

Role of Medium-Chain Triglycerides for Prevention of Alzheimer's Disease

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DEMENTIA
a public health priority

What are the symptoms?

Who is affected?

What is the cause?

What does it cost?

Dementia is the single largest health issue in the 21st century, and Alzheimer's disease represents 50-70% of all dementia cases

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Alzheimer's disease
Alois Alzheimer

- Characterised by the accumulation of Amyloid plaques (Amyloid- β) and neurofibrillary tangles (tau)
- Risk factors:
 - Cardiovascular risk
 - Metabolic syndrome
 - Diabetes
 - Lifestyle choices

Healthy Neuron

Healthy Brain vs. Severe AD

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Brain Metabolism in Alzheimer's disease

- Brain requires large amounts of energy, mainly glucose, however in AD
 - ↓ glucose uptake & metabolism
 - ↓ energy
 - ↓ cognitive performance
- Only significant back-up energy source for the brain are ketones

Medium-chain triglycerides (MCT) are quickly digested into Medium-chain fatty acids (MCFA), which are then absorbed and transported to the liver where they are preferentially metabolized into energy in the form of ketone bodies.

Fat storage
 Diet
 Medium-chain fatty acids from coconut oil

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A ketogenic diet improves cognition in Alzheimer's disease: Results of a 6-month MCT

Capric Acid (C10) 42%
Caprylic Acid (C8) 58%

15g twice daily MCT oil over 6 months

- Plasma ketone increased by 247%
- Positron Emission Tomography (PET) scan, brain ketone metabolism increased by 230%

Measures of cognition improved compared to baseline

- Episodic memory
- Attention & processing speed

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Message & Action

The effect of medium-chain triglycerides (MCT) supplementation on cognitive performance in Alzheimer's disease: A randomized controlled trial

3 Groups supplemented for 4 weeks:

- Placebo-consume 0g (placebo gel with similar caloric intake)
- Group 1- consume 12g MCT supplement (gel)
- Group 2- consume 18g MCT supplement (gel)

When compared to placebo, MCT ingestion significantly enhanced cognitive performance in tasks of trail making and digit span.

There was no significant difference amongst the 2 MCT groups

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Coco-MCT in AD: Study Design

+ Coconut Oil = ?

<p>Cognitively normal men & women</p> <p>50-77 years old (n=20)</p> <p>MQ Health Clinic</p> <p>Once a week for 9 weeks (including baseline and end-of-treatment testing)</p>	<p>MCT oil derived from coconut oil (CocoMCT®)</p> <p>7-week sequential consumption- oral</p>	<p>Phase 1 clinical trial</p> <p>Primary Aim: Safety and dosage effects</p> <p>Secondary Aim: Effects on cognition</p>	<p>Blood Lipids</p> <p>Ketone Levels</p>	<p>Other important factors measured</p> <p>Cognitive Performance</p> <p>Pre-, Mid- and Post- Intervention</p>
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Coco-MCT in AD: Study Design

Stage	1	2	3	4	5	6	7	8
Intervention	5mL water 3 times daily	5mL CocoMCT® 3 times daily	10mL CocoMCT® 3 times daily	15mL CocoMCT® 3 times daily	20mL CocoMCT® 3 times daily	25mL CocoMCT® 3 times daily	30mL CocoMCT® 3 times daily	35mL CocoMCT® 3 times daily
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Assessments	Assessments: Pre (Baseline)		Assessments: Mid				Assessments: Post (End-of-Treatment)	

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Assessments

Initial

- Anthropometric Measures
- Blood Pressure

Blood Tests

- Lipid Profile
- Lipoprotein Profile
- Plasma Fatty Acids
- Glucose
- Ketones
- Full Blood Count
- E'LFT's
- Insulin
- AD-Biomarkers
- Interleukin 17
- Postprandial Ketone
- Postprandial Glucose

Questionnaires

- Memory Complaint Questionnaire (MAC-Q)
- Geriatric Depression Scale (GDS)
- Activities of Daily Living Questionnaire (ADLQ)
- Food Frequency Questionnaire (FFQ)
- 3-Day Food Record
- International Physical Activity Questionnaire (IPAQ)
- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
- World Health Organisation Quality of Life (WHOQOL-BREF)


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Cognitive Assessments

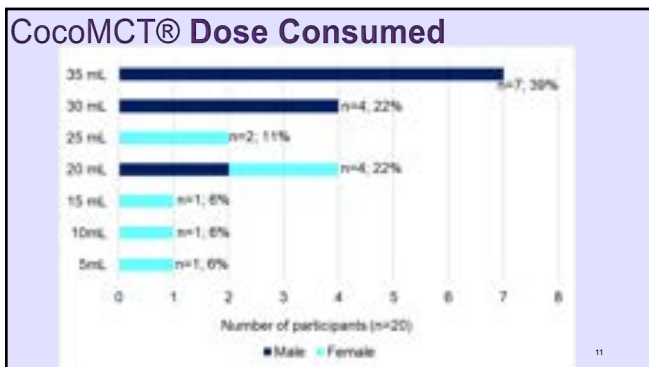
Neuropsychological

- Montreal Cognitive Assessment (MOCA)
- Trail Making Tests
- Verbal Fluency (Phonemic, Semantic, Action)
- National Institutes of Health- Executive Abilities: Measures and Instruments for Neurobehavioural Evaluation and Research (NIH EXAMINER) Computer-Based Battery
 - Flanker
 - Set Shifting
 - Continuous Performance Task
 - Dot Counting
 - nBack
 - Saccades/Antisaccades



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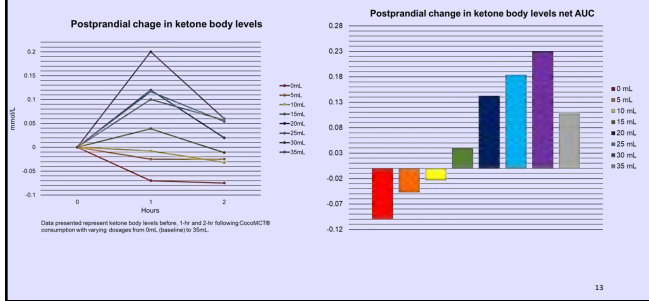


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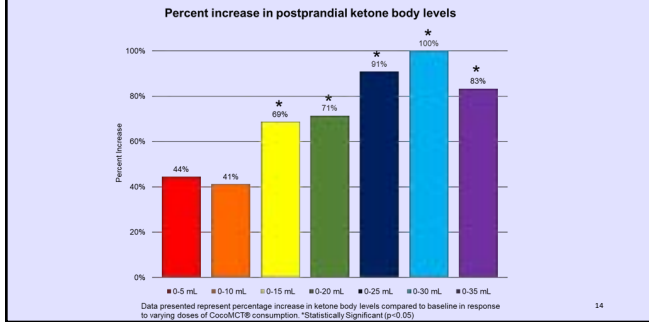
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Ketone Body Results



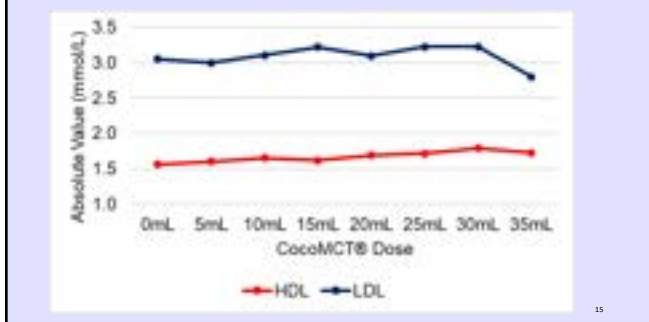
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Ketone Body Results



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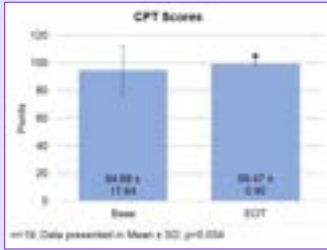
Blood Lipid Results



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Cognitive Results: Baseline to EOT

• Non-parametric Wilcoxon Signed Rank Test was performed to compare cognitive performance. Significant improvement shown as $\alpha=0.05$.

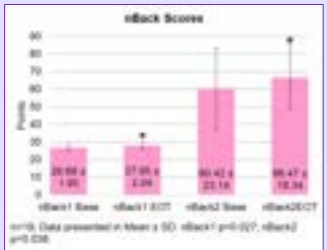


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Cognitive Results: Baseline to EOT

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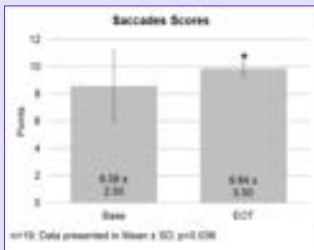


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Cognitive Results: Baseline to EOT

• Non-parametric Wilcoxon Signed Rank Test was performed to compare cognitive performance. Significant improvement shown as $\alpha=0.05$.




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Summary

Intervention: consumed increasing doses of coconut oil 3 times a day for 7 weeks



5mL water 3 times daily	5mL CocoMCT® 3 times daily	10mL CocoMCT® 3 times daily	15mL CocoMCT® 3 times daily	20mL CocoMCT® 3 times daily	25mL CocoMCT® 3 times daily	30mL CocoMCT® 3 times daily	35mL CocoMCT® 3 times daily
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Primary Aim: To determine a safe and effective dose (to increase ketone bodies) of CocoMCT® consumed
 Secondary Aim: To examine the effects of CocoMCT® consumption on cognition

Measures: blood lipids, ketone bodies, cognition

Outcomes:

- Increase in plasma ketone body levels
- Improved cognitive performance in areas of working memory, inhibitory processing, problem solving and motor control



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Conclusion

CocoMCT® consumption increased postprandial ketones, without significant impact to blood lipids or BMI.

CocoMCT® consumption showed improvement in cognitive performance in cognitively normal older adults.

Further longitudinal study with a larger sample size is warranted to further assess cognitive performance long-term.

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Recent Publication (August 2022)

Medium-chain fatty acids for the prevention or treatment of Alzheimer's disease: A systematic review and meta-analysis

Carolina B. Castro, Cintia B. Dias, Heidi Hillebrandt, Hamid R. Sahraei, Pratiksha Chatterjee, Tejal M. Shah, Stephanie J. Fuller, Manohar L. Garg, Ralph N. Martins


Background: In preclinical Alzheimer's disease (AD) the brain gradually becomes insulin resistant. As a result, brain glucose utilization is compromised, causing a cellular energy deficit, which leads to the accumulation of free radicals, consequently increasing inflammation and damaging neurons. When glucose utilization is impaired, ketone bodies offer an alternative energy source. Ketone bodies are synthesized from fats, obtained either from our diet or adipose tissue. Dietary medium-chain fatty acids (MCTA) are preferentially metabolized into ketone bodies, having the potential to supply the insulin-resistant brain with energy.

Aim: This systematic review and meta-analysis aims to review the effect of MCTA supplements on circulating ketone bodies and cognition in individuals with subjective cognitive decline, mild cognitive impairment, and AD.

Methods: A comprehensive search of electronic databases was performed on 12 August 2019 to retrieve all suitable publications; alerts were then set to identify any publications after the search date up until 31 January 2021.

Results: All studies (n=12) assessing change in blood ketone body levels due to MCTA supplementation reported a significant increase. Cognition outcomes (n=13), however, varied reporting either no improvement (n=4), improvement (n=7) or improvement only in apolipoprotein E allele-4 (APOE ε4) non-carriers (n=2). One study reported an increase in regional cerebral blood flow in APOE ε4 non-carriers and another reported an increase in energy metabolism in the brain.

Conclusion: This review provides evidence that supplementation with MCTA increases circulating ketone body levels resulting in increased brain energy metabolism. Whether this MCTA-mediated increase in brain energy metabolism improves cognition remains to be determined.



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Medium-chain fatty acids in combination with a multidomain lifestyle intervention in Alzheimer's disease prevention



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COMBAT-AD

Cognition, Molecular Biomarkers And preventative Treatments for Alzheimer's Disease



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Study Aims

- Determine the effect of MCFA supplementation combined with a multimodal lifestyle intervention plan on:
 - Cognitive function and quality of life
 - Neuroimaging and blood-based biomarkers of Alzheimer's disease
- Explore between-subject differences (e.g., age, sex, comorbidities, cognitive reserve) in response to the intervention
- Evaluate the intervention for cost-effectiveness

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
Research Plan

- Primary Outcomes:**
 - Cognition
 - Quality of life
- Safety outcomes:**
 - Side effects
 - Glucose
 - Insulin
 - Blood lipids
 - Liver function
 - Renal function
 - Anthropometric measurements
 - Blood pressure
 - ECG
- Secondary Outcomes:**
 - Between-group differences in post-dose circulating ketone body levels (fasting and postprandial)
 - Cerebral blood flow
 - Brain FDG PET
- Tertiary Outcomes:**
 - AD Biomarkers
 - Fatty acids
 - Gut microbiome

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Study Design

 Men & women with Subjective Cognitive Decline (SCD)	 MCFA Supplement or Placebo	 Significant gastrointestinal disorder Renal/Liver disease	 Uncontrolled diabetes Arthritis Allergy to nuts or seafood History of stroke/head injury Substance misuse	 Dementia Regular consumption of any ketogenic supplement Participation in another intervention trial within 30 days of baseline
60-79 years old	24-month oral consumption with 2-week titration period	Mycardial infarction within 2 years	Uncontrolled blood lipids	
Sedentary lifestyle	Multimodal lifestyle intervention	Hypertension	Neuropsychiatric disorder	

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For 24 months participants will:

- ✓ Consume MCFA-rich supplement
- ✓ Follow a multidomain lifestyle approach
 - Physical activity
 - Dietary advice (i.e. MIND diet)
 - Brain training
 - General health education
- ✓ Be assessed every 6 months

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Screening

Dementia Status:

- Montreal Cognitive Assessment (MOCA)
 - Score >26 required

SCD:

- Memory Assessment Clinic Questionnaire (MAC-Q)
 - Score >25 required
- McCusker Subjective Cognitive Impairment Inventory (McSCI)
- Short form of the Informant Questionnaire of Cognitive Decline in the Elderly (Short IQCODE)

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Randomisation

Randomisation of participants to supplement or placebo (1:1 ratio) will be performed using a randomisation table created by an individual not involved in the study, using a computer-generated system to ensure allocation of concealment.

Participants, researchers and study statisticians will be blinded to the treatment allocation

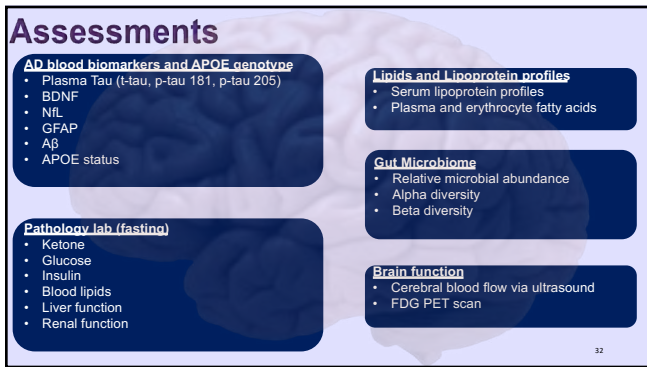
Randomisation will be undertaken in blocks of 16, stratified by age, sex and APOE ε4 carriage.

Since all participants will follow the multidomain lifestyle program of the AU-ARROW study, randomisation to supplement or placebo will be independent from the parent study.

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Neuropsychological Assessments

Measure	Domain
Telephone Montreal Cognitive Assessment (MOCA)	Short-term memory, executive functions, attention, concentration, working memory, language, orientation to time and place
Clinical Dementia Rating (CDR)	Severity of dementia
Story Memory (SR)	Verbal contextual memory
Digit Symbol Substitution Test (DSST)	Complex information processing
Mini Mental State Exam (MMSE)	Orientation, Attention, Memory, Language, and Praxis
Free and Cued Selective Reminding Test (FCSRT)	Verbal learning, attention, and memory
Visual Paired Associates Learning (VPA)	Visual memory and learning
Number Span	Verbal attention, working memory
Trail Making Test (TMT) A and B	Executive function, set shifting
Verbal Fluency- FAS	Language skills, verbal fluency
Verbal Fluency- Animals, Vegetables, Fruits	Semantic knowledge, verbal fluency
Clock Drawing Task	Visual constructive ability
Cogstate One Card Learning (OCL)	Visual learning
Cogstate Face Name Associative Memory Exam (FNAME)	Memory
Cogstate Behavioral Pattern Separation Object (BPSO)	Memory
Cogstate Detection (DET)	Psychomotor function
Cogstate Identification (IDN)	Attention
Cogstate One Back (OBS)	Working memory
Cambridge Contextual Reading Test (CCRT)	Pre-morbid intellectual functioning

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Neuropsychological Assessments							
Task	Screen	Baseline 1	Baseline 2	Month 6	Month 12	Month 18	Month 24
Screening	IMcGA	X					
	CDR	X					
AU-ARROW	ECSTRT	A		B	C	A	B
Neuropsychological Test Battery (NTR) Primary Outcomes	SR	"Greg Fortune"		"David Lewis"	"Laura Jackson"	"Greg Fortune"	"David Lewis"
	VPA	A		B	C	A	B
	Number Span (Forwards, Backwards, Sequencing)	A		B	C	A	B
	Verbal Fluency (FAS, Animal, Fruit, Vegetable)	X		X	X	X	X
	DSST	A		B	C	A	B
	TMT A & B	X		X	X	X	X
Secondary/	MMSE	X		X	X	X	X
Experimental Outcomes	Clock Drawing Task	X		X	X	X	X
	Cogstate OCL			X	X		X
	Cogstate FNAME			A	B		C
	Cogstate BPS-O			X	B		C
	Cogstate DET			X	X		X
	Cogstate IDH			X	X		X
	Cogstate OSK			X	X		X
	BrainHQ Assessments			X	X	X	X
Other	CCRT	X					
