

Pseudo-time Models Reveal Major Endothelial Contributions To Early Alzheimer Disease Pathogenesis:

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Novel pseudo-time models of AD highlight brain endothelial proteins as early and robust components of disease progression which diverge very early in disease pathogenesis near the point of amyloid positivity.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS
Emerging evidence suggests that brain endothelial dysfunction is an early core pathology in AD upstream of amyloid and tau. Pseudo-time modeling provides a powerful, data-driven approach to reconstruct disease trajectories from cross-sectional biomarker data, enabling integration of canonical AD markers with emerging biomarkers that reflect other pathologies such as neuronal/synaptic injury, astrocytic and microglial dysregulation, and endothelial injury.	We performed Olink CSF proteomics in a large well-characterized cohort of AD ($n=976$) from whom we had detailed clinical, cognitive, genetic and imaging assessments. Pseudo-time models depicted the progression of participants across the clinicopathological spectrum of AD. CSF biomarkers, including >800 brain endothelial proteins, synaptic markers (Ng, SNAP-25, and SYT-1), neuronal injury markers (NFL, VILIP-1), and glial markers (YKL-40, GFAP, TREM2) were plotted against pseudo-time using generalized additive models.	A B	Pseudo-time modeling revealed a temporally layered biomarker architecture in AD. Established synaptic and neuronal injury markers (Ng, SNAP-25, VILIP-1, NFL) diverged early along pseudo-time, closely aligned with amyloid positivity. Glial markers (YKL-40, GFAP, TREM2) showed progressive increases with tau emergence. Notably, endothelial proteins exhibited coherent and heterogeneous trajectories: SDC4, increased robustly with amyloid and accelerated with tau positivity, whereas SMOC1 diverged early but progressed more gradually. showed stage-specific acceleration in tau-positive disease.	Novel pseudo-time models of AD highlight brain endothelial proteins as early and robust components of disease progression which diverge very early in disease pathogenesis near the point of amyloid positivity. CONTACT Rawan Tarawneh, MD Rawan.Tarawneh@health.slu.edu ALZHEIMER'S ASSOCIATION AAIC 26