

Plasma Metabolomic Pathways In Young Versus Older Onset Mild Cognitive Impairment (MCI)



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Young vs older adults with MCI exhibit distinct plasma metabolic signatures, suggesting age-related differences in the biological mechanisms underlying mild cognitive impairment.

Introduction

- MCI represents a transitional stage between normal aging and dementia.
- Characterized by subjective cognitive complaints, objective cognitive impairment, but preserved daily functioning [1].
- Limited research comparing metabolomic pathways in young versus older onset MCI [2].

Aims and Objective

- To investigate age-dependent metabolic impairments in adults with young (45-60years) versus older (61-75years) onset MCI.
- To identify early metabolic signatures relevant to disease onset and dementia prevention.

Methods

Participant screening

Department of Neurology, AIIMS, New Delhi

Inclusion criteria

- Age 45-70 years
- Amnesic MCI (NIA-AA 2011 criteria)
- Written informed consent
- Able to read and understand English/Hindi
- ≥5 years formal education

Exclusion criteria

- Advanced malignancy, significant systemic illness
- Other neurological disorder/major psychiatric illness
- Drugs affecting cognition, psychoactive medication, alcohol abuse
- Major surgery in previous 6 months
- TSH > 10μU/ml
- Visual/auditory impairment

MCI participants

Younger adults with MCI (n=17)

Older adults with MCI (n=18)

Detailed Neuropsychological assessment Blood sample collection (8-12hrs fasting)

- Routine biochemical investigation

Plasma processing for metabolomics:

- Centrifugation: 2500 rpm, 15 min
- Aliquoted into cryovials
- Stored at -80°C till metabolomics

Protein extraction for untargeted metabolomics

Methanol precipitation → vacuum drying; CentriVac Cold Trap → Reconstitution 25μL of (3:17, methanol: water)

- Untargeted LC-MS/MS Analysis
- Orbitrap fusion MS+ UPLC Ultimate 3000

Metabolite Separation

- Reverse Phase (HSS T3)
- HILIC (X Bridge BEH Amide)
- Positive & Negative Ion Modes

- Data Processing & Metabolite identification
- Progenesis QI for metabolomics features with QC CV< 30%

Statistical Analysis

- Identification of differential Metabolites
- Between young vs Older onset MCI

Results

Table 1: Baseline characteristics of Young versus older participants with MCI

Variables	Young (45-60 years) (N =17)	Older (61-75 years) (N= 18)
Age (years), Mean ± SD	54.7 ± 2.9	68.4 ± 4.1
Males, n(%)	15(88.2%)	16(88.9%)
Education (years), Mean ± SD	13.1 ± 3.4	13.4 ± 4.6
Education, n(%)		
Upto class 8th	3(17.6%)	4(22.2%)
9th to 12th	7(41.2%)	4(22.2%)
Graduate to Postgraduate	7(41.2%)	10(55.6%)
Duration of disease (Months), Median (IQR)	36(18,36)	60(36,60)
Risk factors		
Hypertension, n(%)	3(17.6%)	6(37.5%)
Type 2 diabetes, n(%)	12(70.6%)	12(66.7%)
Coronary artery disease, n(%)	3(17.6%)	4(22.2%)
Positive family history, n(%)	3(17.6%)	4(22.2%)
Cognitive Examination Scale		
ACE-III Total score, Mean ± SD	87.7 ± 3.2	85.2 ± 7.4

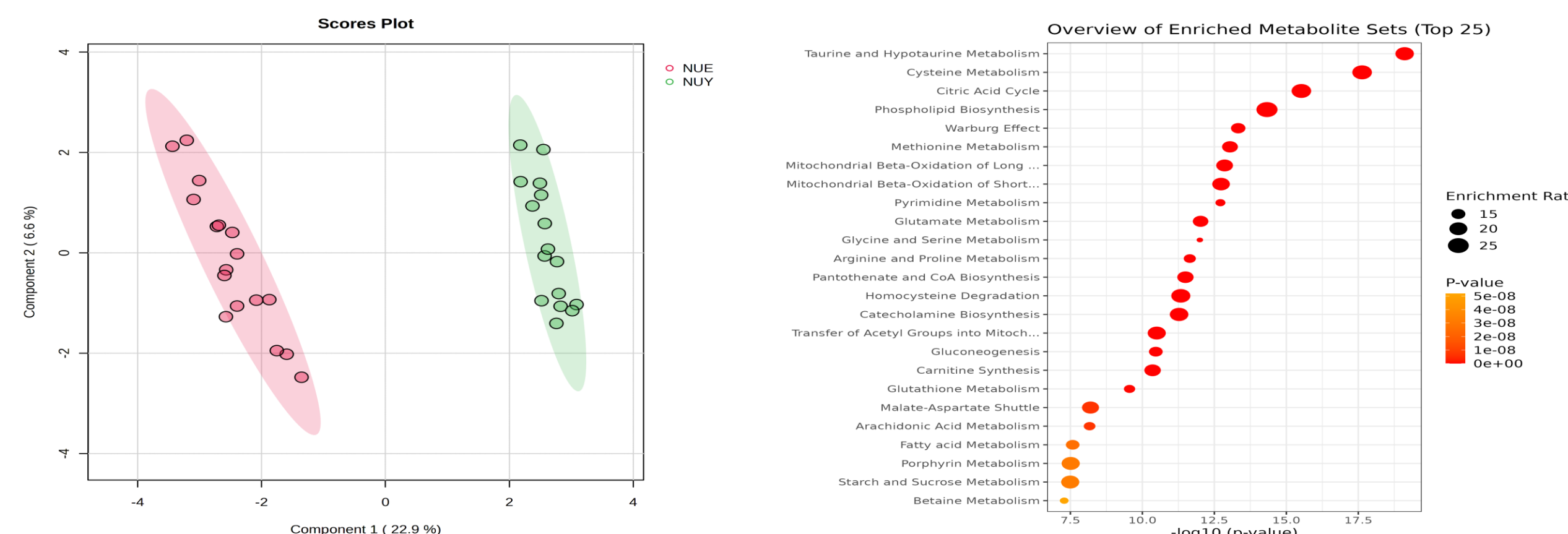


Fig 1: Partial least squares discriminant analysis(PLS-DA) utilizing all detected metabolites demonstrated a distinction between the 2 groups with principal component 1, NUE: Olderly group, NUY: Young group.

Fig 2: Displaying an overview of enriched metabolites sets

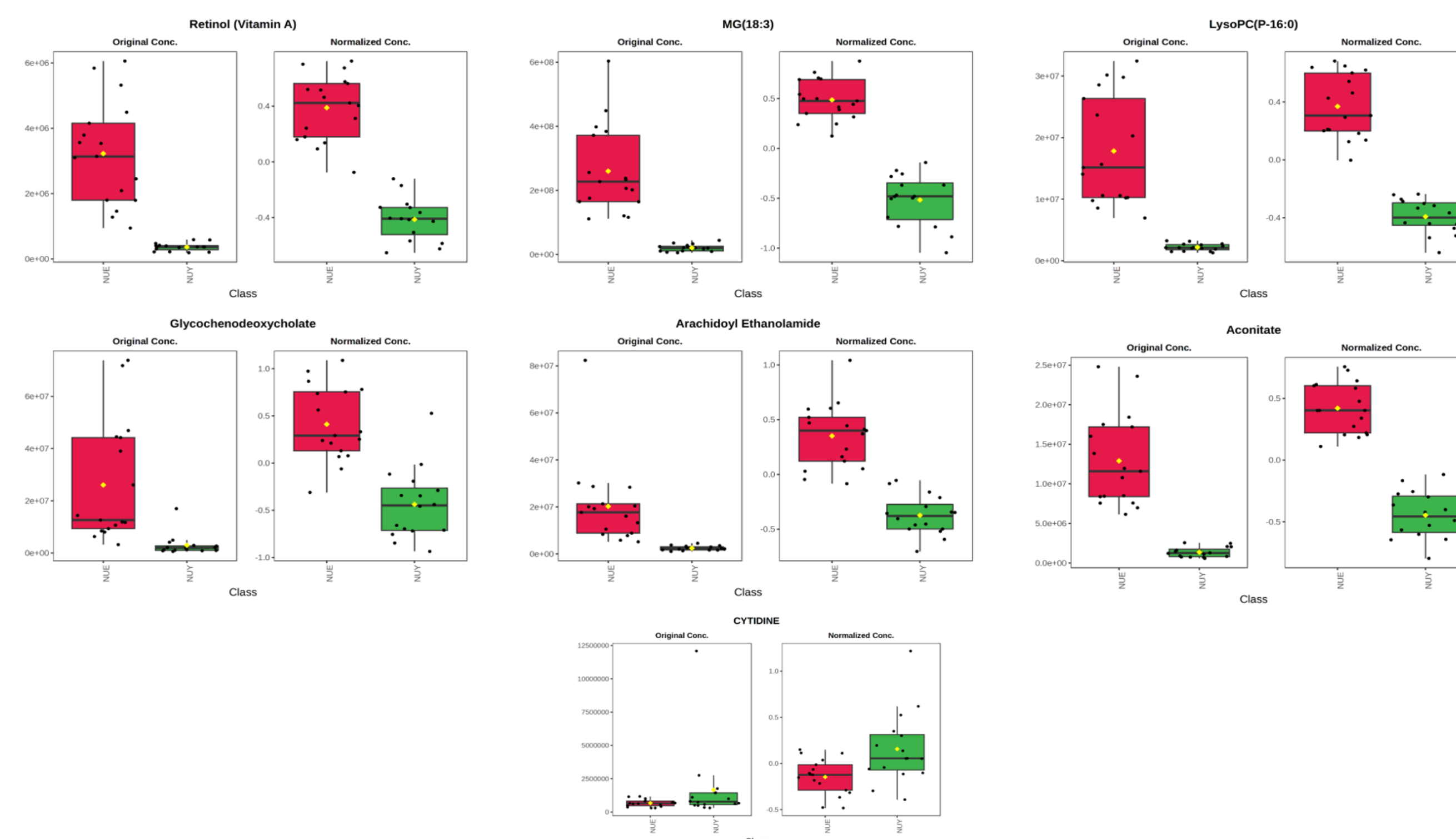


Figure 3: Box plots of selected metabolites comparing young onset MCI (NUY, 45–60 years) and older onset MCI (NUE, 61–75 years).

Conclusions

- Older adults with MCI: ↑ Carnitine, aconitate, histidine, and retinol (altered energy, amino acid, and vitamin metabolism pathways)
- Younger adults with MCI: ↑ C17:0 and C17:1 fatty acids (altered lipid metabolism)
- Findings indicate age dependent metabolic alterations underlying MCI.

Future Directions

- Needs comparison with a healthy control group.
- Assess longitudinal metabolomic changes and correlation with clinical conversion to dementia

References

1. Duff K. Mild cognitive impairment: quantifying a qualitative disorder. Neurol Clin. 2024;42(4):781-792. doi:10.1016/j.ncl.2024.05.007
2. Lista S, González-Domínguez R, López-Ortiz S, et al. Integrative metabolomics science in Alzheimer's disease: relevance and future perspectives. Ageing Res Rev. 2023;89:101987.doi:10.1016/j.arr.2023.101987

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