Circulating and gut-derived metabolites linked to cognitive function in later life

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Introduction

- Alzheimer's disease and related dementias are increasing in prevalence, emphasizing the need to identify biological disease markers.[1]
- The gut–brain axis represents a bidirectional pathway through which microbial metabolites may influence neuroinflammation, neurotransmission, and cognitive function.[2]
- Metabolomic profiling enables measurement of both circulating (plasma) and gut-derived (fecal) metabolites implicated in energy metabolism and amino acid pathways.[3]
- Few studies have integrated plasma and fecal metabolomic profiles to examine associations with global and domain-specific cognitive performance in older adults at-risk for dementia.[4]

Hypotheses:

1. Higher plasma concentrations of serine, methylamine, and citric acid will be positively associated with global cognitive performance (MoCA scores), whereas higher plasma concentrations of capric acid will be negatively associated with MoCA scores in older adults.
2. Higher fecal concentrations of dihydroxyacetone and higher plasma concentrations of tyrosine will be negatively associated with executive function and processing speed performance in older adults.

Methods

Study Design:

- Parallel-arm clinical trial, participants were randomized to attend a Mediterranean Diet or a Modified Mediterranean Ketogenic Diet group program
- Participants (N = 65) at risk for dementia. Included community adults ages 56-85 years with and without mild cognitive impairment.

Independent Variables:

- Fecal and Plasma Metabolites collected at baseline assessment

Dependent Variables:

- Cognitive scores evaluated via a screening telephone MoCA final score (final education-corrected scores were used).
- Age and Education corrected T-scores from 8 subtests from the NIH Toolbox Cognitive Battery were used (Dimensional Change Card Sort Test, The Face Name Associative Memory Exam, The Flanker Inhibitory Control and Attention Task, The List Sorting Working Memory Test, The Picture Sequence Memory Test, The Ray Auditory Verbal Learning Test, and The Ray Auditory Verbal Learning Test Delay).

Analyses:

- Pearson correlations in SPSS (v31) were used to examine relationships between fecal, plasma metabolites, and cognitive measures.
- Fecal and Plasma Metabolomes were measured using the global untargeted approach via a high-throughput Nuclear Magnetic Resonance system. Quantified using Chenomx 8.6 and total intensity normalization was performed prior to downstream analysis.

Results

Sample Characteristics:

Table 1: Demographic Information for Participants

Variable	Category	Mean (SD)	Valid Percent (%)
Age (years)		70.03 (5.88)	
Gender			
Male	N = 18		25.4%
Female	N = 53		74.6%
Race/Ethnicity	White		43.7%
	African American		43.6%
	Hispanic		5.6%
	Other		4.2%
Education Level	Less than High School		1.4%
	High School Diploma		7%
	Some College		8.5%
	Associate's degree		9.9%
	Bachelor's Degree		26.4%
	Masters		35.2%
	Doctorate		11.3%

- Participants (N=65) were adults aged 56-85 years, with or without mild cognitive impairment. The sample consisted primarily of females from a rural community, most of whom identified as White and held a master's degree.

General Trends in Metabolites:

Table 2: Significant Pearson Correlations between Plasma Metabolites and Cognitive scores at Baseline

Cognitive Test	Plasma Metabolite	R value	P value
MoCA Final Score	Capric Acid	-.397*	.027
	Citric Acid	.485*	.012
	Glutamine	.315*	.017
	Methylamine	.462*	.018
DCCS	Methylamine	-.450*	.021
Speed Matching	Acetate	.262*	.049
	Alanine	.279*	.035
	Lactate	.303*	.022

- Significant positive correlations were observed between Speed Matching performance and acetate ($r = .262$, $p = .049$), alanine ($r = .279$, $p = .035$), and lactate ($r = .303$, $p = .022$).
- MoCA final score was similarly negatively correlated with capric acid ($r = −.397$, $p = .0027$).
- In contrast, positive correlations were observed between citric acid and MoCA final score ($r = .485$, $p = .012$).

Table 3: Significant Pearson Correlations between fecal metabolites and cognitive scores at baseline.

Cognitive Test	Fecal Metabolite	R Value	P Value
FLANKER	1,3-Dihydroxyacetone	-.360**	.005
	Tyrosine	-.280*	.031
Speed Matching	Alanine	-.269*	.039
	Methanol	-.256*	.05

- Negative correlation was observed between 1,3-dihydroxyacetone and FLANKER scores ($r = -.360$, $p = .005$).
- Negative correlations were observed between Speed Matching performance and alanine ($r = −.269$, $p = .039$), methanol ($r = −.256$, $p = .050$), and tyrosine ($r = −.411$, $p = .001$).
- Tyrosine was also negatively correlated with Flanker performance ($r = −.280$, $p = .031$).

Conclusions

Plasma Metabolites:

- Our first hypothesis was directly supported, as higher plasma citric acid, serine, and methylamine were positively associated with global cognitive performance (MoCA scores).
- Elevated plasma citric acid and lactate, key intermediates in energy metabolism, suggest that enhanced mitochondrial and glycolytic activity may contribute to improved cognitive efficiency in older adults.[5]
- Higher plasma serine and methylamine, metabolites involved in amino acid metabolism and neurotransmitter regulation, suggest a potential role in supporting synaptic function and global cognitive performance.[6]
- Higher plasma capric acid was negatively associated with MoCA scores, consistent with our hypothesis, confirming a potential link between altered fatty acid metabolism and reduced global cognitive performance in older adults.[7]

Fecal Metabolites:

- Our second hypothesis was partially supported: Higher fecal 1,3-dihydroxyacetone was negatively associated with executive function, and higher fecal tyrosine was negatively associated with processing speed and executive function performance.
- Elevated fecal 1,3-dihydroxyacetone, a glycolytic intermediate, may reflect altered microbial carbohydrate metabolism that could influence downstream energy availability relevant to executive functioning.[8]
- Higher fecal tyrosine, a precursor in catecholamine synthesis, may indicate disrupted microbial–host amino acid metabolism, potentially contributing to variability in cognitive processing efficiency.[9]

Future Directions

Long-Term and Larger-Scale Studies:

- Future research should expand on this study by conducting longitudinal and intervention-based analyses to determine whether changes in plasma and fecal metabolite profiles correspond to changes in cognitive performance over time.[10]

Mechanistic Insights and Biomarker Integration:

- Future studies could explore specific metabolic pathways (e.g., mitochondrial bioenergetics, amino acid metabolism, and gut microbial fermentation pathways) to clarify mechanistic links between metabolite variability and cognitive aging, particularly given that the present findings were cross-sectional and limited to baseline associations.[2,5,6]

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