participant underwent two MRSI scans at approximately the same time of day at baseline and the 8-week follow-up. Participants were positioned supine in the scanner. Brain total Cr (tCr) was measured using a semi-LASER MRSI sequence (echo time/repetition time = 35/2000 ms, field of view = 20 cm, matrix = 10 × 10, slice thickness = 2.5 cm) on an axial slab above the lateral ventricle, encompassing the frontal and parietal brain regions. The sequence included a prospective frequency correction function to minimize the effects of frequency drifts due to system instability and/or subject motion during the scan.[22] The Cr signal was quantified using LCModel software[23] as a ratio to water signals acquired from the same slab without water suppression after taking into account partial volume effects from cerebral spinal fluid,[24,25] and reported in international units (IUs).

2.9 | Statistical analyses

This study's primary objective was to investigate the feasibility of an 8-week CrM intervention and the intervention-associated changes in brain tCr and cognitive performance in patients with AD. Continuous data are expressed as mean ± SD, and categorical data are presented as frequency and percentages. We calculated percent compliance as the total number of CrM servings each participant reported consuming divided by the number of servings they were expected to take during

the intervention. For inferential statistical analyses, data from all participants allocated to the CrM intervention were included. We used paired *t*-tests to analyze the mean changes from baseline in serum Cr levels at 4 and 8 weeks, safety labs at 8 weeks, brain tCr at 8 weeks, and cognition at 8 weeks. Effect sizes were calculated using Cohen's d_z for paired samples. We used linear mixed models, including the interaction of time and sex and subject ID as a random effect, to explore differences in brain Cr and cognition changes between male and female participants. We used Pearson correlation to investigate correlation between changes in serum Cr and changes in brain tCr as well as changes in brain tCr between changes in cognitive performance. All statistical analyses were performed using R software (version 4.1.1; R Foundation, Vienna, Austria). A two-sided *p*-value less than .05 was considered statistically significant for all analyses.

3 | RESULTS

3.1 | Feasibility and safety labs

The CABA trial aimed to allocate 20 participants to the CrM intervention and enrolled 22 participants over 17 months (December 2022 to May 2024) to do so. Participant flow is illustrated in Figure S1. The KU ADRC pre-screened 276 individuals for interest and preliminary eligibility and referred 52 patients to the CABA study team for further eligibility assessment and a more detailed explanation of the study. Of these, 20 were deemed ineligible due to not meeting McKhann criteria, 6 declined participation, and 4 could not be contacted. Twenty-two participants were enrolled in the CABA study; however, two were excluded for elevated renal labs at safety screening. Twenty participants who met McKhann criteria for dementia due to AD (age 73.1 ± 6.3 years) were allocated to the 8-week CrM intervention. Baseline demographic characteristics are presented in Table 1.

All 20 participants allocated to the intervention completed the CABA study. Study partners reported a total of 13 adverse events, all mild, which included cramping/muscle pain, diarrhea, constipation, nausea, facial flushing, and sleep disturbance. Nineteen participants met the criteria for protocol compliance by reporting consumption of ≥80% of expected CrM doses (Figure 1A). We conservatively considered one participant protocol non-compliant for providing incomplete CrM compliance trackers, but this participant was still included in all compliance analyses. Among all participants, mean self-reported dose compliance was 90.0%.

Two serum Cr values were missing at baseline, and two additional values were missing at 4 weeks due to the laboratory performing incorrect assays on these serum samples. Thus, data from 16 participants were available for the analysis of baseline to 4-week change in serum Cr, and data from 18 participants were available for the analysis of baseline to 8-week change. Serum Cr values were significantly elevated at 4 and 8 weeks from baseline (0.6 ± 0.4 mg/dL vs 14.0 ± 9.9 mg/dL and 15.0 ± 13.6 mg/dL, respectively; $p < .001$ for each, Figure 1B).

There were no significant changes from baseline to 8-weeks in safety labs from the comprehensive metabolic panel, except for a slight increase in serum creatinine (Table 2).

TABLE 1 Demographics and baseline characteristics.*

	n = 20
Age, years, mean ± SD	73.1 ± 6.3
Sex *n* (%)	
Female	7 (35.0%)
Male	13 (65.0%)
Race, ethnicity, *n* (%)	
African American, not Hispanic	1 (5.0%)
Asian, not Hispanic	1 (5.0%)
White, not Hispanic	17 (85.0%)
Other, Hispanic	1 (5.0%)
Education, *n* (%)	
Completed high school	2 (10.0%)
Associate's	6 (30.0%)
Bachelor's	6 (30.0%)
Master's	2 (10.0%)
Doctorate, Professional	4 (20.0%)
BMI, kg/m^2	25.2 ± 3.7
Waist circumference, cm	93.0 ± 9.3
Mini-Mental State Examination	21.6 ± 4.4
APOE ε4 carriers	13 (65.0%)
Plasma p-tau217, pg/mL	1.1 ± 0.5[†]
Amyloid positive	18 (90%)
AD8 Score	4.3 ± 1.9

Abbreviations: APOE, apolipoprotein E; p-tau217, phosphorylated tau-217; AD8, Ascertain Dementia 8-item Questionnaire.
*Values are mean ± SD unless indicated as frequency (%).
[†]*n* = 19.

3.2 | Brain tCr

MRS-derived Brain tCr concentrations increased from baseline to 8 weeks (330.5 ± 36.8 IU vs 366.9 ± 57.5 IU, $p < .001$, Cohen's $d_z = 1.01$, Table 2, Figure 2). Baseline mean tCr concentration and 8-week mean tCr change were similar between male and female participants.

3.3 | Cognitive function

The CrM intervention was associated with improvement in total cognition (75.3 ± 13.9 vs 78.6 ± 13.5, $p = .02$, Cohen's $d_z = 0.58$), fluid cognition (59.1 ± 14.7 vs 63.5 ± 15.8, $p = 0.004$, Cohen's $d_z = 0.74$, Figure 3A), list sorting working memory (66.2 ± 18.7 vs 74.2 ± 20.3, $p = .001$, Cohen's $d_z = 0.87$, Figure 3B), and oral reading recognition (98.0 ± 7.18 vs 103 ± 7.23, $p < .001$, Cohen's $d_z = 0.1.03$, Figure 3C). There was a trending improvement in the flanker inhibitory control and attention test (68.1 ± 15.4 vs 73.0 ± 13.9, $p = .05$, Cohen's $d_z = 0.33$ Figure 3D). There was no change in crystalized cognition or in the other individual cognitive tests. All cognitive results are reported in Table 2. Change in cognition was similar between sexes.

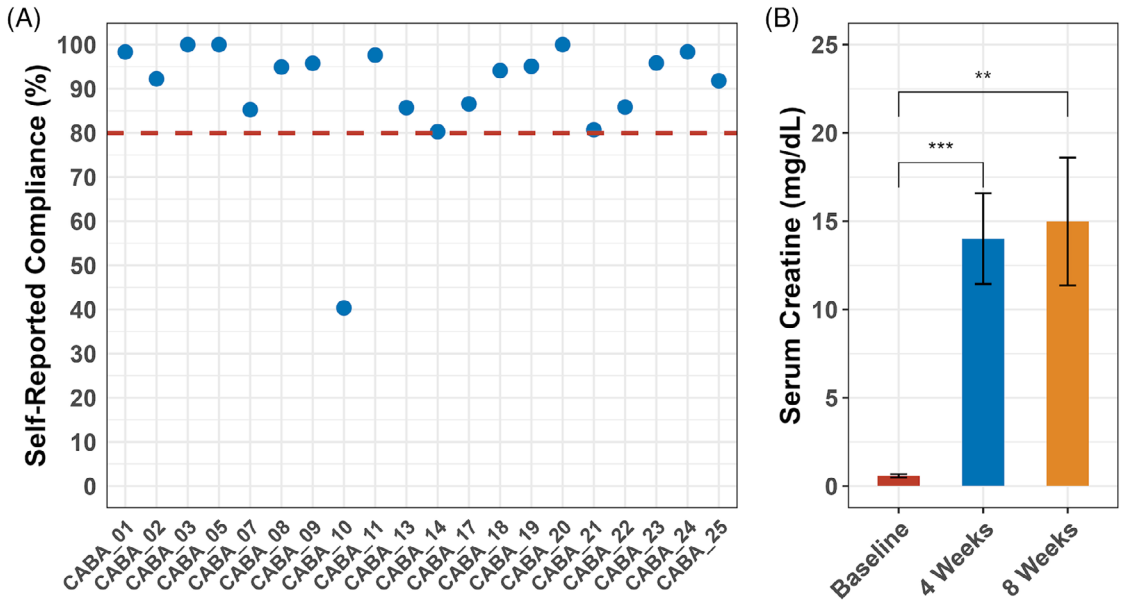

FIGURE 1 Creatine to Augment Bioenergetics in Alzheimer's (CABA) compliance measures. **(A)** Dot plot illustrating individual self-reported compliance with the intervention from daily CrM compliance trackers. The red dotted line indicates the 80% compliance threshold for protocol adherence. **(B)** Bar plots with error bars (mean ± standard error) comparing serum Cr values from baseline to 4 weeks and 8 weeks. Due to missing serum Cr values, the total sample size is $n = 16$ across all conditions. $^{**}p < .01$; $^{***}p < .001$; CrM, creatine monohydrate; Cr, creatine.

3.4 | Correlation between change in serum Cr and brain tCr

Changes in serum Cr and change in brain tCr were positively correlated ($r = 0.49$, $p = .004$), as illustrated in Figure S2.

3.5 | Correlation between change in brain tCr and cognition

Brain tCr change was positively correlated with change in oral reading recognition ($r = 0.60$, $p = .005$) and crystalized cognition ($r = 0.48$, $p = .03$). Change in brain tCr was not correlated with change in any other measure of cognition. All correlations between change in brain tCr and change in cognition are summarized in Table 3.

4 | DISCUSSION

This pilot trial found that 8 weeks of CrM supplementation was feasible and well tolerated in patients with AD. There were no withdrawals from this study, and 19 of 20 participants reported ≥80% compliance with the CrM intervention. One participant did not track their supplement consumption for 4 weeks, preventing us from being able to quantify their compliance; however, this participant was at least mildly compliant as indicated by increased serum Cr at the 4- and 8-week visits. The most common complaint was cramping or muscle pain that resolved after the first few weeks on the intervention, aligning with previous studies demonstrating a good safety profile for CrM supplementation.[26] In addition, we demonstrated improvements in our secondary outcome measures of brain tCr concentration and cognition, providing preliminary evidence that justifies investigating CrM supplementation in AD with larger efficacy trials.

The diagnosis of AD was defined biologically recently, requiring the presence of elevated brain amyloid, even in individuals who may be asymptomatic.[18] In this pilot trial, we allocated 20 participants who met the criteria for clinical diagnosis of dementia due to probable AD. Recognizing that including patients with a clinical diagnosis did not ensure the enrollment of a sample of patients with AD pathology, we measured plasma p-tau217[27] in 19 of 20 participants at baseline to assess the likelihood of AD-related pathology. Because tau pathology is an AD feature downstream of amyloidosis,[28] elevations of plasma p-tau217 are indicative of AD neuropathology.[29] The average p-tau217 concentration was 1.14 pg/mL, with 18 of 19 participants exceeding the cutoff of 0.4 pg/mL,[17] indicating a high likelihood of AD pathology in 90% of all allocated participants. Furthermore, 65% of participants carried at least one *APOE* ε4 allele, the most significant genetic risk factor for late-onset AD, and had an average Ascertain Dementia 8-item Questionnaire (AD8) score of 4.3, exceeding the threshold of >3 for detecting dementia due to probable AD.[30] Collectively this suggests that the feasibility and intervention-associated results from our trial are applicable to patients with AD.

We measured fasting serum Cr levels at baseline, 4 weeks, and 8 weeks as an objective biomarker of compliance. All participants had elevated serum Cr at 4 and 8 weeks, providing objective complementary evidence to the CrM trackers that the intervention was feasible. Because we only measured serum Cr at three timepoints, we are limited in using this biomarker to broadly describe compliance. Previous work shows that a single 20 g dose of CrM can exhibit a 2–3 h serum Cr half-life,[31] but the temporal fluctuation of serum Cr

TABLE 2 CABA Results*,†

	Baseline $n = 20$	8 weeks $n = 20$	p-value
Blood safety labs			
ALT, U/L	19.2 ± 9.1	23.9 ± 15.0	0.25
AST, U/L	20.2 ± 7.7	22.4 ± 9.3	0.42
Blood Urea Nitrogen, mg/dL	19.4 ± 4.0	19.9 ± 5.3	0.76
Calcium, mg/dL	9.43 ± 0.4	9.21 ± 0.5	0.13
Carbon Dioxide, mmol/L	28.3 ± 2.3	29.1 ± 1.5	0.18
Chloride, mmol/L	104 ± 1.8	104 ± 2.4	0.77
Creatinine, mg/dL	0.94 ± 0.2	1.25 ± 0.3	0.001
Glucose, mg/dL	90.6 ± 13.3	96.3 ± 16.0	0.22
Potassium, mEq/L	4.18 ± 0.3	4.25 ± 0.3	0.38
Sodium, mEq/L	140 ± 1.6	140 ± 1.8	0.36
^{1}H Magnetic Resonance Spectroscopy			
Brain Creatine, IU	330.5 ± 36.8	366.9 ± 57.5	<0.001
Cognition			
Mini-Mental State Examination	21.6 ± 4.4	21.0 ± 5.2	0.33
NIH Toolbox Battery			
Total Cognition	75.3 ± 13.9	78.6 ± 13.5	0.02
Fluid Cognition	59.1 ± 14.7	63.5 ± 15.8	0.004
Crystalized Cognition	100 ± 10.5	102 ± 9.2	0.45
Flanker Inhibitory Control and Attention	68.1 ± 15.4	73.0 ± 13.9	0.05
Dimensional Change Card Sort	79.0 ± 16.2	81.7 ± 13.6	0.38
List Sorting Working Memory	66.2 ± 18.7	74.2 ± 20.3	0.001
Picture Vocabulary	104 ± 14.5	101 ± 12.1	0.08
Oral Reading Recognition	98.0 ± 7.18	103 ± 7.23	<0.001
Picture Sequence Memory	82.3 ± 5.60	80.8 ± 6.1	0.32
Pattern Comparison	62.3 ± 13.9	63.8 ± 15.6	0.52

Abbreviation: IU, international units.
*Values are means ± SD.
†Mean differences were assessed using a paired-sample t-test. Significance was set at $p < .05$.

concentration in individuals consistently taking high-dose CrM (as in our study), with cellular saturation of Cr, has not been well characterized previously. Future trials with CrM should consider optimizing strategies of measuring serum Cr to better assess compliance and Cr physiology.

Because the CABA study was a small, single-arm pilot trial of short duration, the preliminary secondary outcome results should be interpreted with caution, yet they provide additional evidence that bioenergetic intervention may be beneficial in the treatment of AD.[32] Brain tCr concentration increased in 85% of participants, with an overall average tCr increase of 11%. Magnitude of change in tCr was variable among participants, which may be partially explained by variations in Cr transport kinetics across the blood–brain barrier, similar to variable transport kinetics in skeletal muscle following CrM supplementation.[33] Changes in serum Cr and brain tCr were positively correlated; however, these results should be interpreted cautiously, as serum Cr and brain tCr were measured on different days. Although previous studies have demonstrated that CrM supplementation increases brain Cr in healthy individuals,[7] our trial is the first to demonstrate this in AD. Our ^{1}H MRS allowed us to measure tCr, instead of both free Cr and PCr. It will be important to measure tCr and PCr using combined ^{1}H/^{31}P MRS in future trials to elucidate the effects of CrM supplementation on both the storage (tCr) and utilization (PCr) of energy as well as the dynamics of bioenergetics via the ratio of free Cr to PCr in AD.

The cognitive improvements observed in this study are also promising, as AD is a progressive disease with expected decline over time. We hypothesized that memory and executive function, the most affected domains in AD,[34–37] would benefit from CrM supplementation. In addition to these domains, participants also improved in oral reading recognition performance, a test that assesses the participant's ability to properly read and pronounce a visually-presented word. Although

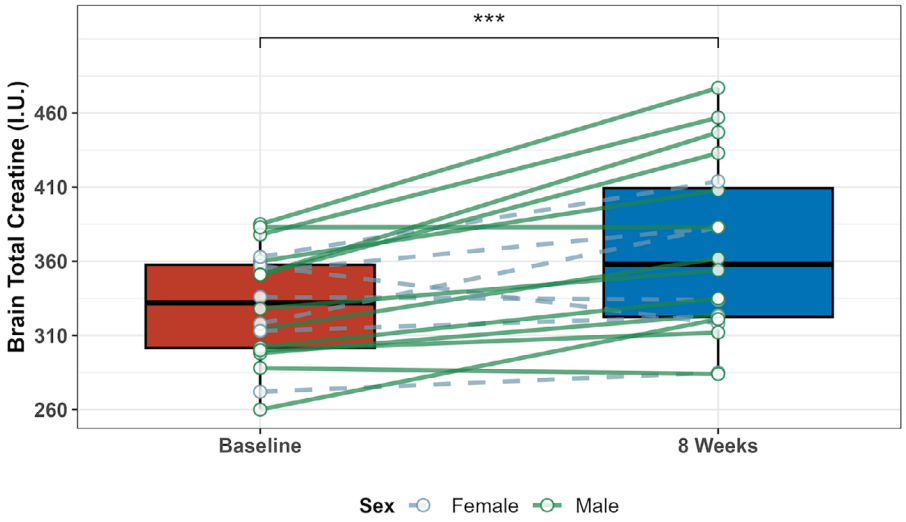

FIGURE 2 Change in brain total Cr after 8 weeks of CrM supplementation. Brain Cr was quantified using ^{1}H MRS. Boxplots display Cr values at baseline and after 8 weeks, with individual changes overlaid. Solid green lines represent male participants, whereas dashed gray lines represent female participants. ***$p < .001$. Cr, creatine; MRS, magnetic resonance spectroscopy; IU, international units.

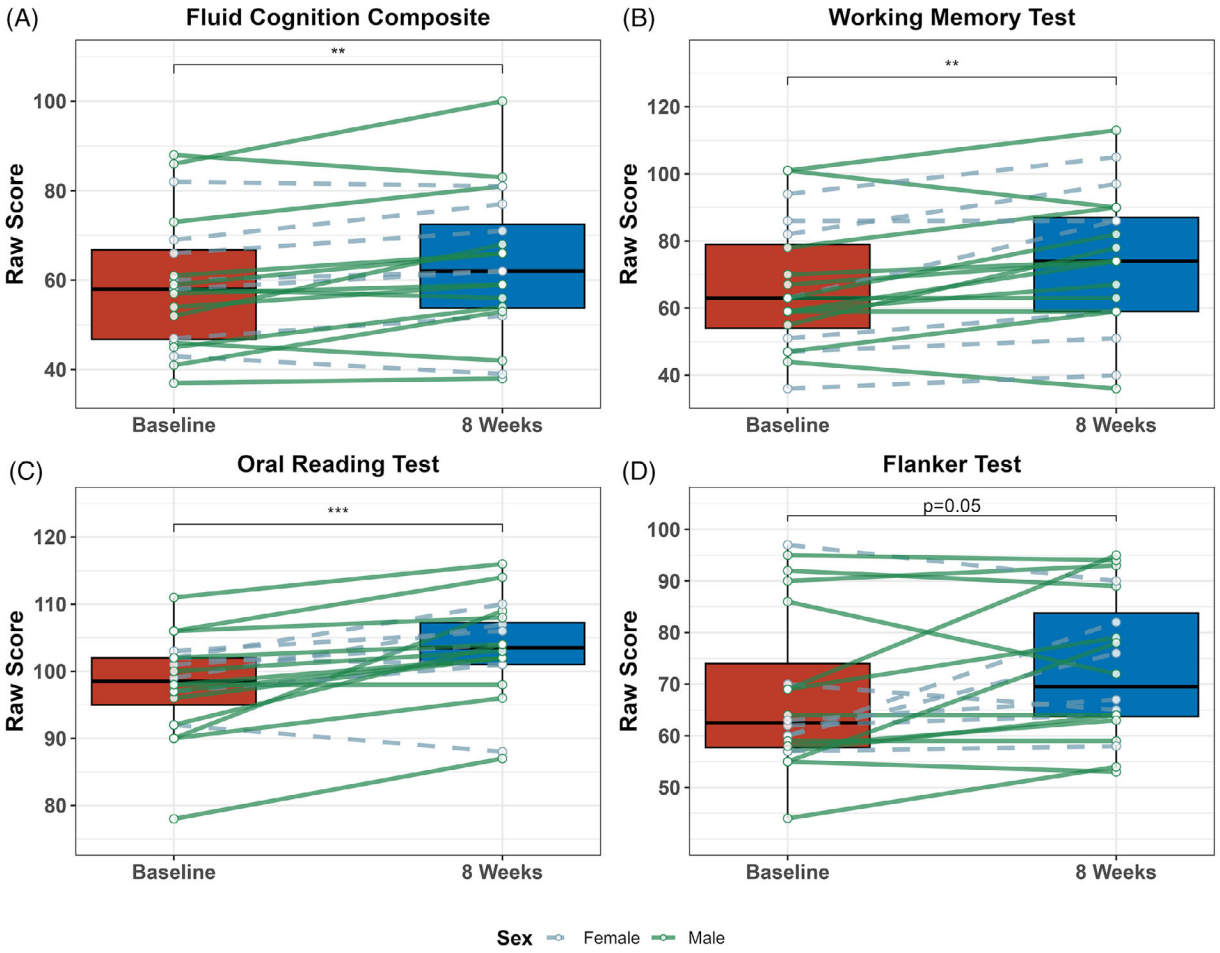

FIGURE 3 Change in cognitive measures after 8 weeks of creatine monohydrate supplementation. All scores were derived with the NIH Toolbox cognitive battery. Boxplots display values at baseline and 8 weeks, with individual changes overlaid. Solid green lines represent male participants, whereas dashed gray lines represent female participants. **$p < .01$; ***$p < .001$.

TABLE 3 Correlations between changes in brain creatine and changes in cognitive scores*

	Correlation	*p*-value
Total Cognition	0.27	0.24
Fluid Cognition	−0.03	0.89
Crystalized Cognition	0.48	0.03
Flanker Inhibitory Control and Attention	−0.10	0.66
Dimensional Change Card Sort	−0.14	0.54
List Sorting Working Memory	0.28	0.23
Picture Vocabulary	0.28	0.22
Oral Reading Recognition	0.60	0.005
Picture Sequence Memory	−0.21	0.38
Pattern Comparison	0.10	0.66

*Correlation coefficients were calculated using Pearson correlation. Significance was set at $p < 0.05$.

practice effects are generally low in AD[38] and modest in the NIH Toolbox,[39] because this was a single-arm trial, we cannot rule out the possibility that improvements may be the result of artifact (test–retest, placebo, and so on). These results merely provide preliminary support for our hypothesis that CrM may be beneficial for cognitive function in AD and suggest that future efficacy trials comparing the effect of CrM against placebo on the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) battery—a common cognitive battery administered in AD clinical trials[40]–are needed to generate evidence that can be compared to other AD clinical trials.

CABA is the first trial to investigate CrM supplementation as a potential adjuvant therapy in humans with AD. Our results are aligned with the results of previous preclinical studies in AD mouse models. These studies suggest that CrM supplementation improves brain mitochondrial function and cognition,[12] with potential differential cognitive effects between males and females; improves brain Aβ and tau;[11] and enhances memory by upregulating the mammalian target of rapamycin (mTOR) complex 1.[41] These potential benefits may be conferred through several bioenergetic mechanisms including increasing the Cr/PCr ratio, reducing oxidative stress, and reducing inflammation.[14] In contrast to one preclinical study,[12] sex did not influence the cognitive results of our study; however, these possible differential effects should continue to be considered and investigated in future trials.

Determining whether AD patients benefit from CrM supplementation will require further investigation. CABA's study design limitations prevent the ability to make conclusions of efficacy; thus we urge caution when interpreting these results. Nonetheless, our study provides the first evidence in humans that CrM supplementation is feasible and may increase brain Cr and offer cognitive benefits to patients with AD. Should CrM provide benefit, the public health implications may be substantial given AD cases are anticipated to rise and CrM is cost-effective with a good safety profile.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All human subjects provided written informed consent in compliance with institutional guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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