

DISCOVERY AND REPLICATION OF METABOLOMIC, FUNCTIONAL, AND CLINICAL FEATURES ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT

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INTRODUCTION

- Reproducible metabolomic and clinical markers of mild cognitive impairment remain insufficiently established due to limited external validation using identical feature sets and modeling frameworks.
- Identifying robust metabolite and clinical signatures may strengthen classification accuracy between cognitively normal and mild cognitive impairment groups, improving model generalizability and translational relevance.

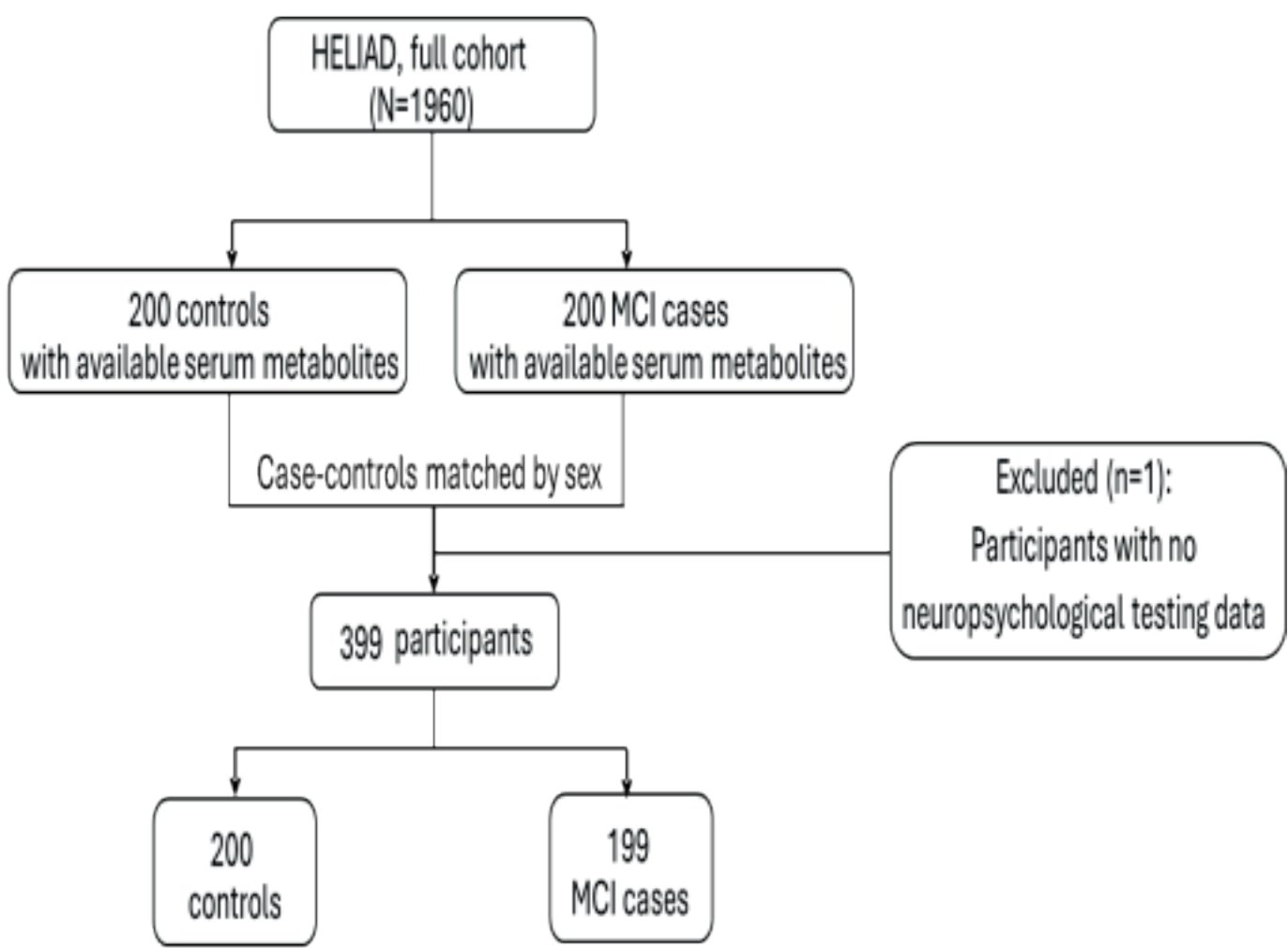
METHODS

Discovery Dataset

Hellenic Longitudinal Investigation of Aging and Diet (HELIAD)

- The participants in this cohort were selected through random sampling from Greek community-dwelling individuals over the age of 65 years.

Figure 1. Flowchart of the HELIAD participants.



Validation Dataset

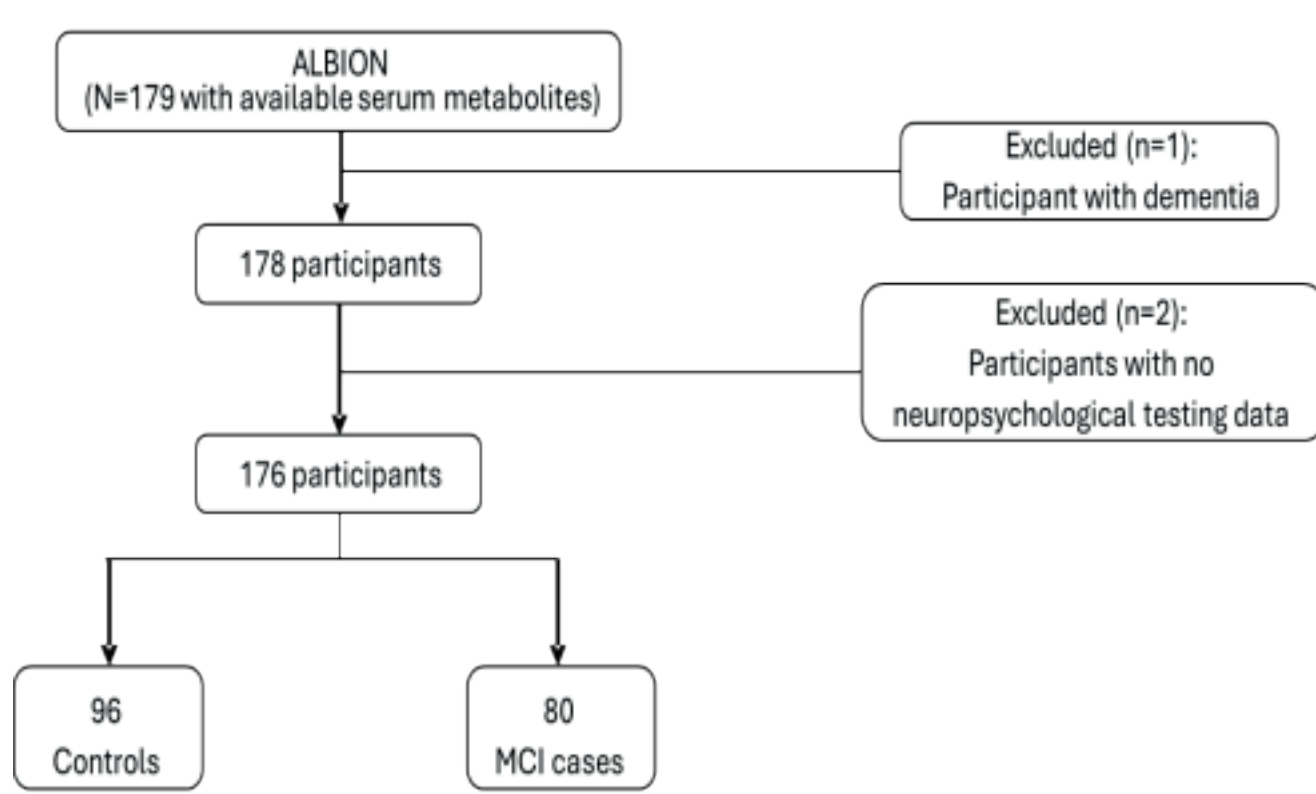
Aiginition Longitudinal Biomarker Investigation Of Neurodegeneration (ALBION)

- Participants aged over 40 who are cognitively normal (CN) or have mild cognitive deficits recruited in Athens, Greece.

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Figure 2. Flowchart of the ALBION participants.



Data Collection

Metabolomics HELIAD & ALBION

- Metabolites were analyzed in serum at baseline.
- Utilized a targeted multi-platform approach (liquid and gas chromatography techniques coupled to tandem mass spectrometry).

Clinical/Demographics HELIAD & ALBION

- Data was collected from the participants' first visit.

Data Structure

Metabolomics HELIAD & ALBION

- 595 metabolites in HELIAD
- 602 metabolites in ALBION

Clinical/Demographics HELIAD & ALBION

- 1720 features HELIAD
- 1450 features in ALBION

Analysis

Identification of metabolites and clinical characteristics

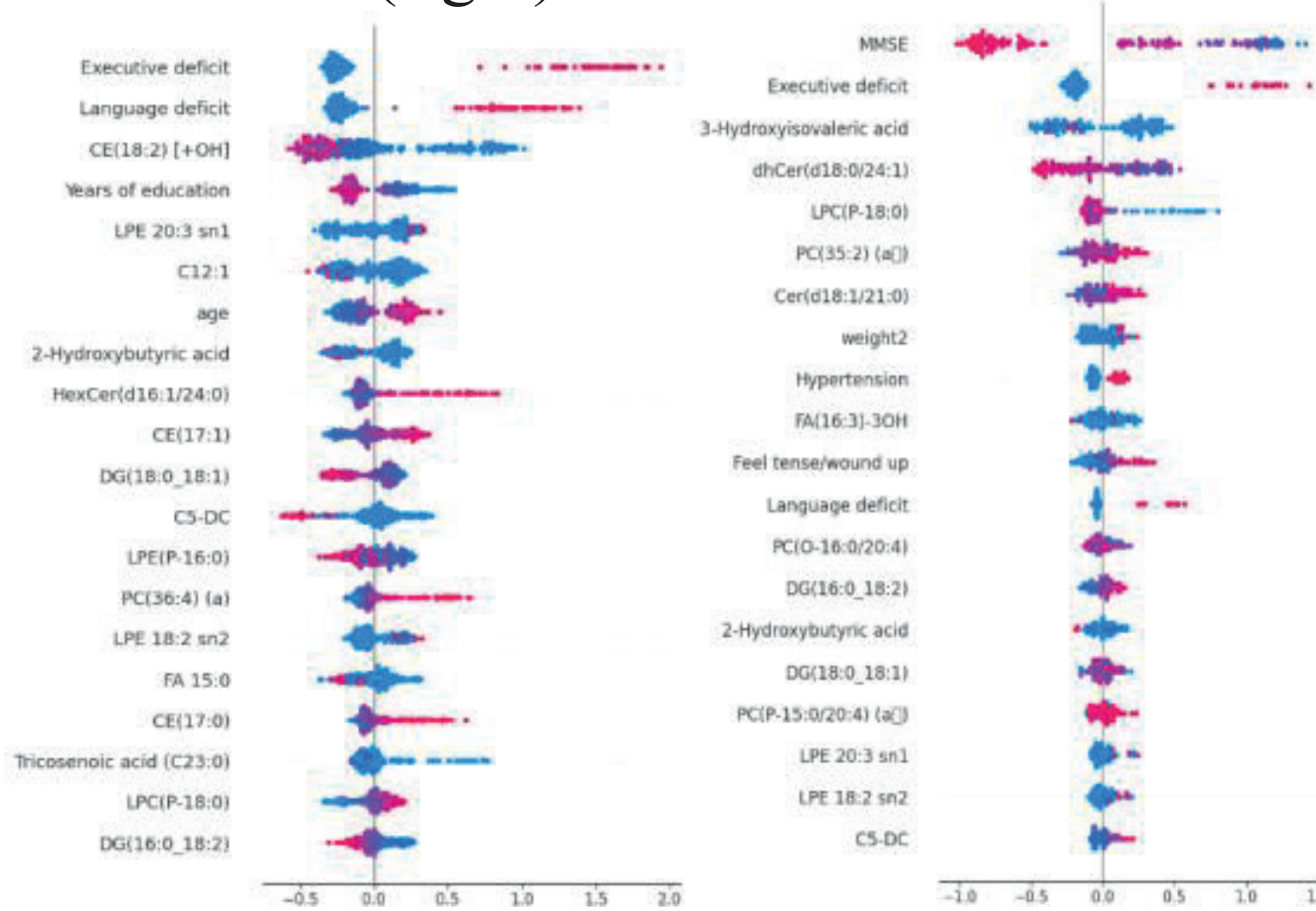
- Mild Cognitive Impairment as the outcome and 595 inverse-normal transformed metabolites and 1720 features as predictors.
- Lasso regression and min-max scaler, with a repeated 10-fold cross-validation. Retaining features that appeared in at least 50% of the folds.
- Evaluation of predictive performance using **Catboost Classifier**.

Acknowledgments

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RESULTS

Figure 3. Feature importance of the final predictors from HELIAD (left) and ALBION (right).



- The SHAP values in HELIAD indicate that an executive and language deficit along with lipid CE(18:2) are the strongest predictors for distinguishing normal to MCI patients.
- In ALBION, the MMSE score, executive deficit and the leucine-derived metabolite 3-Hydroxyisovaleric acid are the strongest predictors.

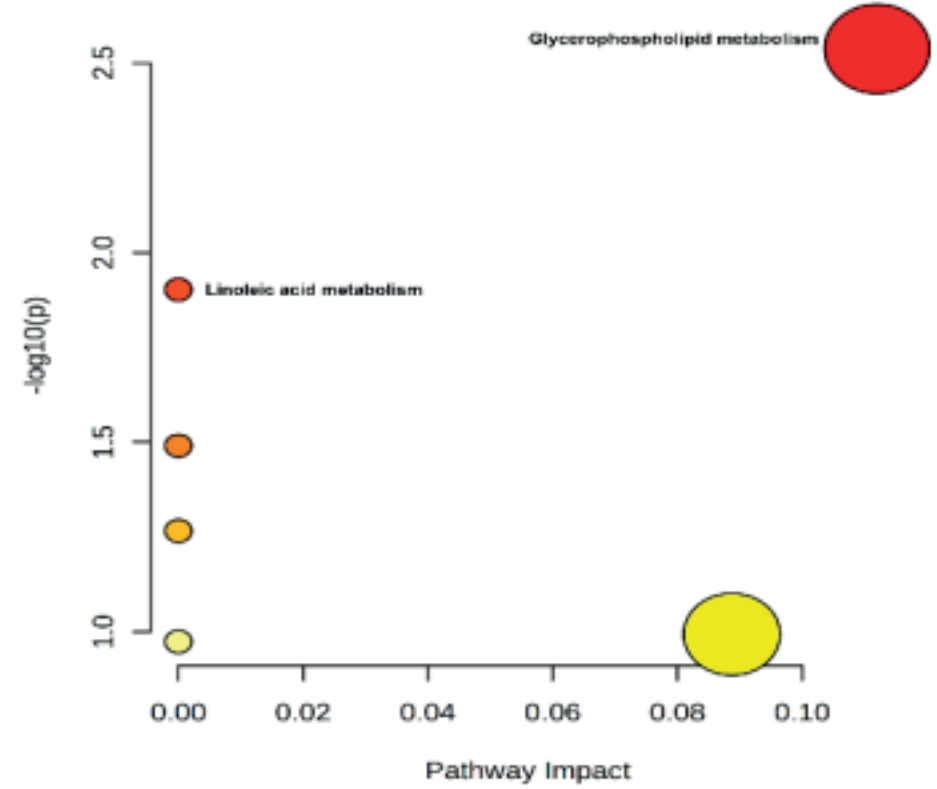
Table 1. Performance metrics for optimized models in each cohort.

	HELIAD	ALBION
ROC AUC	0.82	0.83
F1 Score	0.72	0.70
Sensitivity	0.68	0.64
Specificity	0.79	0.87

Pathway Analysis

- Pathway enrichment analysis of the 25 metabolites highlighted **glycerophospholipid metabolism** as the top-ranked pathway (raw p = 0.0029).
- Additional pathways with nominal enrichment included **linoleic acid**, **α -linolenic acid**, **propanoate**, **tyrosine** and **arachidonic acid metabolism**.
- The enriched pathways predominantly relate to lipid and membrane metabolism, supporting metabolic alterations associated with cognitive status.

Figure 4. Bubble plot for top ranked pathways.



CONCLUSIONS

- Our findings suggest a combination of 26 metabolites and 9 clinical-demographic features exhibited moderate to high performance for distinguishing mild cognitive impairment from cognitive normal across two cohorts of adults.
- Variation in feature importance in SHAP was observed in some metabolites and may be due to differences in characteristics of cohort populations, such as age, education and diet.
- Understanding the impact of these metabolites and clinical features on cognition may better inform individualized – precision medicine aspects of cognitive aging and neurodegeneration.