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INTRODUCTION

- Alzheimer's disease (AD) is increasingly recognized as a multi-system failure syndrome driven by decades-long accumulation of cardiovascular, metabolic, immune, endocrine, and neuropsychiatric dysregulation.
- Sequential pattern mining methods model ordered dependencies between individual clinical events, capturing transitivity.
- The tSPM+ algorithm mines all pairwise transitive temporal relationships among clinical events, while MLHO selects the most AD-predictive sequences from the high-dimensional feature space.
- We aimed to identify disease-medication trajectories preceding AD and determine whether these patterns differ by sex and APOE genotype, with the goal to advance precision preventative strategies.

METHODS

- 862 FHS participants (400 AD, 462 controls), aged ≥ 55 years
- Stratified by sex (60.2% female in AD) and APOE- $\epsilon 4$ status (36.9% carriers in AD)

tSPM+ ALGORITHM

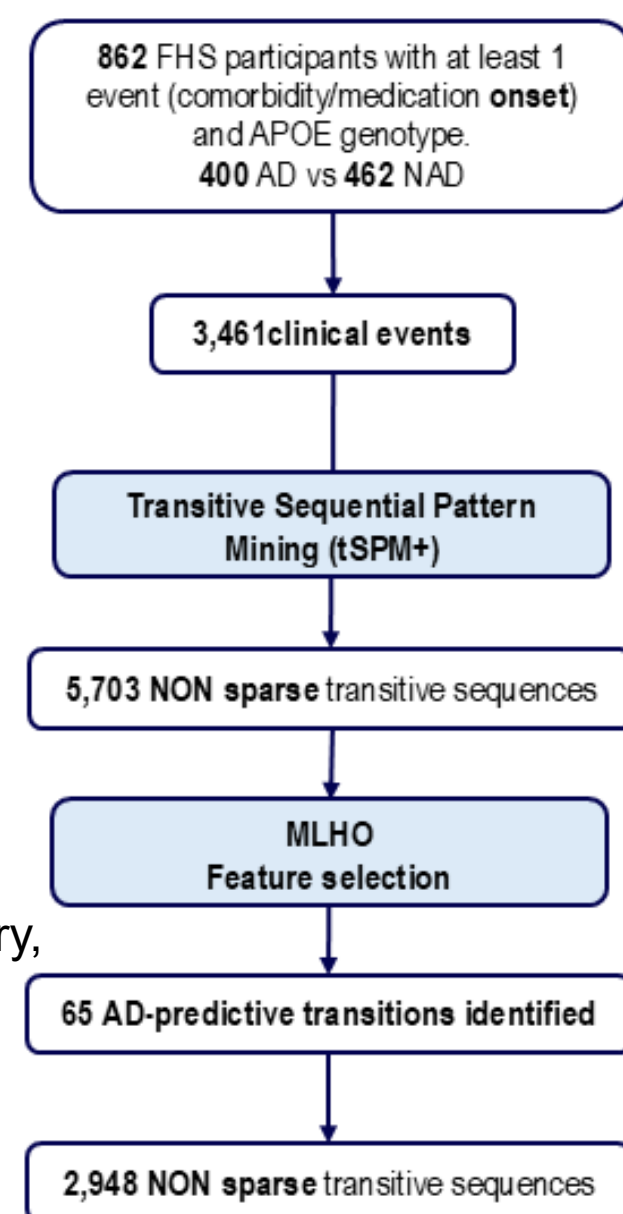
- For each patient, all pairwise event pairs (A $\rightarrow$ B) with A preceding B are mined transitively

MLHO FEATURE SELECTION

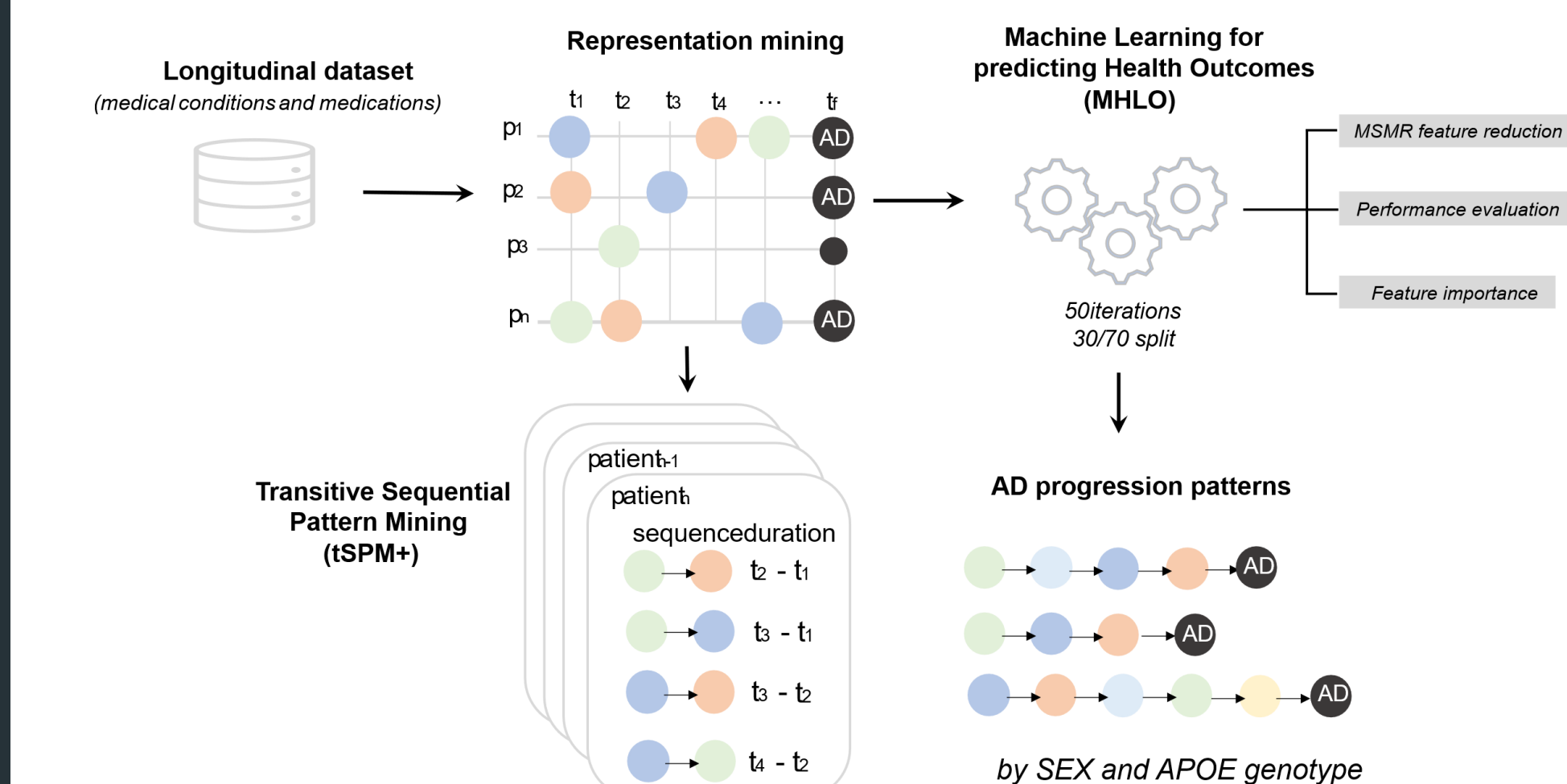
- Mutual information filter ranks sequences by information content about AD outcome.
- 50 independent iterations, 70/30 train-test split

TRAJECTORY RECONSTRUCTION

- Each MLHO-selected transition mapped to 5 physiological systems: Cardiovascular, Endocrine, Immune/Anti-inflammatory, Metabolic, Neuropsychiatric
- Full patient sequences reconstructed via backward tracing from AD diagnosis
- Sequences stratified by sex and APOE- $\epsilon 4$ status; validated against longitudinal MMSE trajectories

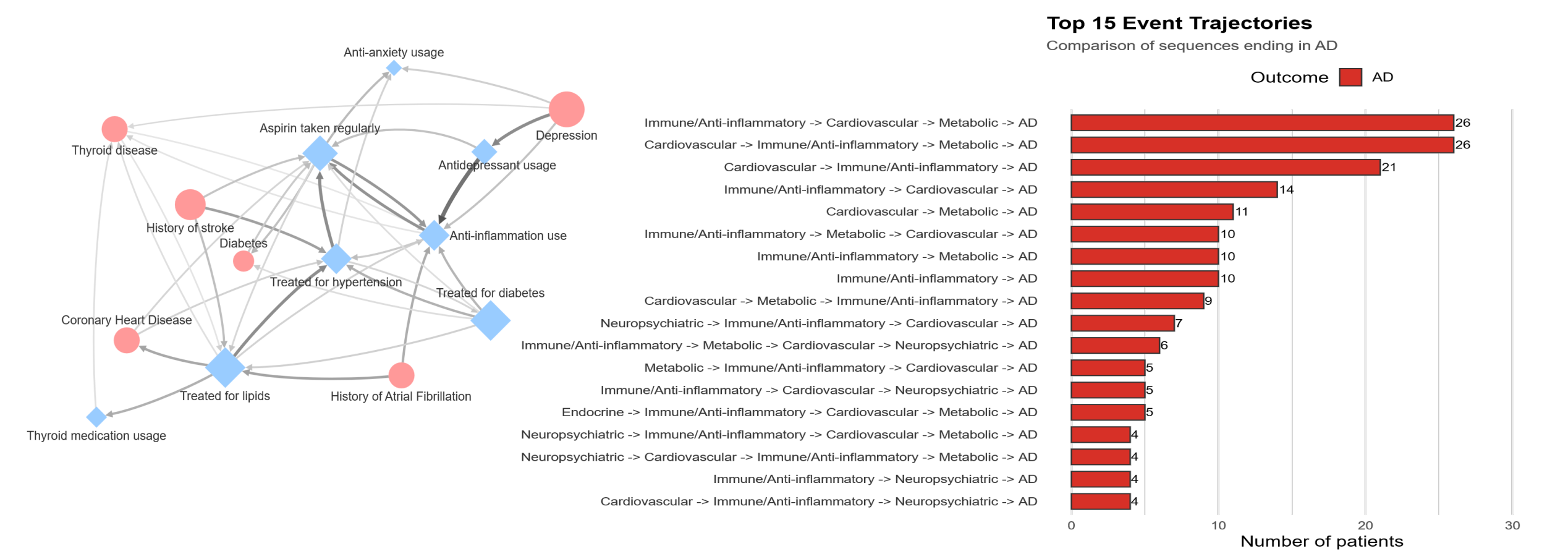


Transitive Sequential Pattern Mining (tSPM+)

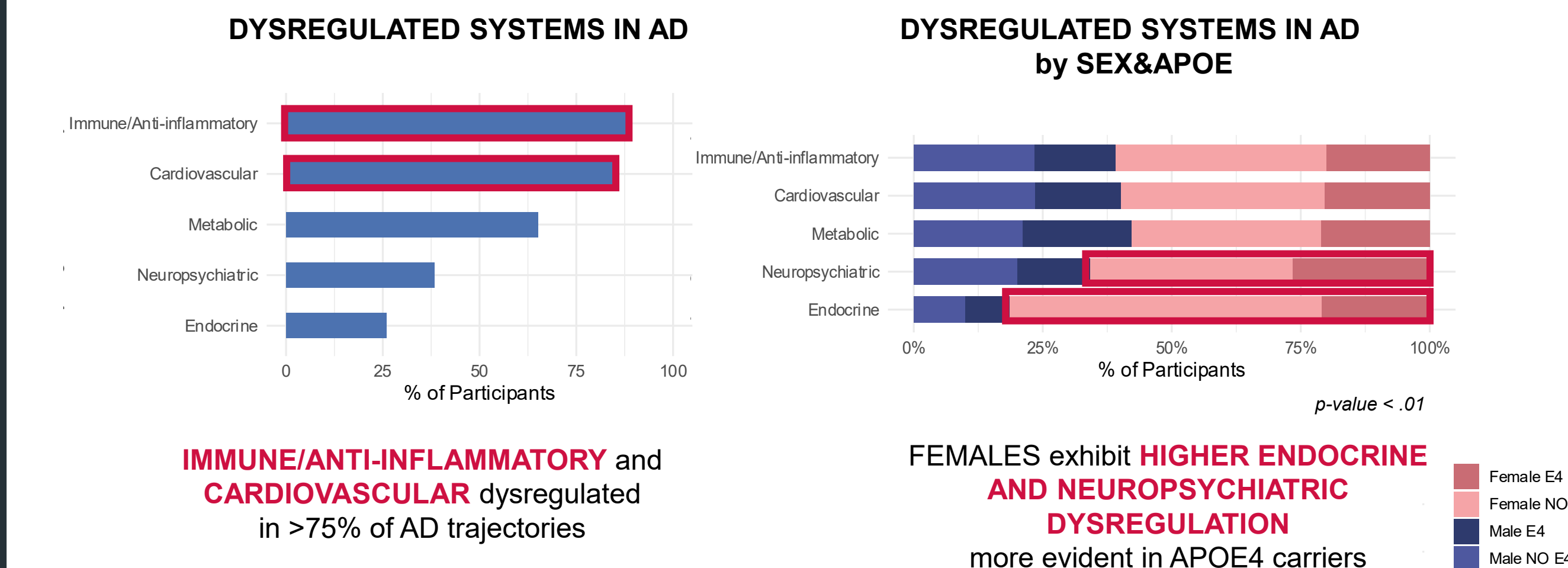


RESULTS

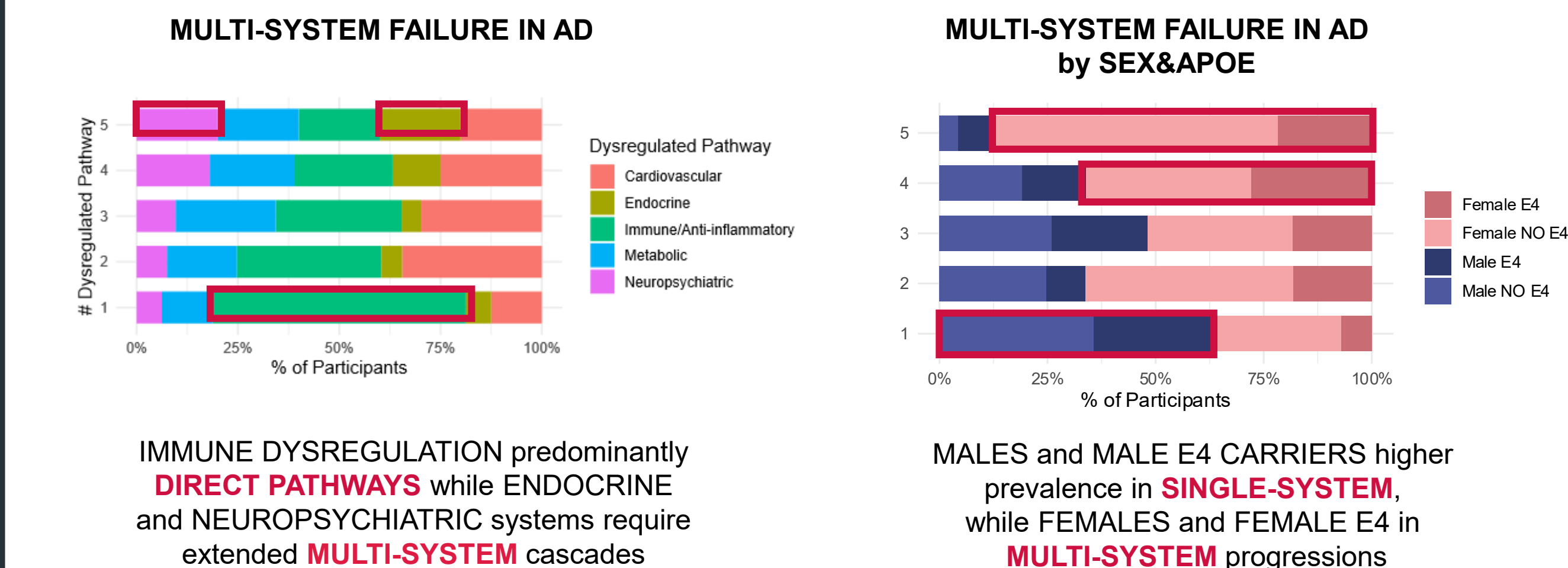
Predictive transitions form interconnected multi-domain patterns to AD



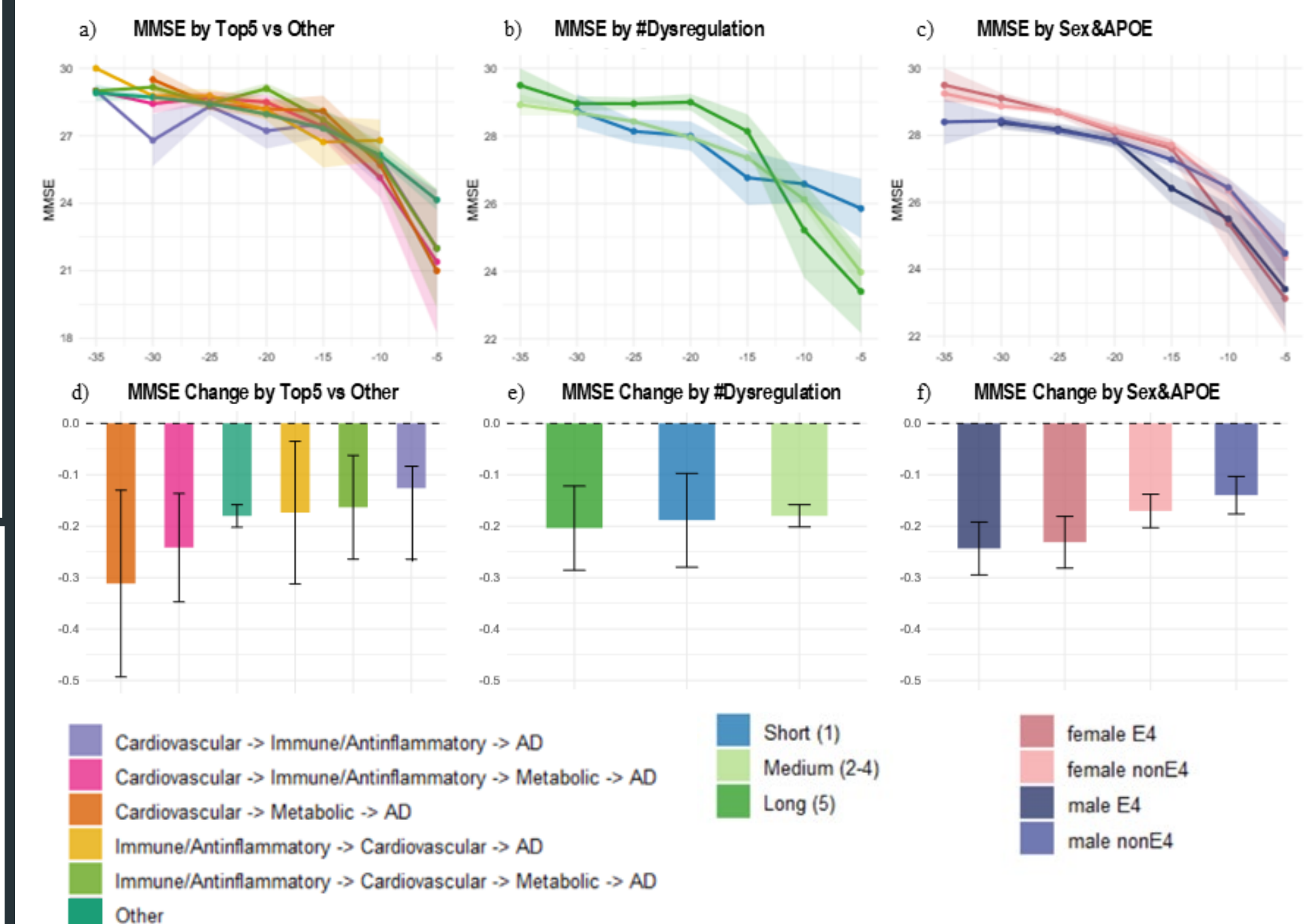
SYSTEM-SPECIFIC PREVALENCE ACROSS PROGRESSION PATTERNS



PROGRESSION PATTERN COMPLEXITY BY SYSTEM



VALIDATION: LONGITUDINAL MMSE TRAJECTORIES BEFORE AD DIAGNOSIS



DISCUSSION

- Our machine learning-based temporal framework successfully identified clinically meaningful, AD-predictive disease-medication trajectories from high-dimensional longitudinal data.
- AD progression follows multi-system pathways that differ fundamentally by sex and APOE genotype.
- Females exhibit prolonged multi-system dysregulation with high endocrine and neuropsychiatric burden, consistent with loss of estrogen neuroprotection during the menopausal transition.
- Males demonstrate concentrated vascular-metabolic cascades, with abbreviated trajectories, predominating in 40% of non- $\epsilon 4$ males.
- APOE- $\epsilon 4$ accelerates multi-system dysregulation; metabolic dysregulation is the key genotype-specific pathway.
- MMSE validation confirms clinical relevance of the trajectories.

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