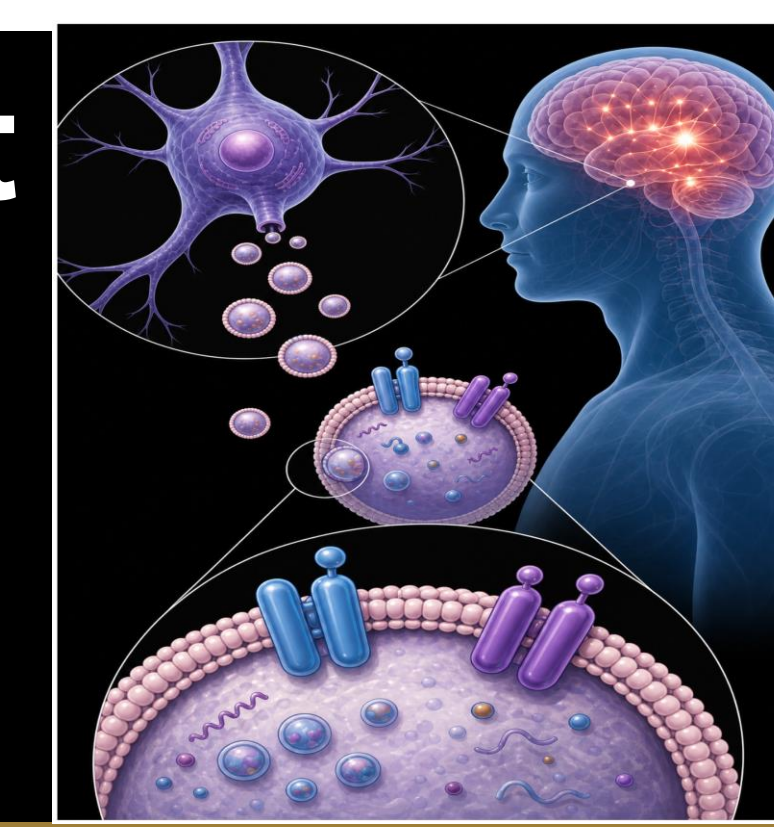


Plasma neuronal vesicle MCT2 and GLUT3 predict dietary intervention responses in mild cognitive impairment, stratified by APOE-ε4 status



Gagan Deep¹, Ashish Kumar¹, Yixin Su¹, Sangeeta Singh¹, Fang-Chi Hsu², Thomas C. Register³, Tina E Brinkley¹, Courtney L Sutphen³, Shannon L Risacher¹, Kiran K Solingapuram Sai⁴, Melissa M Rundle¹, Suzanne Craft¹
¹Wake Forest University School of Medicine, Winston Salem, NC, United States; ²Department of Biostatistics and Data Science, Division of Public Health Sciences; ³Department of Pathology, Section on Comparative Medicine; ⁴Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States.

1 ABSTRACT

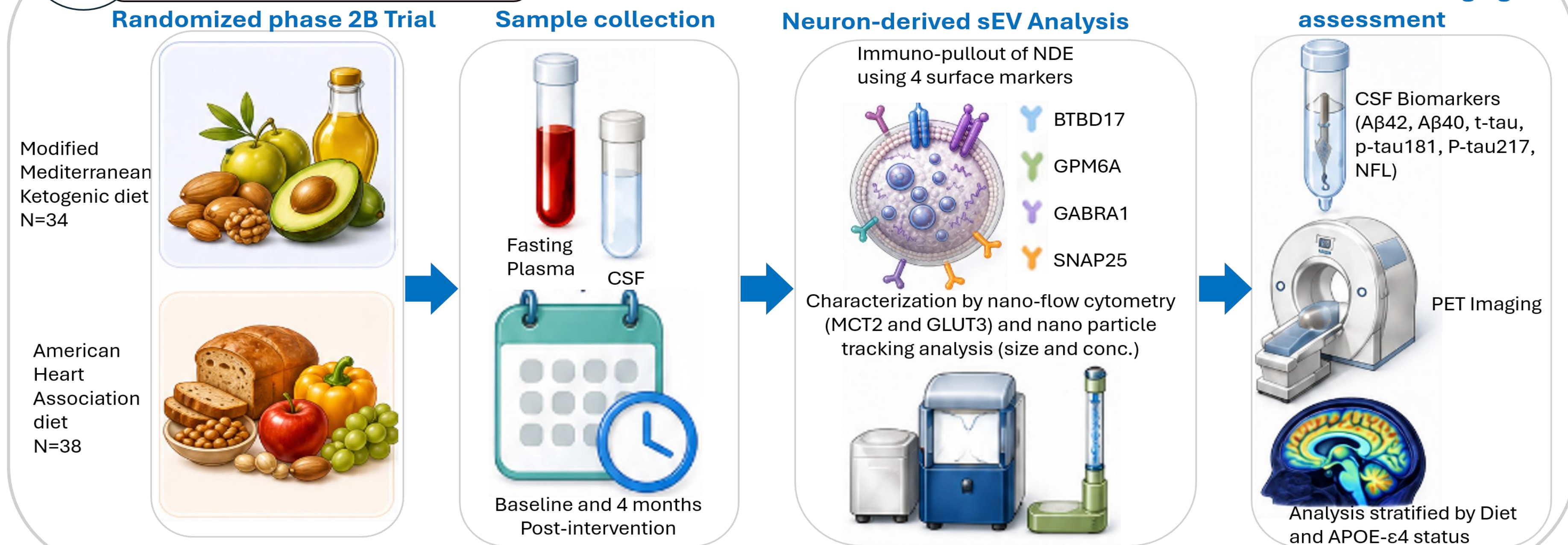
Background: Modified Mediterranean-Ketogenic diet (MMKD) has shown favorable effects on CSF amyloid beta (Aβ) and cerebral ketone uptake in adults at risk for or with mild cognitive impairment (MCI), compared with a low fat American Heart Association diet (AHAD). Neurons rely on GLUT3 for glucose transport that is reduced in Alzheimer's disease (AD). MCT2, a high affinity monocarboxylate transporter, has potential to be modulated by diet and ameliorate bioenergetic deficits in AD. Plasma neuron-derived small extracellular vesicles (NDE) offer a window into neuronal biology to track AD pathology and intervention effects. In a randomized Phase 2B trial, we assessed whether neuronal expression of MCT2 and GLUT3 predicted responses to MMKD and/or AHAD interventions in individuals with MCI.

Methods: Fasting plasma was obtained from participants at baseline and after completion of a 4-month MMKD diet (n=34) or AHAD diet (n=38). CSF biomarkers (Aβ42, Aβ40, t-tau, p-tau181, NFL, p-tau217), and FDG and 11C-acetoacetate PET were assessed at baseline and post-intervention. NDE were immuno-pulled-out from plasma using 4 novel surface markers (BTBD17, GPM6A, SNAP25 and GABRA1), characterized for size, concentration, and surface expression of MCT2 and GLUT3 by nano-flow cytometry. Correlations were assessed for NDE data with CSF biomarkers and PET measures with stratification by dietary arms (MMKD or AHAD) and APOE-ε4 status.

Results: There was no effect of diet on NDE size or concentration. In MMKD participants, baseline NDE GLUT3 levels inversely correlated with change in CSF p tau181 (r=-0.355, p=0.046) which was prominent in APOE-ε4 non carriers (r=-0.582, p=0.003). In MMKD APOE-ε4 carriers, the change in CSF Aβ42/40 ratio was inversely correlated with baseline NDE MCT2 (r=-0.800, p=0.009) and NDE GLUT3 (r=-0.783, p=0.012) levels. In AHAD participants, baseline NDE MCT2 levels positively correlated with change in CSF Aβ40 (r=0.354, p=0.036); while among AHAD APOE-ε4 carriers, higher NDE GLUT3 correlated positively with change in CSF Aβ42 (r=0.830, p=0.002) and Aβ40 (r=0.818, p=0.003). Across both groups, change in NDE-MCT2 levels positively correlated with change in FDG uptake in specific brain regions- cingulum (r=0.394, p=0.030) and temporal (r=0.369, p=0.044).

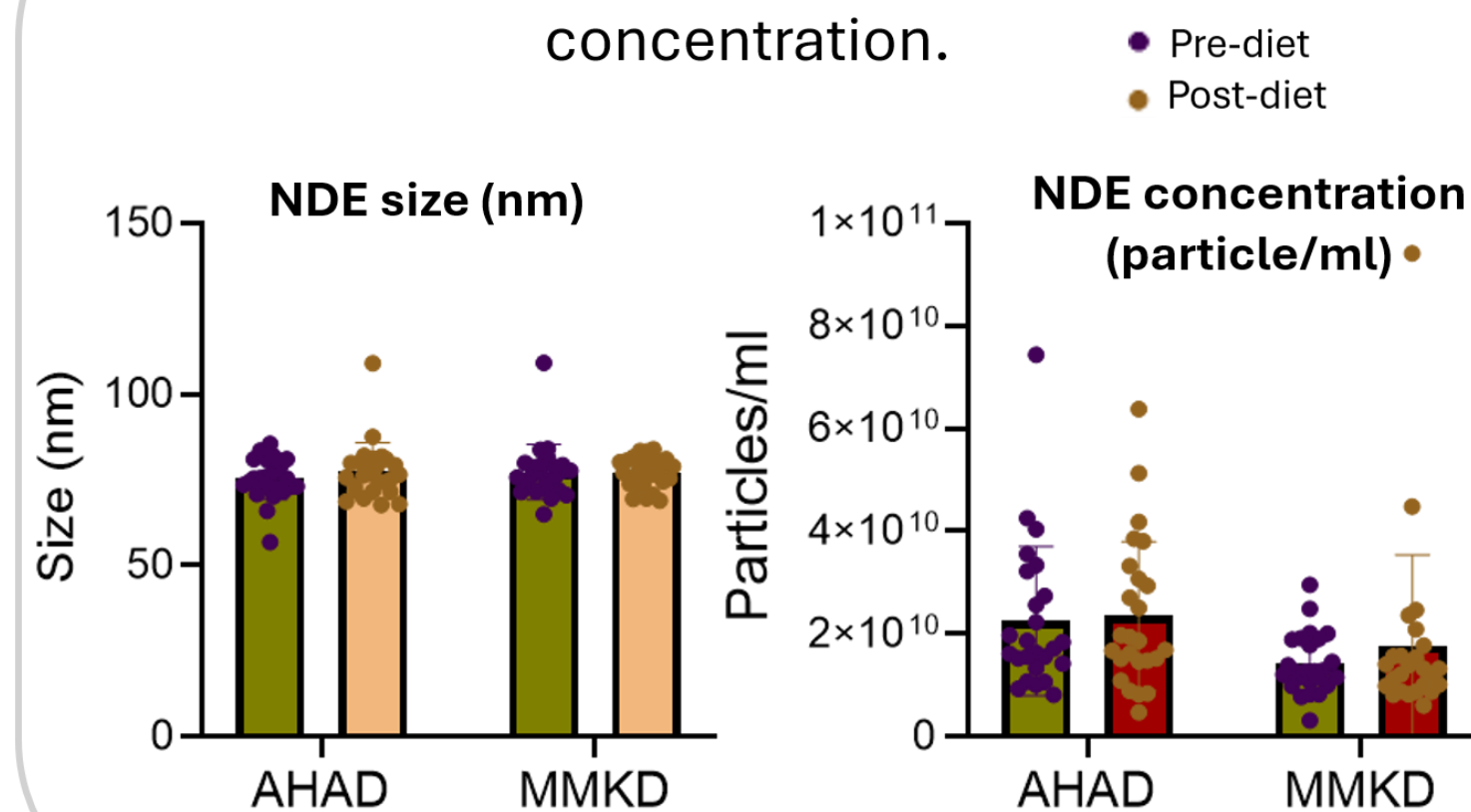
Conclusions: Overall, NDE profiling offers a promising mechanistic readout of diet-induced neuronal metabolic shifts and a potential tool for precision nutrition strategies in AD.

2 METHODOLOGY

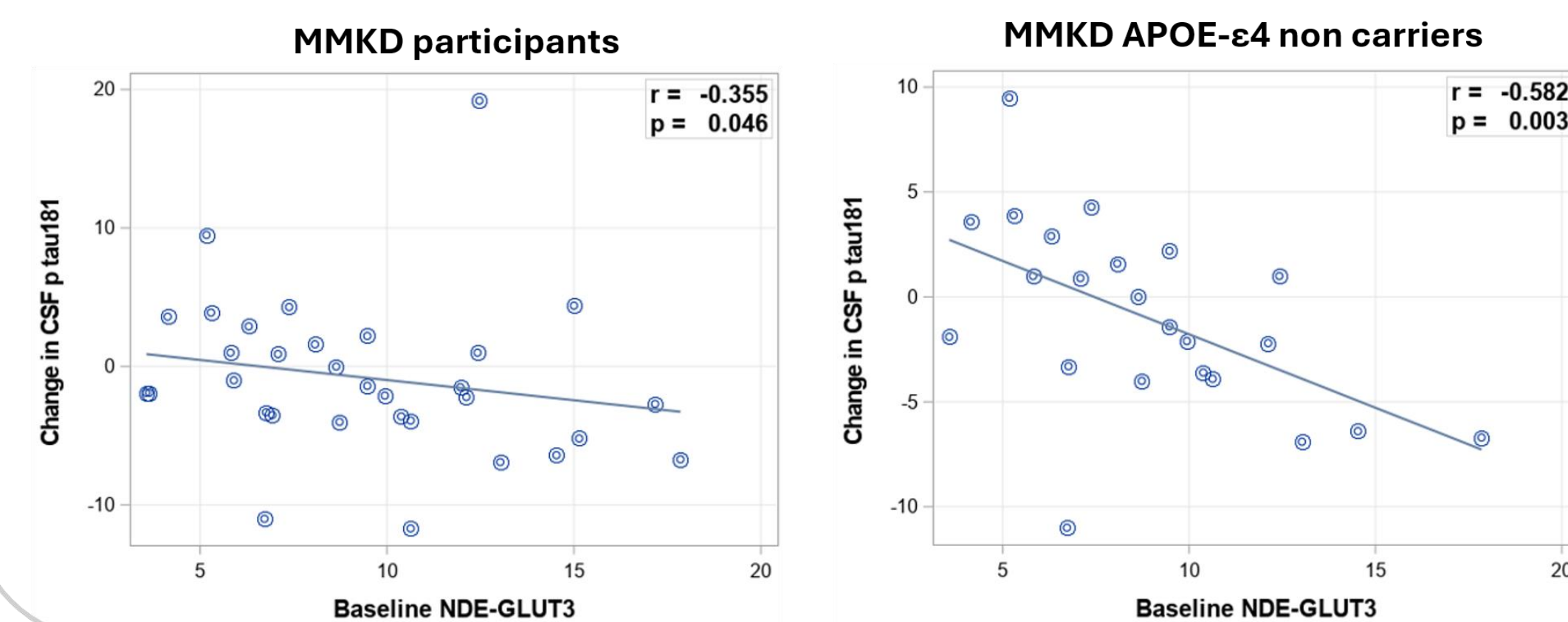


3 Results

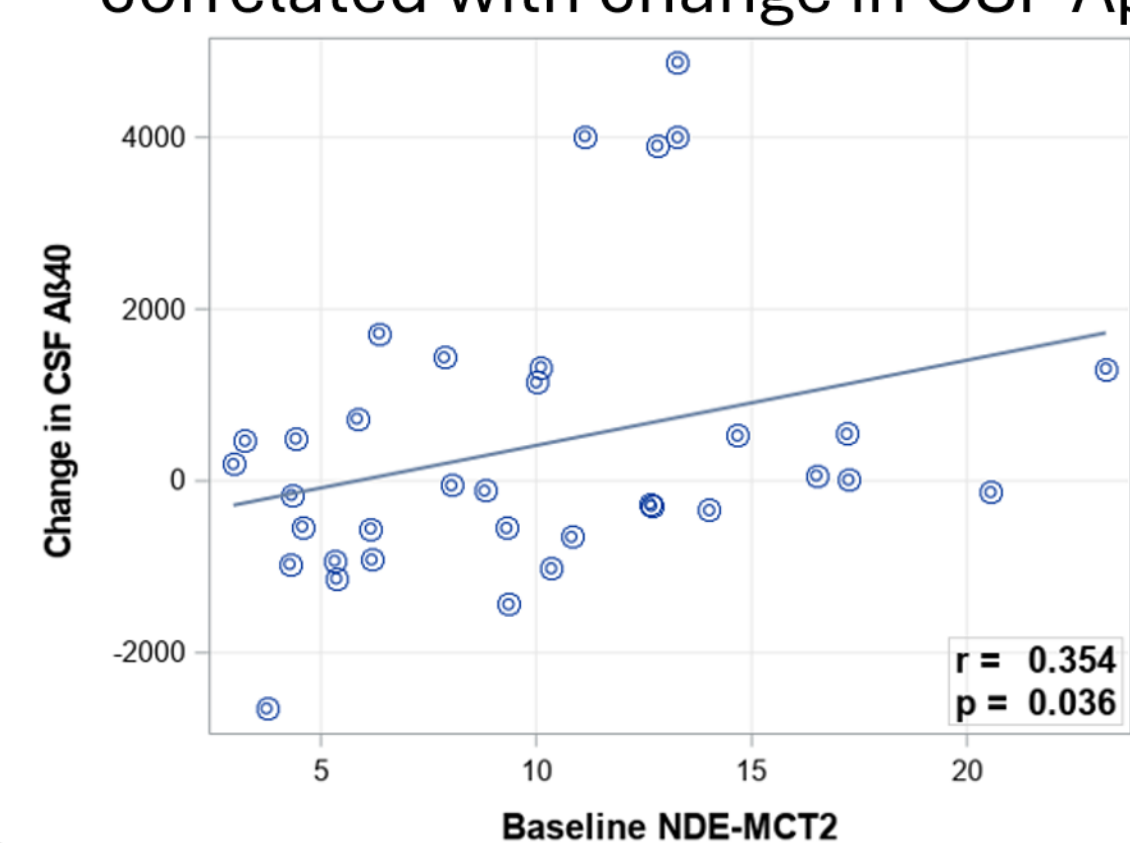
I. There was no effect of diet on NDE size and concentration.



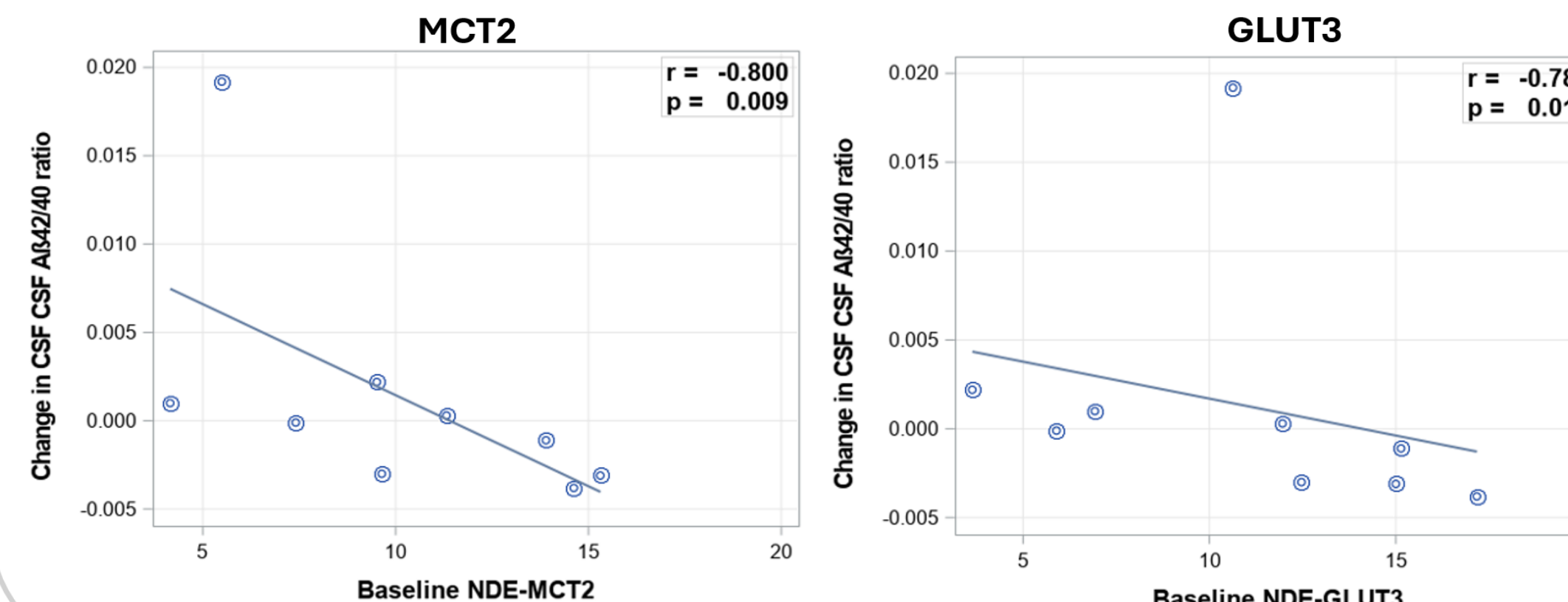
II. MMKD: Baseline NDE GLUT3 inversely correlated with change in CSF p-Tau181; effect more prominent in APOE-ε4 non carriers.



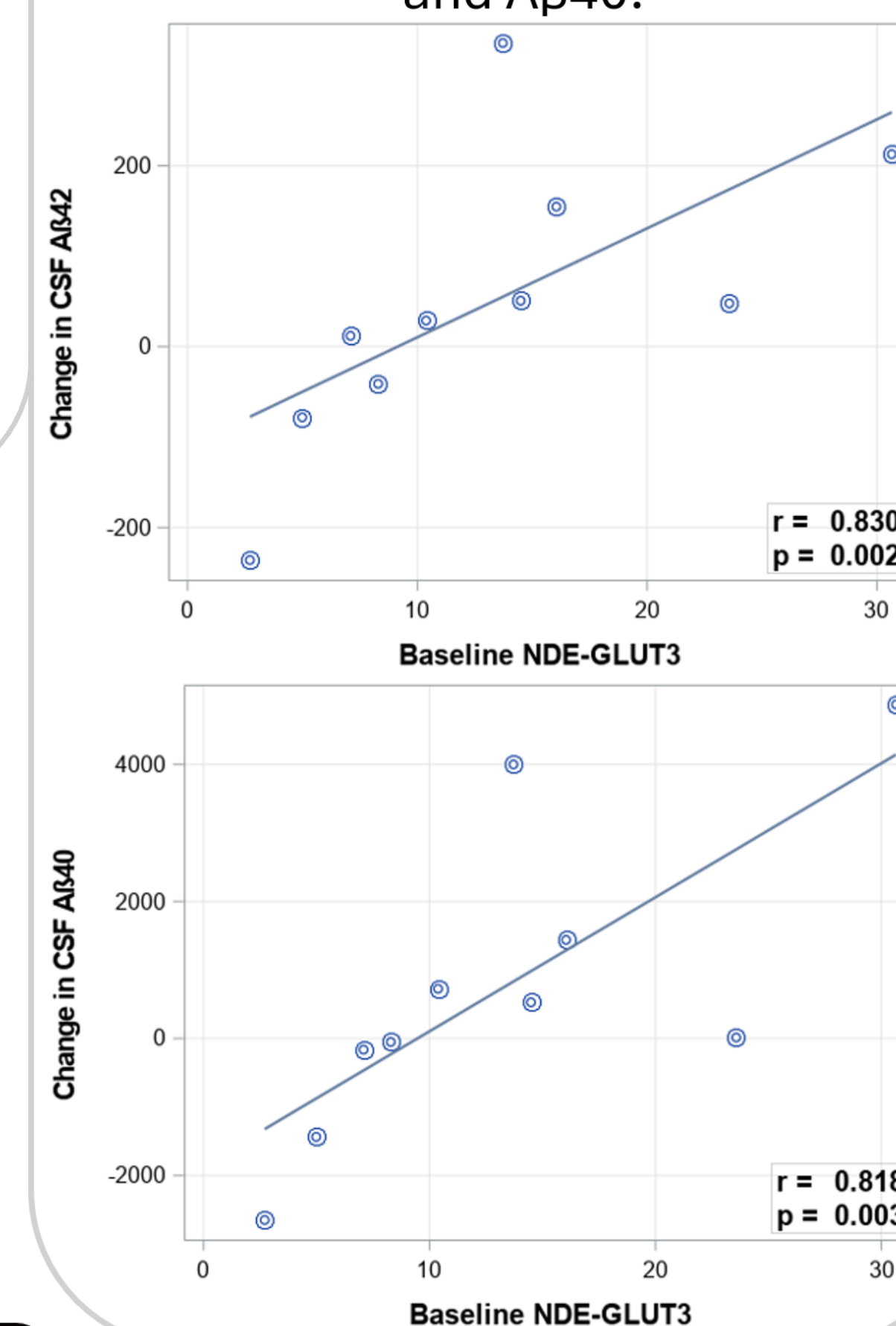
III. AHAD: Baseline NDE MCT2 positively correlated with change in CSF Aβ40.



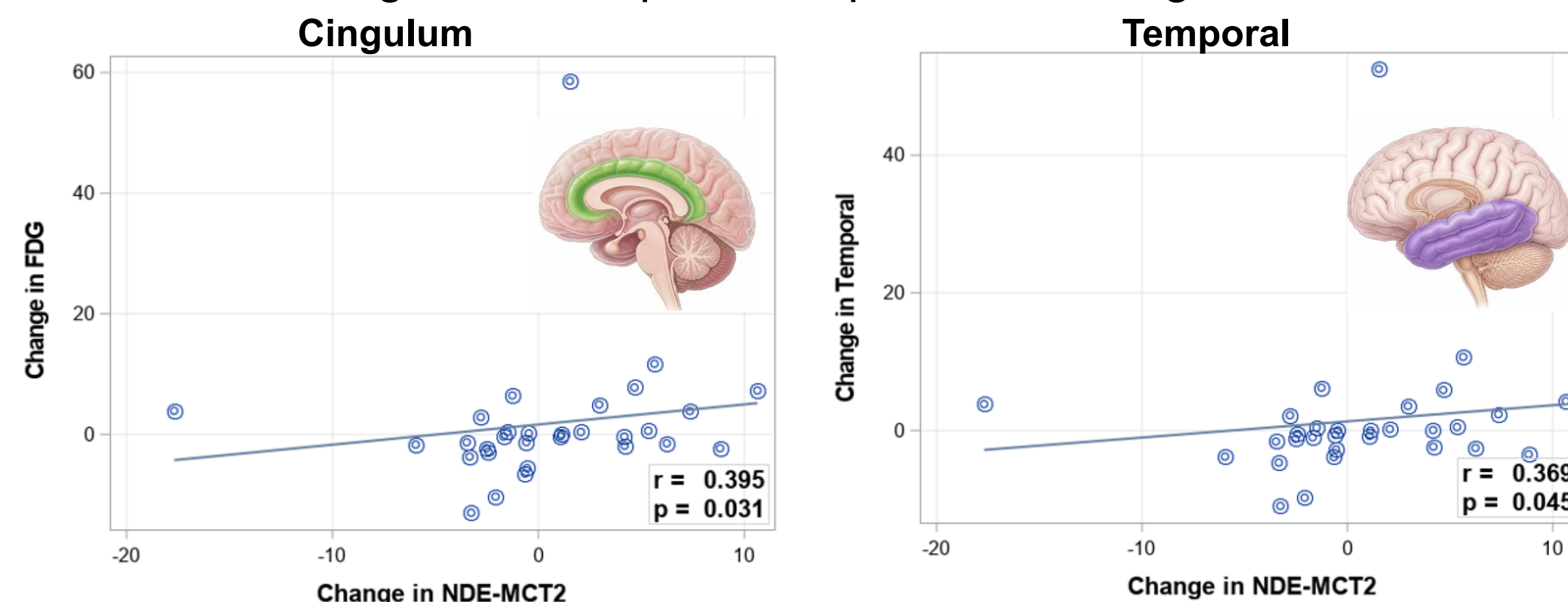
IV. MMKD APOE-ε4 carriers: Change in CSF Aβ42/40 ratio inversely correlates with baseline NDE MCT2 and GLUT3.



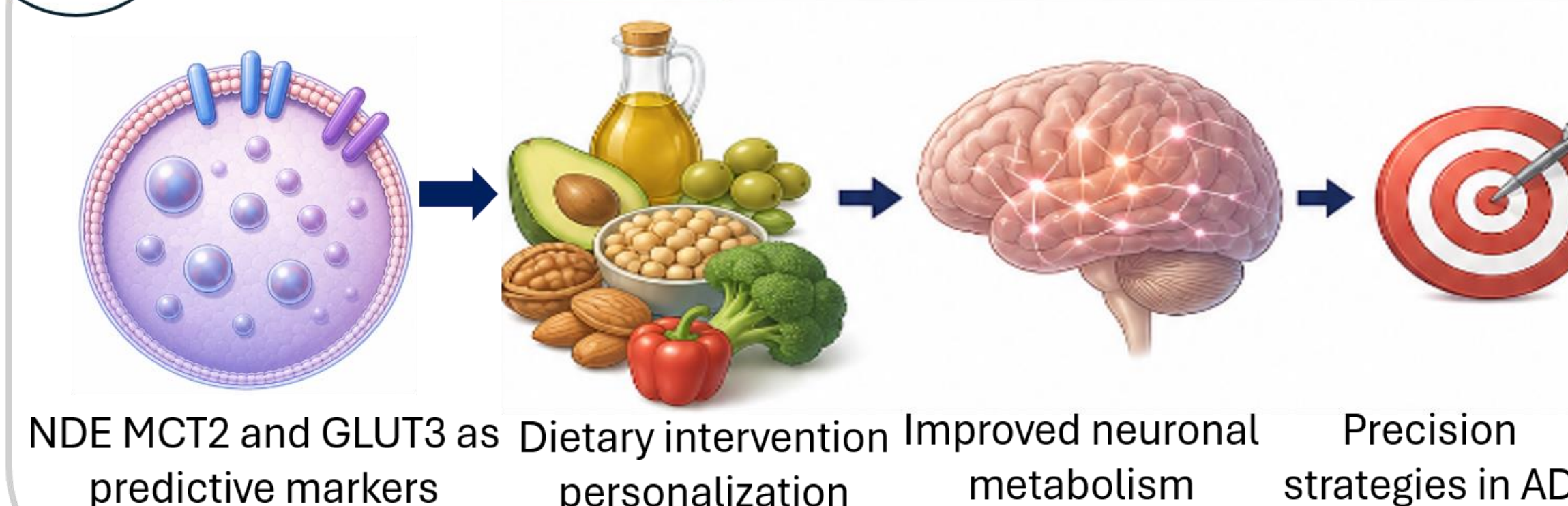
V. AHAD APOE-ε4 carriers: Higher baseline NDE GLUT3 positively correlated with change in CSF Aβ42 and Aβ40.



VI. Across both groups: Change in NDE-MCT2 levels positively correlated with change in FDG uptake in specific brain regions.



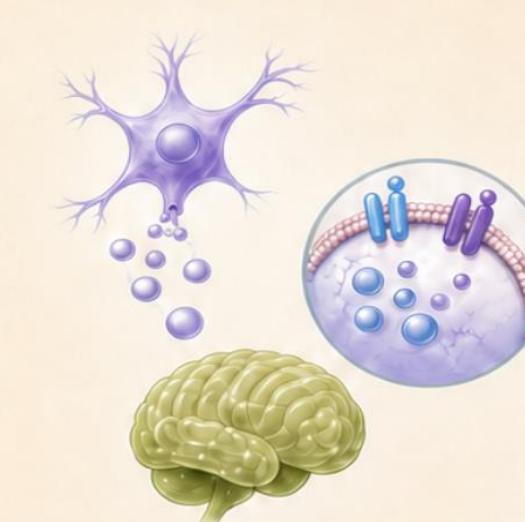
5 Conclusion



4 Discussion

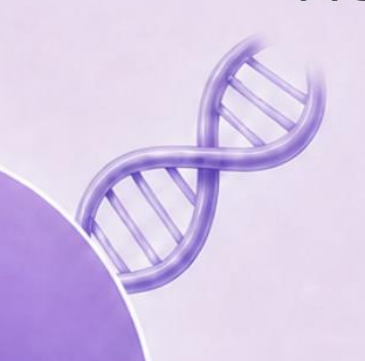
Diet-Biomarker Interactions

MCT2 and GLUT3 in NDE reflect neuronal metabolic adaptations that predict differential responses to MMKD and AHAD



APOE-ε4 Modulation

Biomarker associations are strongly influenced by APOE-ε4 status, highlighting patient stratification for precision medicine in MCI



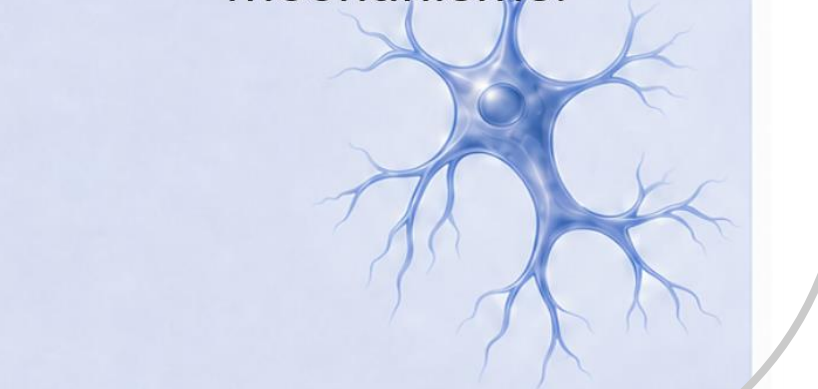
Metabolic imaging Link

Change in NDE-MCT2 parallel improvements in FDG uptake in key brain regions, supporting its relevance to neuronal biogenesis



Mechanistic Insight

NDE profiling from plasma offers a minimally invasive window into neuronal biology and diet-induced therapeutic mechanisms.



6 References

- Kumar et al, 2023, Alzheimers Dement. 2023 Nov;19(11):4952-496
- Kumar et al, 2022, Brain Commun. 2022 Oct 19;4(6):fcac262.
- Cleary et al, 2025, Alzheimers Dement. 2025 Feb;21(2):e14497.



Funding: NIA, R01, AG084696