

Serum Lipid Ratios Reveal Early Metabolic Signatures Of Genetic Alzheimer's Risk Beyond Protein Biomarkers (*PSEN1*-E280A)

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Introduction //

Alzheimer's disease (AD) is a multifactorial condition in which metabolic and neuropathological changes develop decades before clinical symptom onset. Fluid biomarkers offer potential to identify early disease-related processes; however, sensitivity in very early stages remains limited. Lipidomics provides a systems-level perspective of metabolic pathway activity, and lipid ratios may capture coordinated metabolic dynamics rather than isolated molecular changes. This study aimed to identify serum lipid ratio signatures associated with genetic AD risk.

Objective //

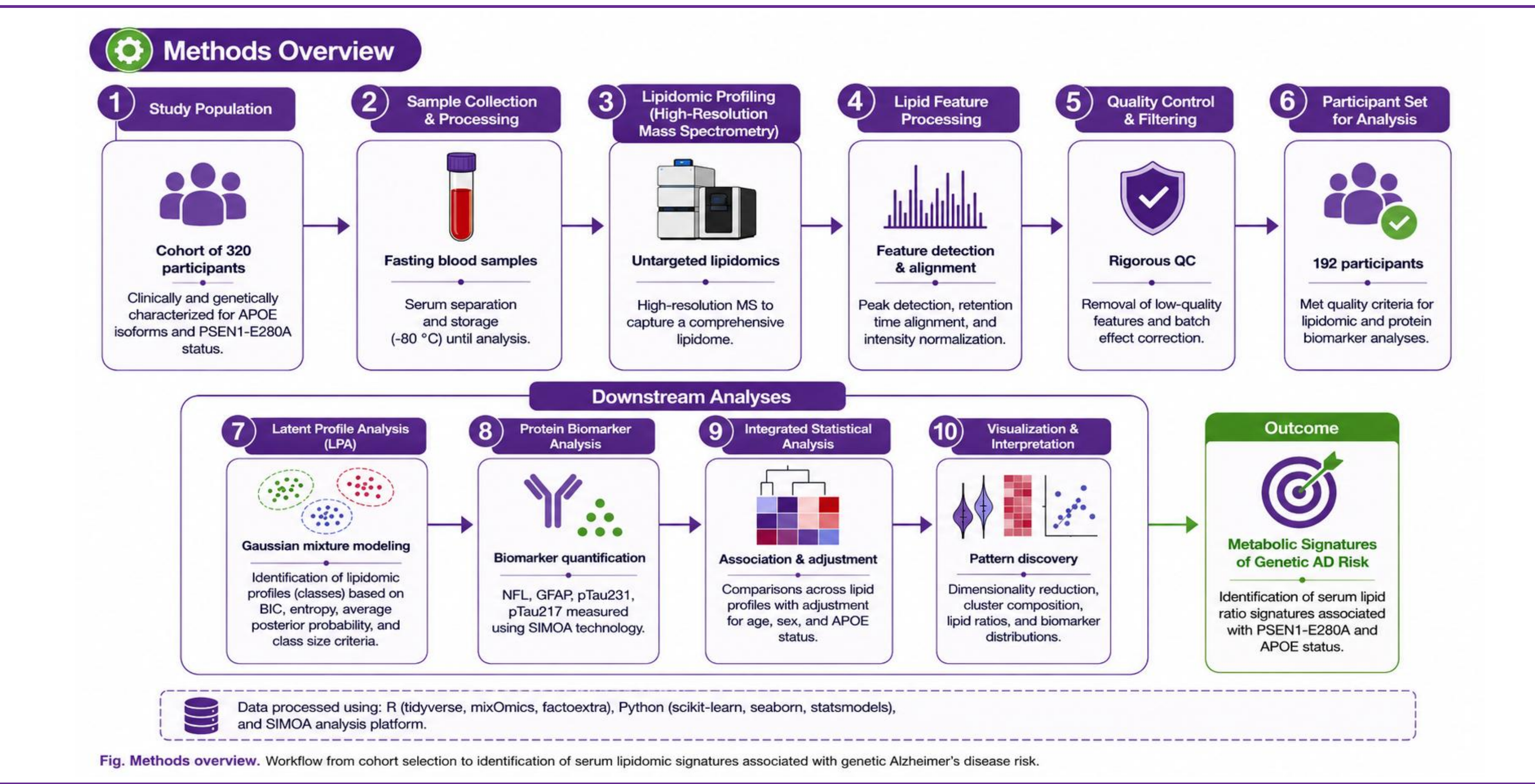
Learning Objective 1: Evaluate the utility of lipidomic profiles compared with established protein biomarkers for early detection of Alzheimer's disease.
Learning Objective 2: Interpret latent profile analysis results to characterize metabolic subtypes relevant to Alzheimer's disease risk stratification.



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Methods //

A cohort of 320 participants, clinically and genetically characterized for *APOE* isoforms and the *PSEN1*-E280A variant, underwent serum lipidomic profiling using high-resolution mass spectrometry. Lipid ratios were derived to reflect pathway-level relationships across major lipid classes. Latent Profile Analysis (LPA) was applied in an unsupervised manner using Gaussian mixture modeling (mclust in R), blind to clinical and sociodemographic data. Model selection was based on BIC, entropy, average posterior probability, and class size criteria. Additionally, 192 participants were analyzed for protein biomarkers (NFL, GFAP, pTau231, pTau217) using SIMOA technology.



Results //

Five lipidomic profiles were identified, showing consistent separation across dimensionality reduction, pairwise distributions, and cluster summaries. One profile displayed a distinct configuration, while the remaining clusters showed partial overlap but preserved separability. Cluster composition varied across age groups, with younger individuals (6-12 years) predominantly represented in one profile and older individuals (≥ 41 years) enriched in others. Distribution also differed by *PSEN1*-E280A carrier status and sex, while *APOE* distribution remained relatively homogeneous across profiles. Profiles were defined by coordinated differences across lipid ratios, including cholesterol balance (FC/CE), phospholipid-related ratios (LPC/PC, PE), sphingolipid-related ratios (ceramides, sphingomyelins, glycosphingolipids), and neutral lipids (CE/TG, MG). These patterns were consistent across visualizations and showed age-dependent variation.

Funding //

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Results //

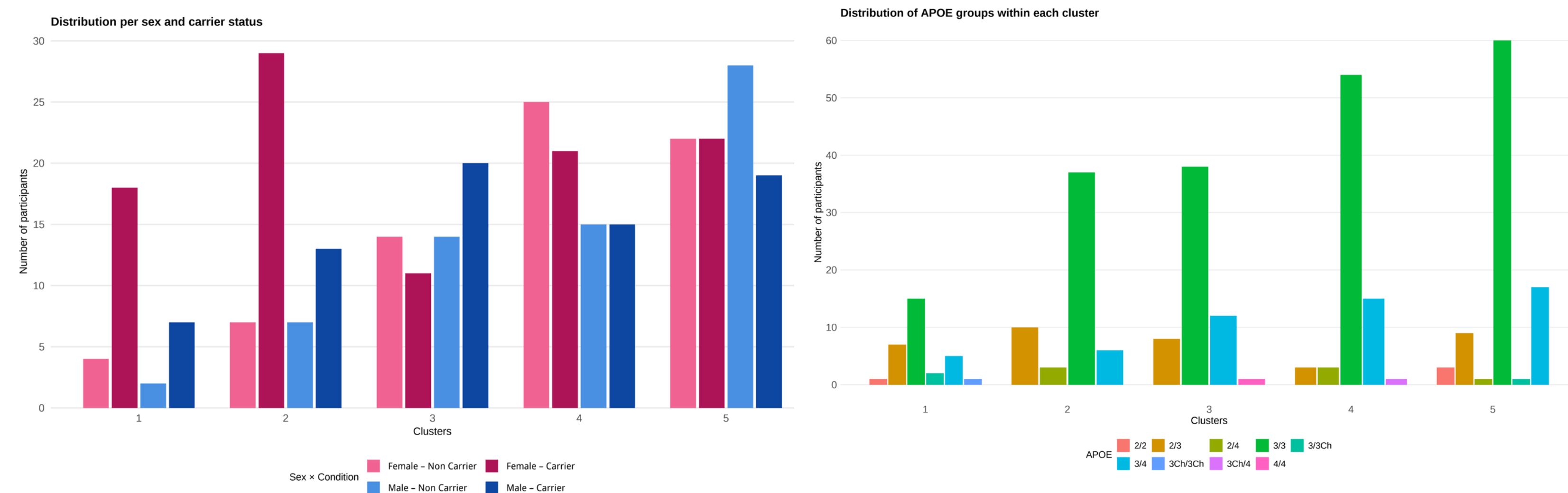


Figure 1. Distribution of the five lipidomic profiles according to sex and *PSEN1*-E280A carrier status.

Figure 2. Distribution of *APOE* genotypes across the five lipidomic profiles, showing no marked profile-specific enrichment.

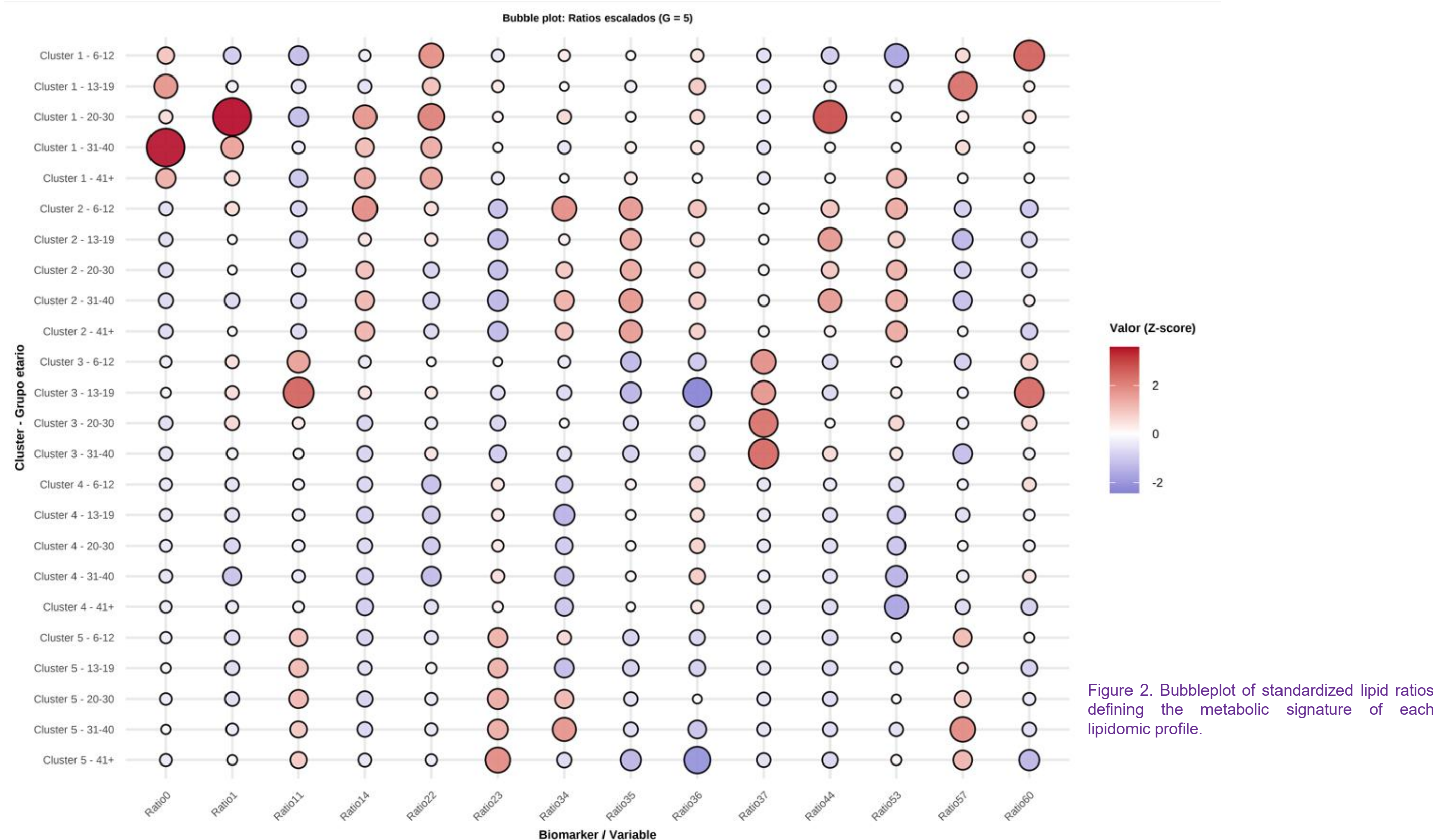


Figure 2. Bubbleplot of standardized lipid ratios defining the metabolic signature of each lipidomic profile.

Conclusions //

Lipidomic ratios identify structured metabolic configurations associated with genetic AD risk.

These profiles exhibit age-modulated variation while preserving internal coherence, supporting their interpretation as coordinated metabolic states. This stratification is detectable early in life and precedes detectable differences in conventional protein biomarkers, supporting lipidomics as an approach for early risk characterization.

Acknowledgments

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