

IDENTIFICATION OF A SERUM METABOLITE SIGNATURE ASSOCIATED WITH AMYLOID PATHOLOGY

Vasiliki-Amaryllis Skyfa, Sotiris Nikoletos, Christopher Papandreou, Georgios Hadjigeorgiou, Efthimios Dardiotis, Mary H. Kosmidis, Mary Yannakoulia, Paraskevi Sakka, Archontoula Drouka, Dora Brikou, Eirini Mamalaki, Eva Ntanasi, Nikolaos Scarneas, Nikolaos Giagkou, George Manias, Athos Antoniadis

INTRODUCTION

- Data on serum metabolites associated with changes in amyloid levels remain limited.
- Understanding these associations may help elucidate early metabolic alterations linked to age-related cognitive trajectories.

METHODS

Discovery dataset

Aiginition Longitudinal Biomarker Investigation Of Neurodegeneration (ALBION)

- Recruited participants aged over 40 who are cognitively normal (CN) or have mild cognitive impairment (MCI) in Athens, Greece.

Data Collection

Metabolomics

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

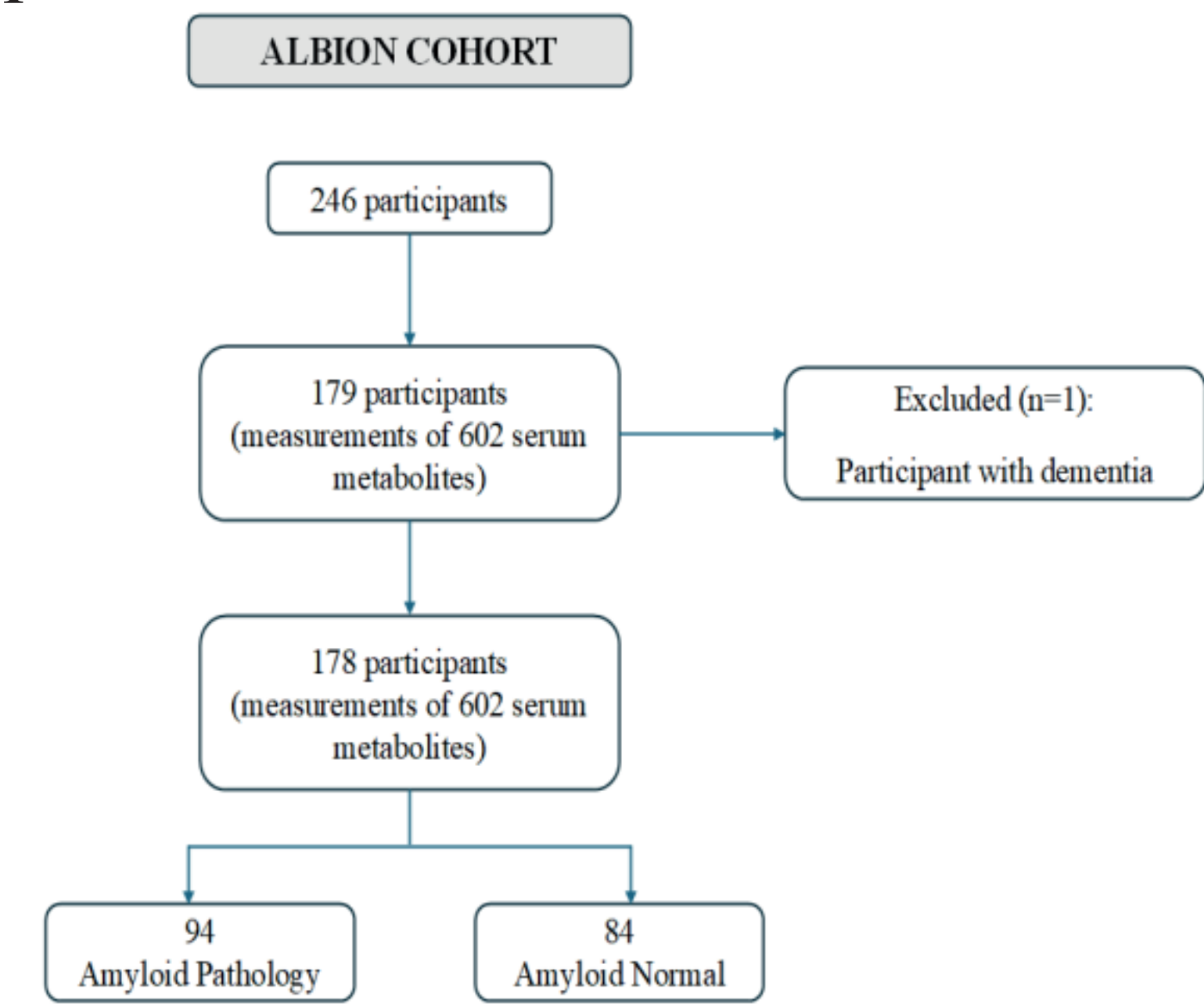
Amyloid pathology

- β -amyloid levels in cerebrospinal fluid were quantified for each participant.
- Participants were categorized as **amyloid-normal** (β -amyloid measurement < 1000) or **amyloid-pathological** (β -amyloid measurement $\geq$ 1000).
- The derived binary variable (**Amyloid Pathology: 0/1**) was used as the response variable in downstream analyses.

CONTACT

ns257@cumc.columbia.edu , papchris@hmu.gr , amaryllis.skyfa@hotmail.gr

Figure 1. Flowchart of the ALBION participants.



Analysis

Identification of metabolites and construction of the classifier

- Binary variable Amyloid Pathology as the outcome and 602 inverse-normal transformed metabolites as predictors.
- LASSO regression for feature selection ($\lambda = 0.005$), within a 100-fold cross-validation framework.
- The 43 metabolites that appeared in at least 50% of the folds were used to train Random Forest (200 estimators), CatBoost (300 iterations) and Logistic Regression classifiers to distinguish AP cases from amyloid-normal individuals.
- Logistic Regression had the best performance and was selected as the final model.

Acknowledgments

This research was funded by the European Union's Horizon Europe research and innovation program under grant agreement no. 101137301 and is supported by the Innovative UK under grant agreement no. 10103541. Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

This study has been funded by the Alzheimer's Association, through the project AARG-NTF-23-1027318.

RESULTS

Table 1. Study sample characteristics.

	Mean or N	SD or %
Age (Years)	64.11	9.31
Education (Years)	13.38	3.85
Sex		
Female	118	66.29
Male	60	33.71
Cognitive status		
Normal	118	66.29
MCI	60	33.71

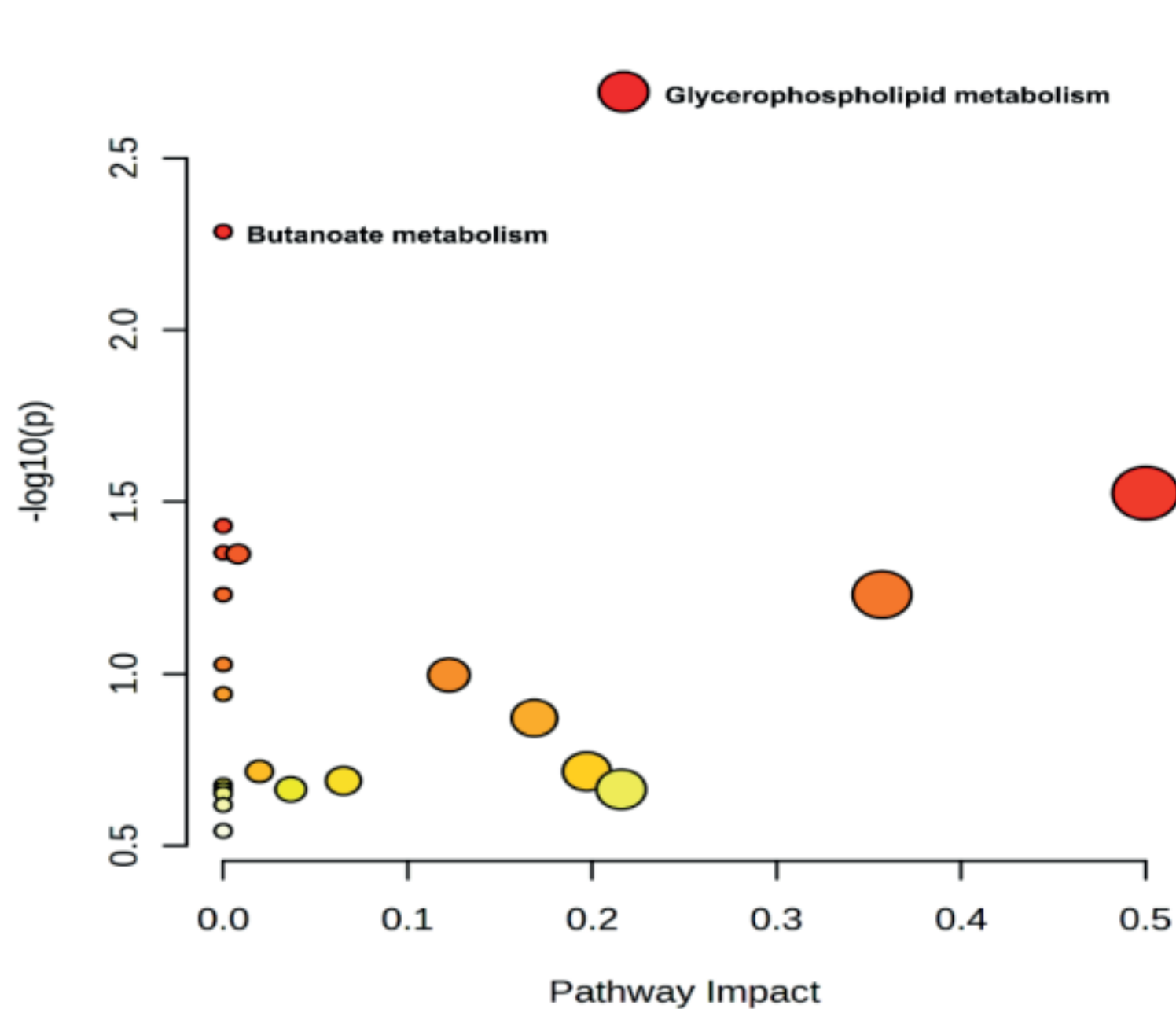
Table 2.

Performance metrics for logistic regression model.

AUC	0.87
Sensitivity	0.80
Specificity	0.81

- Metabolites positively associated with amyloid pathology in the Lasso logistic model included multiple lipid classes, amino acids, and carbohydrate-related metabolites.
- Metabolites negatively associated with amyloidosis included several sphingolipids and glycerophospholipids.

Figure 2. Pathway analysis of the 43 metabolites.



CONCLUSIONS

- Using machine learning techniques, we identified a **43-metabolite signature** with strong discriminatory performance for distinguishing individuals with pathological versus normal amyloid levels.
- The selected metabolites were enriched in **lipid, fatty-acid, and membrane remodeling pathways**, supporting a link between amyloid pathology and systemic metabolic alterations.
- These results highlight a candidate **metabolite panel for amyloid pathology identification** and support further investigation of metabolomics-based risk profiling in neurodegenerative disease.