

Linking Brain Lipid Dysregulation to Protein Alterations in Post-Mortem Alzheimer's Disease

Melissa Savard, MSc^{1,3}; Cynthia Picard, PhD^{1,3}; Isabel Sarty, MSc^{1,3}; Judes Poirier, PhD^{1,2,3}

¹Douglas Mental Health University Institute, Montréal, QC, Canada | ²Department of Psychiatry, McGill University | ³Centre for Studies in the Prevention of Alzheimer's Disease

AAIC 2026
Abstract #767

Central message: AD-associated sterol dysregulation maps to coordinated proteomic programs involving inflammation, coagulation, vascular biology and cellular stress.

BACKGROUND

Sterol lipids are essential for synaptic signaling, membrane organization, and myelin maintenance. Because brain cholesterol is largely produced and metabolized locally, disturbances in sterol homeostasis may have particularly important consequences for neuronal function.

Alzheimer’s disease is associated with altered cholesterol synthesis intermediates and oxysterols, including metabolites generated through enzymatic turnover and oxidative modification. These changes may influence oxidative stress, neuroinflammation, vascular function, and cellular stress responses. However, it remains unclear whether AD-associated sterol abnormalities correspond to isolated molecular changes or to coordinated remodeling of the broader brain proteome.

Objective

To integrate sterol and high-throughput proteomic measurements from post-mortem frontal cortex and determine whether AD-associated brain sterols are linked to distinct protein-level and biological pathway signatures.

RESULT 1: DIAGNOSIS-ASSOCIATED STEROL ALTERATIONS

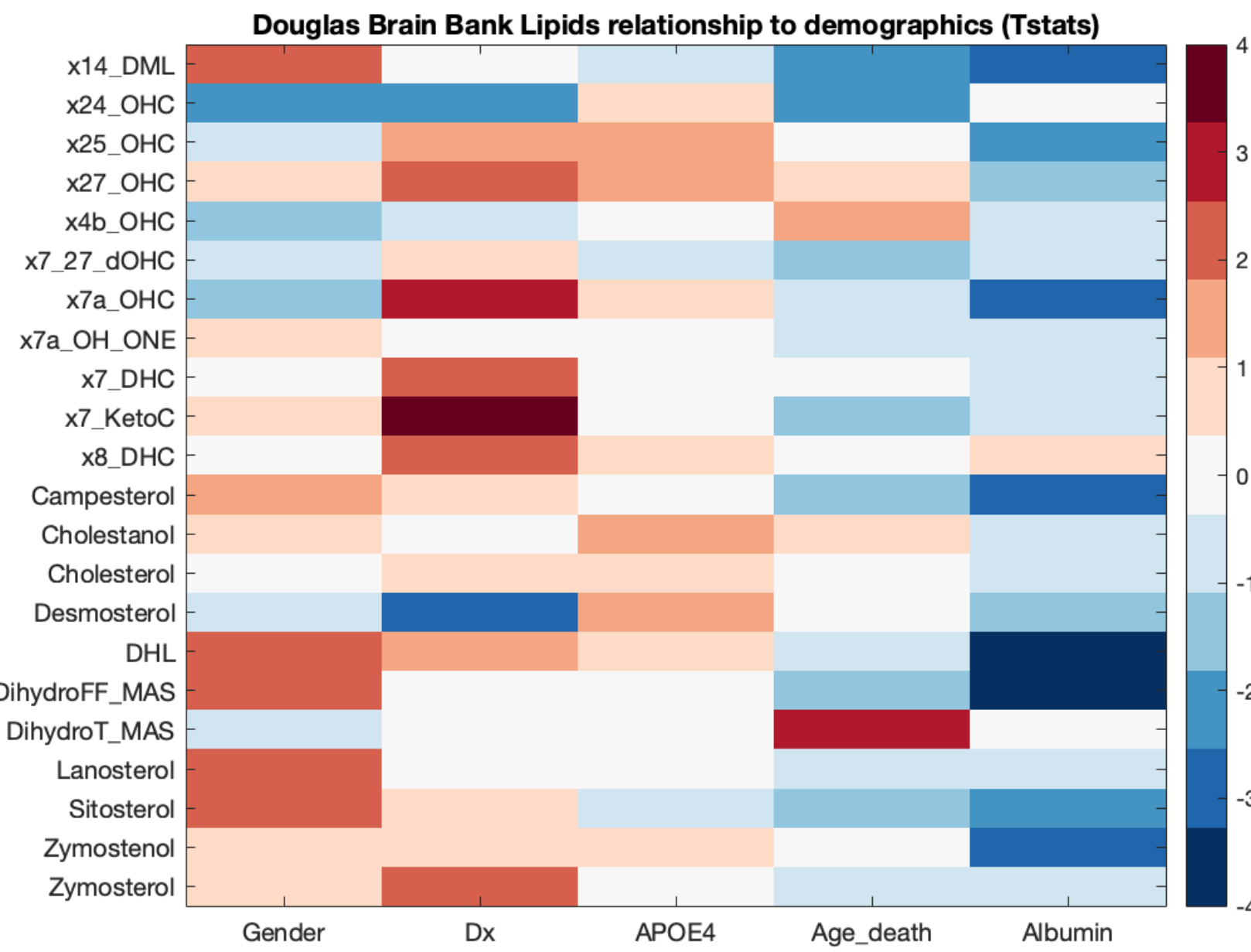


Figure 1. Diagnosis-associated sterol alterations. Heatmap of adjusted regression *t*-statistics for 22 sterols. Positive values indicate higher levels in AD and negative values lower levels in AD. Models were adjusted for age at death, sex, APOE ε4 status, and albumin.

RESULT 2: PROTEOME-WIDE STEROL ASSOCIATIONS

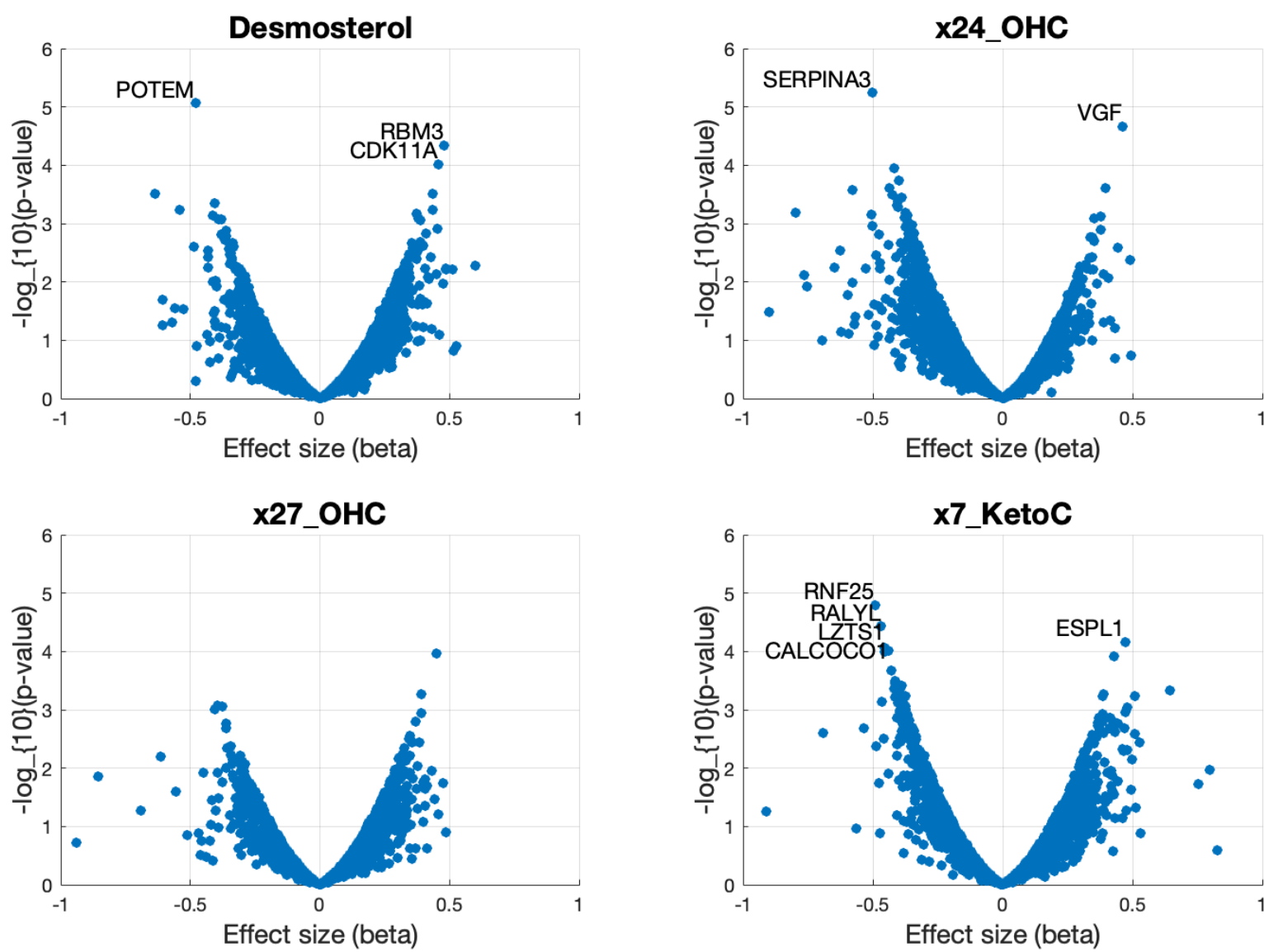
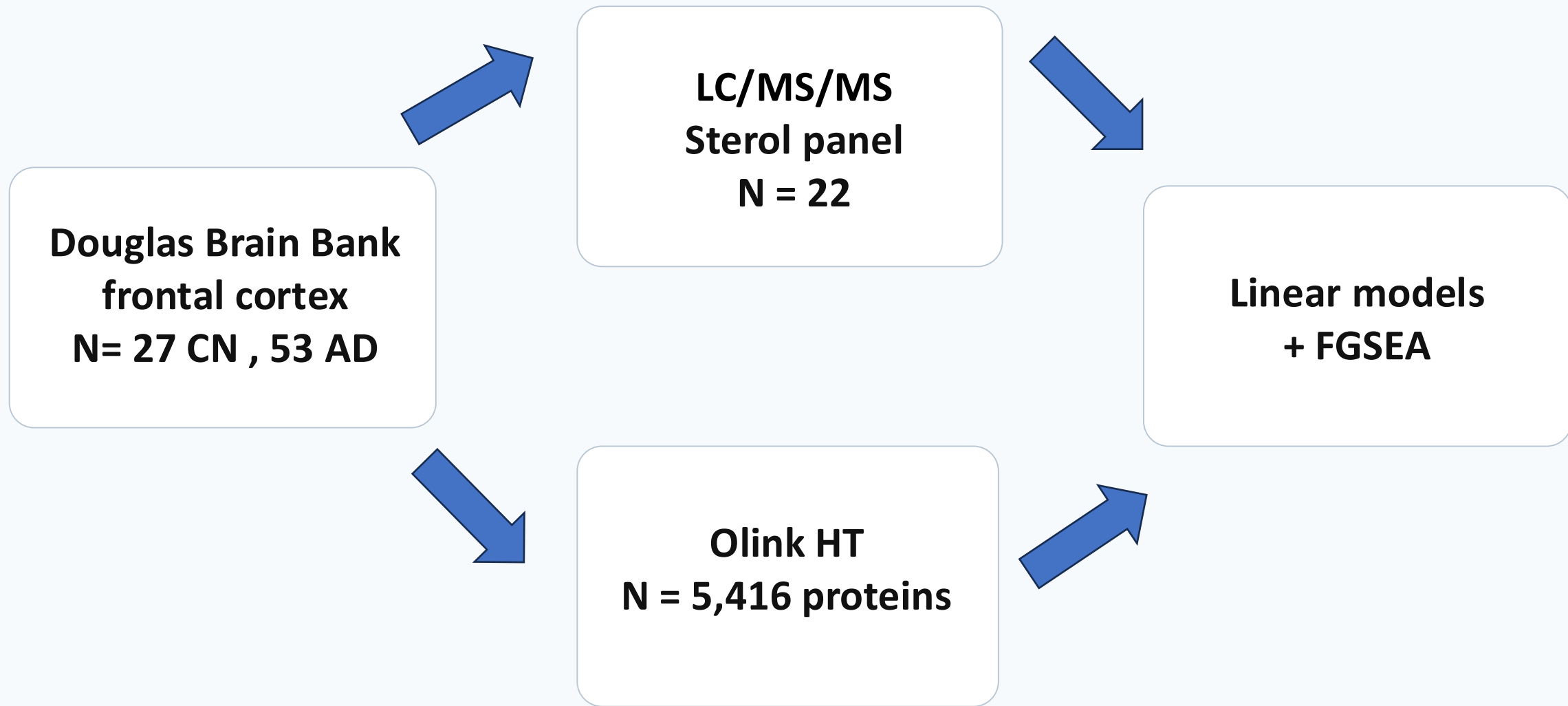


Figure 2. Proteome-wide sterol associations. Volcano plots show adjusted associations between selected sterols and 5,416 proteins. Positive standardized β values indicate direct associations and negative values inverse associations. Labeled proteins represent the strongest signals.

STUDY DESIGN



STATISTICAL ANALYSIS

Diagnosis models. Each of the 22 sterols was analyzed using a separate multivariable linear regression model, with sterol concentration as the outcome and AD diagnosis as the main predictor. Models were adjusted for age at death, sex, APOE ε4 status, and albumin concentration. The diagnostic coefficient represented the adjusted difference between AD and control donors. Diagnosis *P* values were corrected across sterols using the Benjamini–Hochberg false discovery rate ($q < 0.1$ was used as the exploratory sterol-screening threshold).

Proteome-wide models. Cortical sterols associated with the diagnosis were then tested against all 5,416 quantified proteins. Separate adjusted linear models were fitted for each sterol–protein pair using the same covariates. Protein β coefficients represented the direction and magnitude of each association, with positive values indicating direct associations and negative values indicating inverse associations.

Pathway enrichment. For each sterol, proteins were ranked according to their regression β coefficients and analyzed using FGSEA with the Hallmark gene-set collection. Positive normalized enrichment scores (NES) indicated pathways enriched among positively associated proteins, whereas negative scores indicated enrichment among inversely associated proteins. Significant pathways were defined at FDR $q < 0.05$.

RESULT 3: PATHWAY ENRICHMENT OF STEROL-ASSOCIATED PROTEIN SIGNATURES

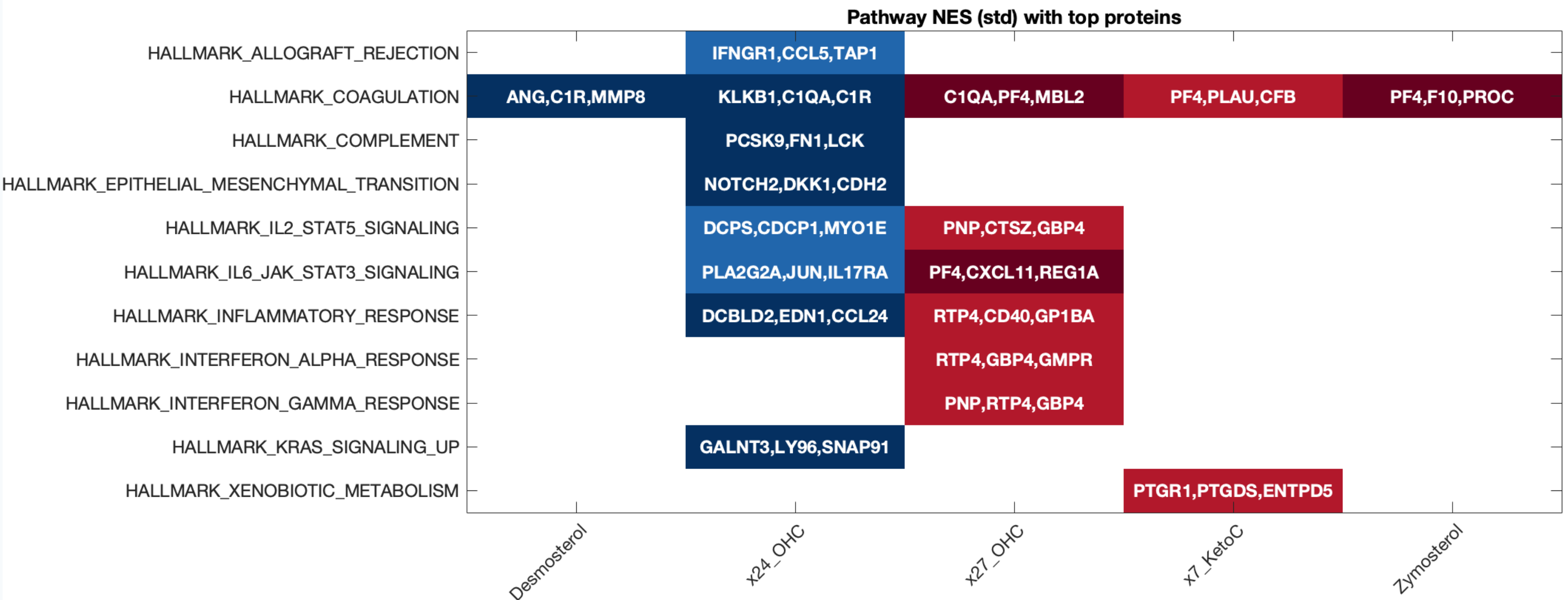
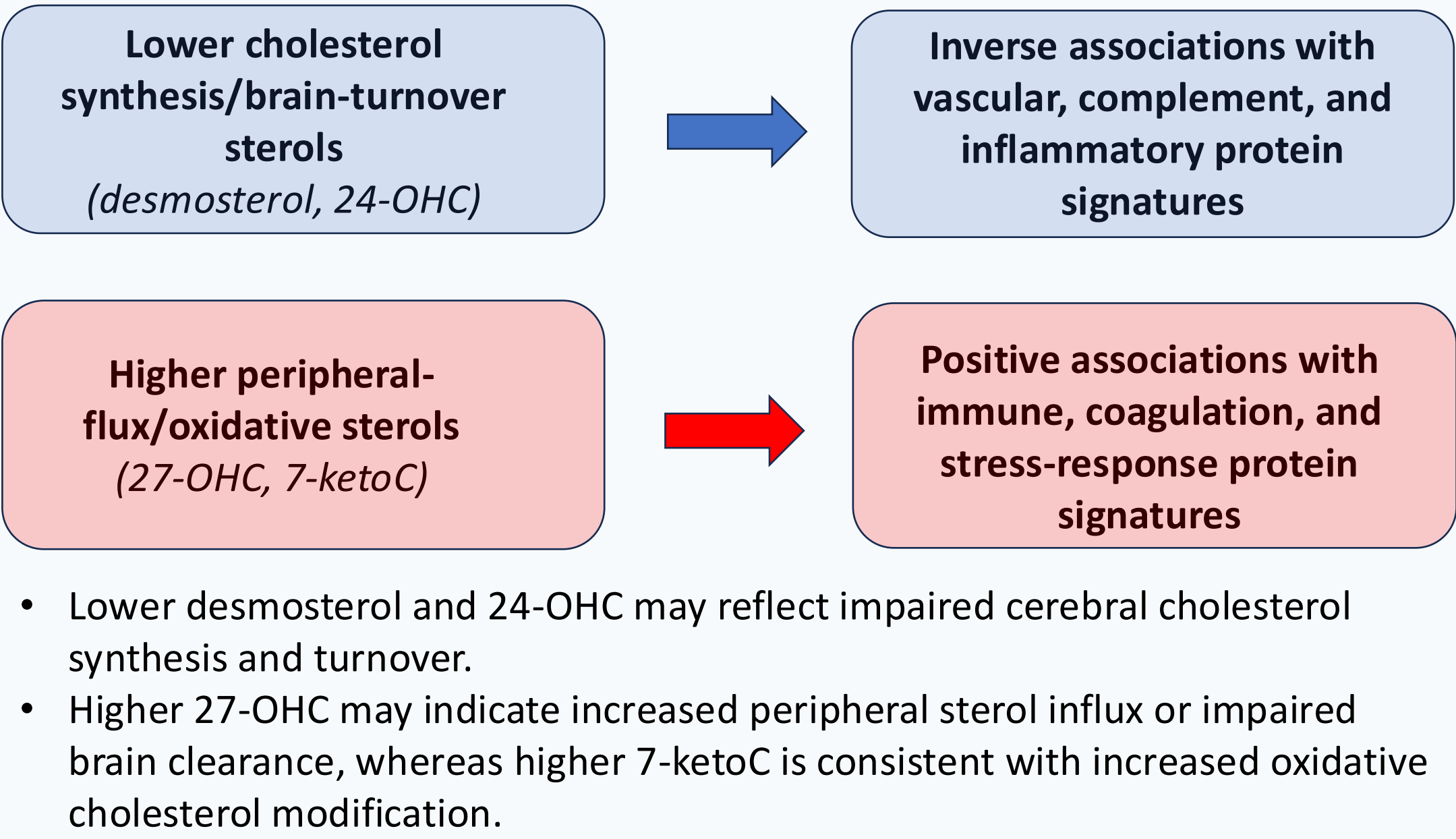


Figure 3. Pathway enrichment of sterol-associated proteins. Proteins were ranked by regression β and analyzed using Hallmark FGSEA. Positive NES indicates enrichment among positively associated proteins; negative NES indicates enrichment among inversely associated proteins. Blank cells indicate FDR $q \geq 0.05$.

BIOLOGICAL INTERPRETATION



CONCLUSION

Eight brain sterols were associated with AD diagnosis and showed distinct proteome-wide association patterns. Lower desmosterol and 24-OHC were linked to inverse vascular, complement, and inflammatory protein signatures, whereas higher 27-OHC and 7-ketoC were linked to positive immune, coagulation/complement activity, and cellular stress-response signatures.

These findings suggest that altered cerebral cholesterol synthesis, turnover, peripheral oxysterol influx, and oxidative modification are each associated with different aspects of AD-related proteomic remodeling.

Together, the results support sterol metabolism as a potential mechanistic link between neurodegeneration, vascular dysfunction, and innate immune activation, and identify specific sterol–protein pathways for validation in larger and independent cohorts.