Causal Relationships Between Blood Metabolites, Cognitive Outcomes, Brain Imaging, and CSF Biomarkers in Alzheimer's Disease: Insights from Digital-Twins

Apoorva Bharthur Sanjay[1], Deepanshi Shokeen[1], So-Youn Shin[1] and Jeanne Latourelle[1]
1. Aitia, Somerville, MA, USA

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Introduction

- Alzheimer's Disease (AD) involves cognitive decline and metabolic dysregulation, with blood metabolites linked to its development.
- However, it remains unclear whether these metabolites actively drive the disease or reflect its progression.
- Identifying causal metabolites and their relationship with biomarkers, cognition and brain structure could provide new insights into AD pathogenesis and lead to better diagnostic and therapeutic strategies.

Methods

- Data Source: ADNI (https://adni.loni.usc.edu)
- 317 Subjects (Control:MCI:Dementia=97:191:29)
- 59k Multi-omic Features (Clinical, Imaging, Biomarker, Genomic, Transcriptomic, Metabolomic) including 122 and 20 serum metabolites measured from Biocrates AbsoluteIDQ p180 and Bile Acids kit, respectively
- AD Outcomes: Cognition Measures and ATN below

Category	Measure
Amyloid (A)	CSF abeta Florbetapir (AV45) SUVR
Tau (T)	CSF pTau
Neurodegeneration (N)	Hippocampus volume Entorhinal thickness FDG PET CSF tTau

GEMINI Digital Twins Pipeline

Reverse Engineering

- Each *in silico* patient of the AD Digital Twins is comprised of an ensemble of Bayesian network models built from the training data using REFS™ causal AI platform [aitia.com]
- A Bayesian network model is a directed graphical representation of causal relationships between variables where each node is a variable, and each arrow is a conditional dependency

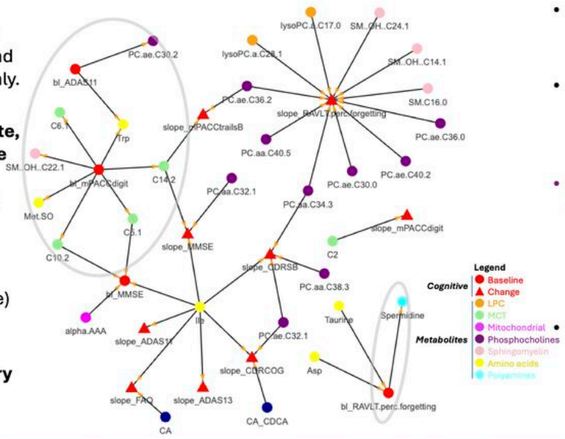
Forward Simulation

- Patient-level outcomes can be estimated in the AD Digital Twins, by *in silico* counterfactual experiments which computationally simulate patient outcome values through model interventions, known in causal inference as 'Do' operations
- These estimations are done fully adjusting for any confounding effects identified in the causal models, which is necessary in causal inference and allows approximation of randomized experiments

Results

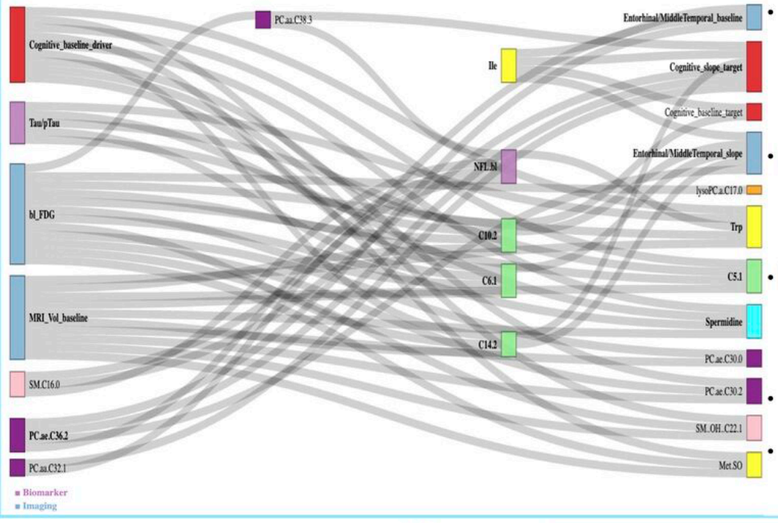
Aitia's Digital Twins identified 30 metabolites in blood with causal links to cognitive measures

- Here, we present part of the causal networks in Digital Twins highlighting "metabolite → cognitive measure" and "cognitive measure → metabolite" only.
- **Some metabolites appear to be reactive to changes in cognitive state, including those occurring during the preclinical stage** (as shown by the nodes inside of the grey circles being driven by red nodes representing baseline cognitive measures).
- mPACC digit (variation of Preclinical Alzheimer Cognitive Composite score) and ADAS11 are upstream of several metabolites, including tryptophan.
- **This suggests executive and memory deficits may precede systemic metabolic alterations.**



- **Most of the cognition-related metabolites are causal drivers of the rate of cognitive decline.**
- **Isoleucine (Ile; amino acid)**: Strongest cognitive metabolic driver affecting **ADAS**, **MMSE**, **CDR**, and **FAQ**.
- **phosphocholines** and **sphingomyelins**: Both drive a sensitive early memory marker, change rate of RAVLT percentage forgetting, while phosphocholines also drive the CDR change rate.
- **This underscores the utility of metabolites as potential biomarkers in Alzheimer's disease for early diagnosis and intervention.**

Details of Cognition-Related Metabolites with Causal Links to ATN Biomarkers: Some Respond to ATN Changes, While Others Contribute to ATN Progression

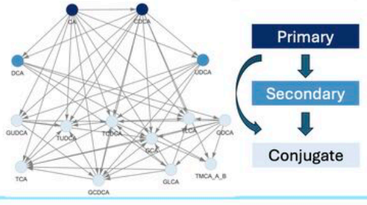


- We further evaluated cognition-related metabolites for their connections with ATN biomarkers, and found that these are more causally linked to **tau and neurodegeneration** than to **Aβ** in Digital Twins, supporting the view that **cognitive decline aligns more with tau pathology** than amyloid burden.
- **Tau/pTau**: Upstream of **medium-chain triglycerides (MCT)**, **spermidine** and **tryptophan**. MCTs especially are reactive to early cognitive state as well as tau/pTau, FDG, and hippocampal volume, while driving middle temporal atrophy.
- **FDG & MRI volumes**: These ND related network hubs drive many cognition-related metabolites, including **PC.ae.C30.0** (phosphocholines) and **lysoPC.a.C17.0** (lysophosphatidylcholine), which affect **cognitive decline rate**.
- **Isoleucine** (Ile; amino acid): Drives both **cognitive and structural changes** in key brain regions.
- **PC.ae.C36.2** (phosphocholines): Central phosphocholine influencing **cognition**, **NFL**, and **temporal lobe structure**.

Proof of Concept – Known Biology

Aitia's Digital-Twins reverse-engineered known bile acid differentiation activity

- We successfully recreated the classical bile acid pathways from data alone in AD Digital Twins (presented here where arrows represent upstream–downstream or causal relationships between bile acids)
- The primary bile acids (CA and CDCA) causally drive the secondary bile acids such as DCA and LCA, both of which then drive their conjugation with glycine or taurine, but not the other way around



Conclusions

- These findings highlight the critical role of Tau pathology, hippocampal atrophy, and glucose hypometabolism in driving metabolic alterations in AD.
- Some metabolites, e.g. **Isoleucine and PC.ae.C36.2**, are causal drivers of cognitive decline and neurodegeneration, while others, like **Tryptophan and Spermidine,** reflect disease progression, offering potential biomarkers for early diagnosis and treatment.
- Metabolites, like MTCs **C10.2, C5.1, C14.2, and C6.1**—downstream of cognitive, tau/pTau, FDG, and hippocampal changes and linked to middle temporal atrophy—may act as intermediates in feedback loops between neuronal stress, metabolism, and degeneration