Predictors of Progression to MCI and AD (Epidemiology):
New Approaches to Understanding the Relationships of Risk Factors to Cognitive Decline

David A. Bennett, MD
Director, Rush Alzheimer's Disease Center
Professor of Neurological Sciences
Rush University Medical Center
Chicago, IL. USA

Rush Alzheimer's Disease Center

RESEARCH FAMILY CARE EDUCATION

Mild Cognitive Impairment (MCI) Symposium 2013
Predicting and Measuring Progression in Early Alzheimer's Disease (AD)
Mount Sinai Medical Center
Miami, FL
January 19, 2013

Acknowledgments

Acknowledgments

Study Participants:
Religious Orders Study
Rush Memory and Aging Project

Disclosures

I have no relevant disclosures.

Objectives

- Change-point models to investigate the relation of risk factors with cognitive decline

- Cross-lagged models to investigate relation of risk factors with cognitive decline and cognitive decline with change in risk factors

- Incorporating neuropathologies into studies of the relation of risk factors to cognitive decline

The Religious Orders Study

- Began in 1993
- > 1,150 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation, blood donation at baseline, and repeated on a subset
- All agreed to brain donation
- > 275 have developed dementia
- > 400 have developed MCI
- > 550 brain autopsies

The Memory and Aging Project
… because memories should last a lifetime
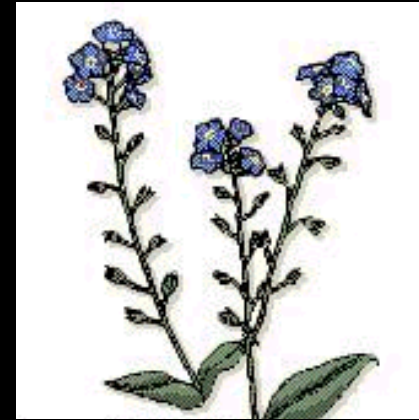
- Began in 1997
- > 1,650 older persons without dementia from across northeastern Illinois
- All agreed to annual clinical evaluation and annual blood donation
- All agreed to donate brain, spinal cord, muscle, nerve
- > 250 have developed dementia
- > 375 have developed MCI
- > 465 autopsies

The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort
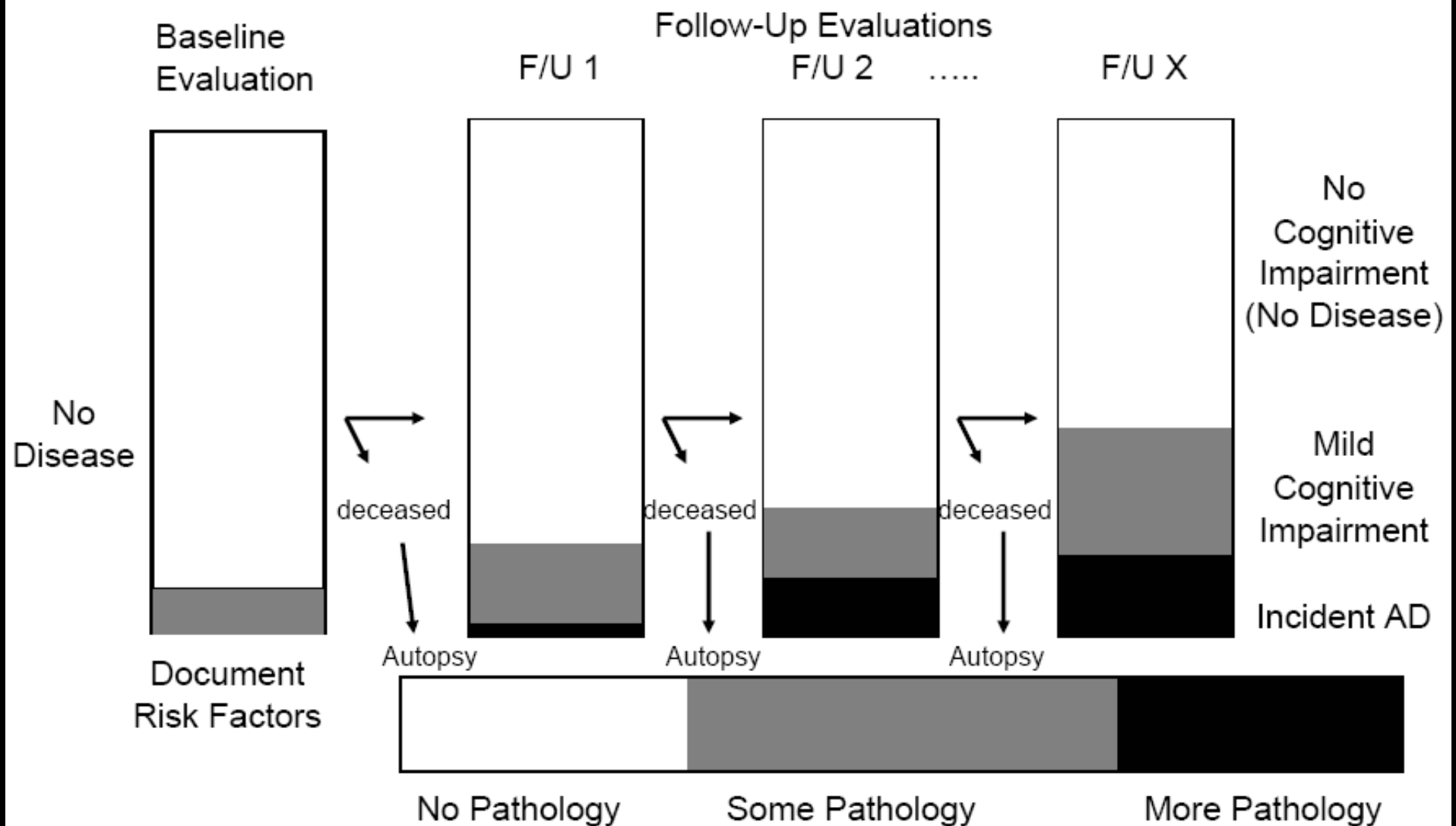
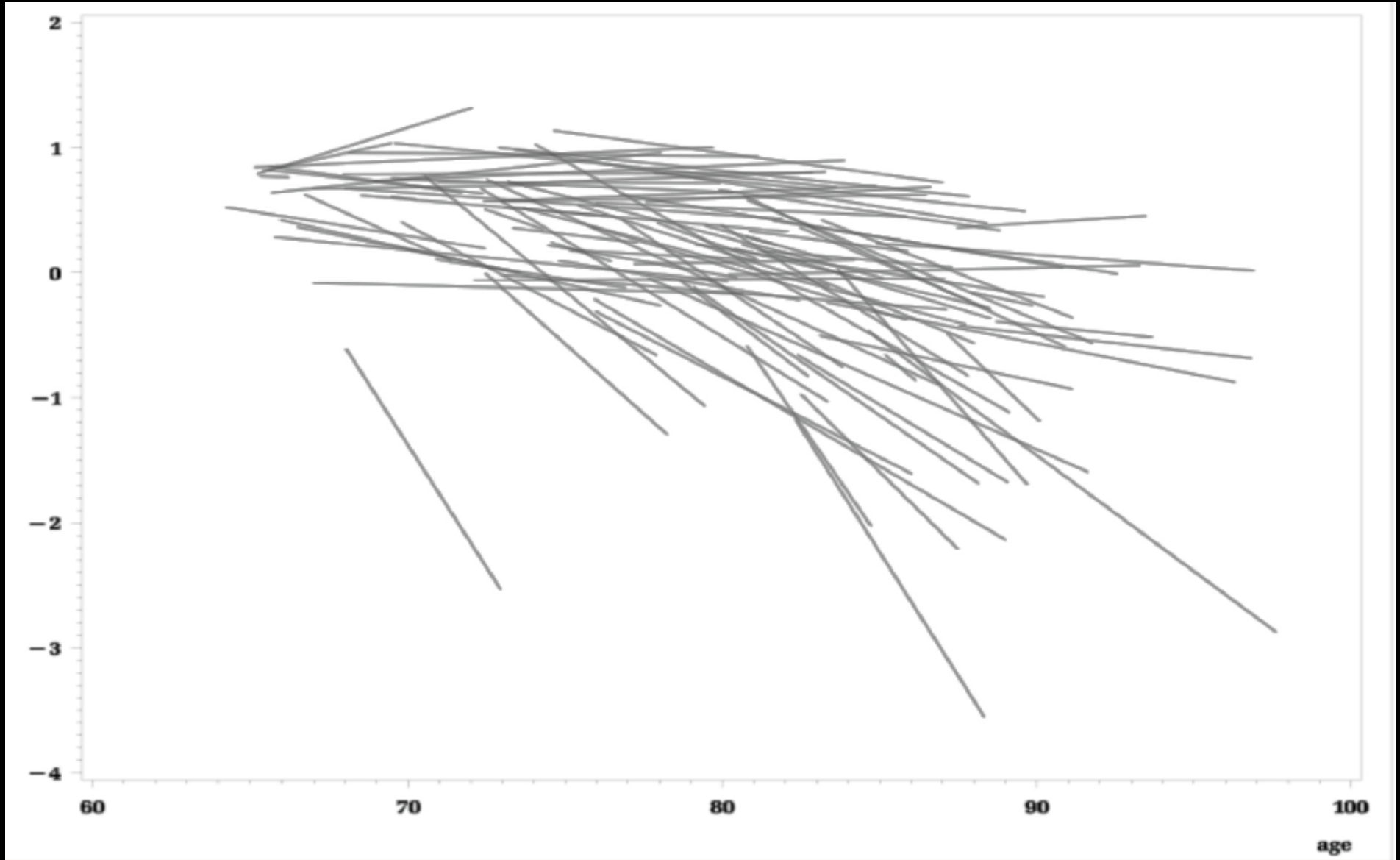Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

Objectives

- Change-point models to investigate the relation of risk factors with cognitive decline

- Cross-lagged models to investigate relation of risk factors with cognitive decline and cognitive decline with change in risk factors

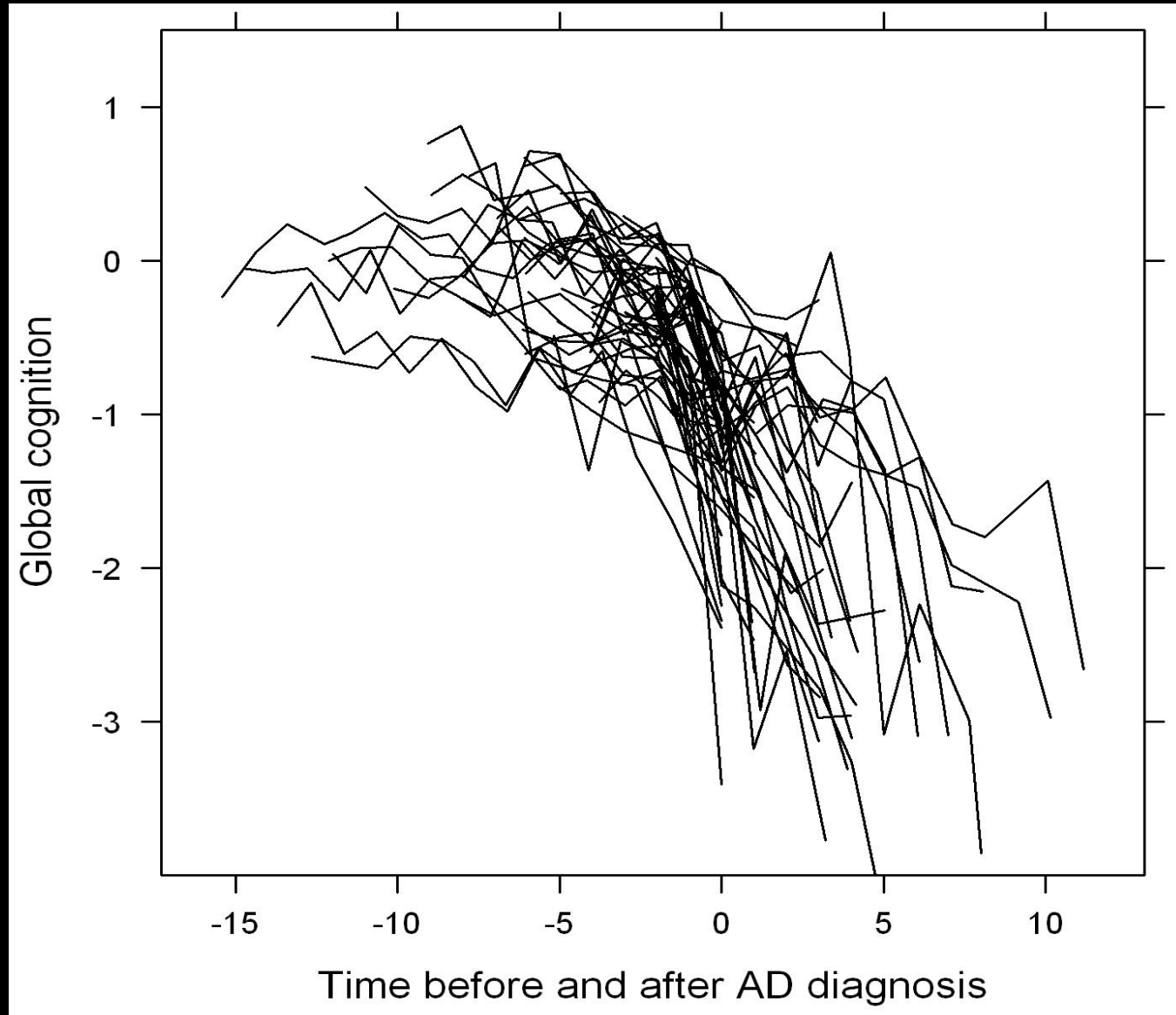- Incorporating neuropathologies into studies of the relation of risk factors to cognitive decline
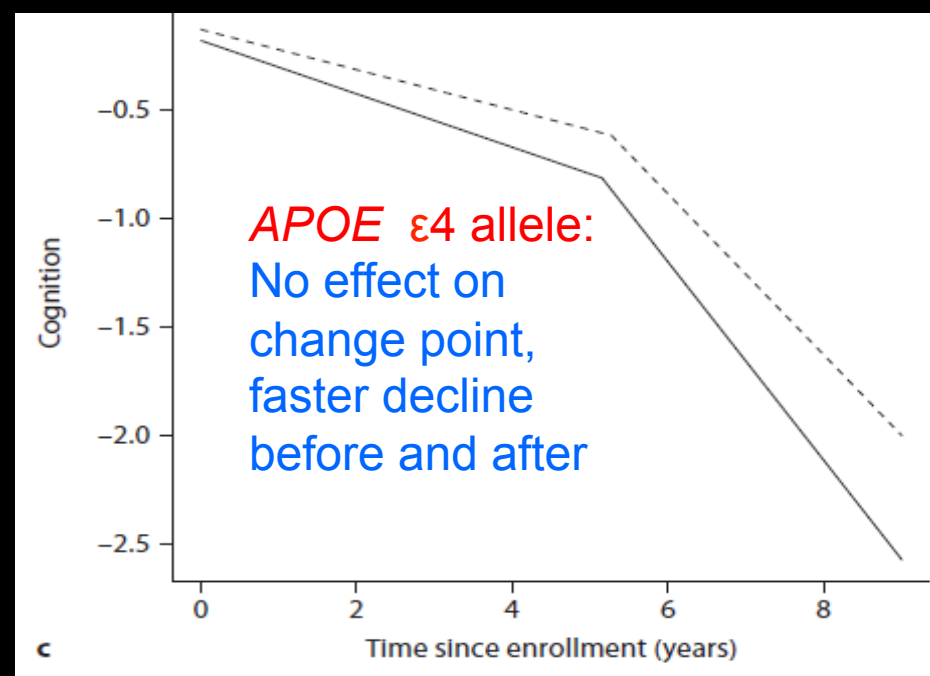
Random Sample of Repeated Measures from Study Participants
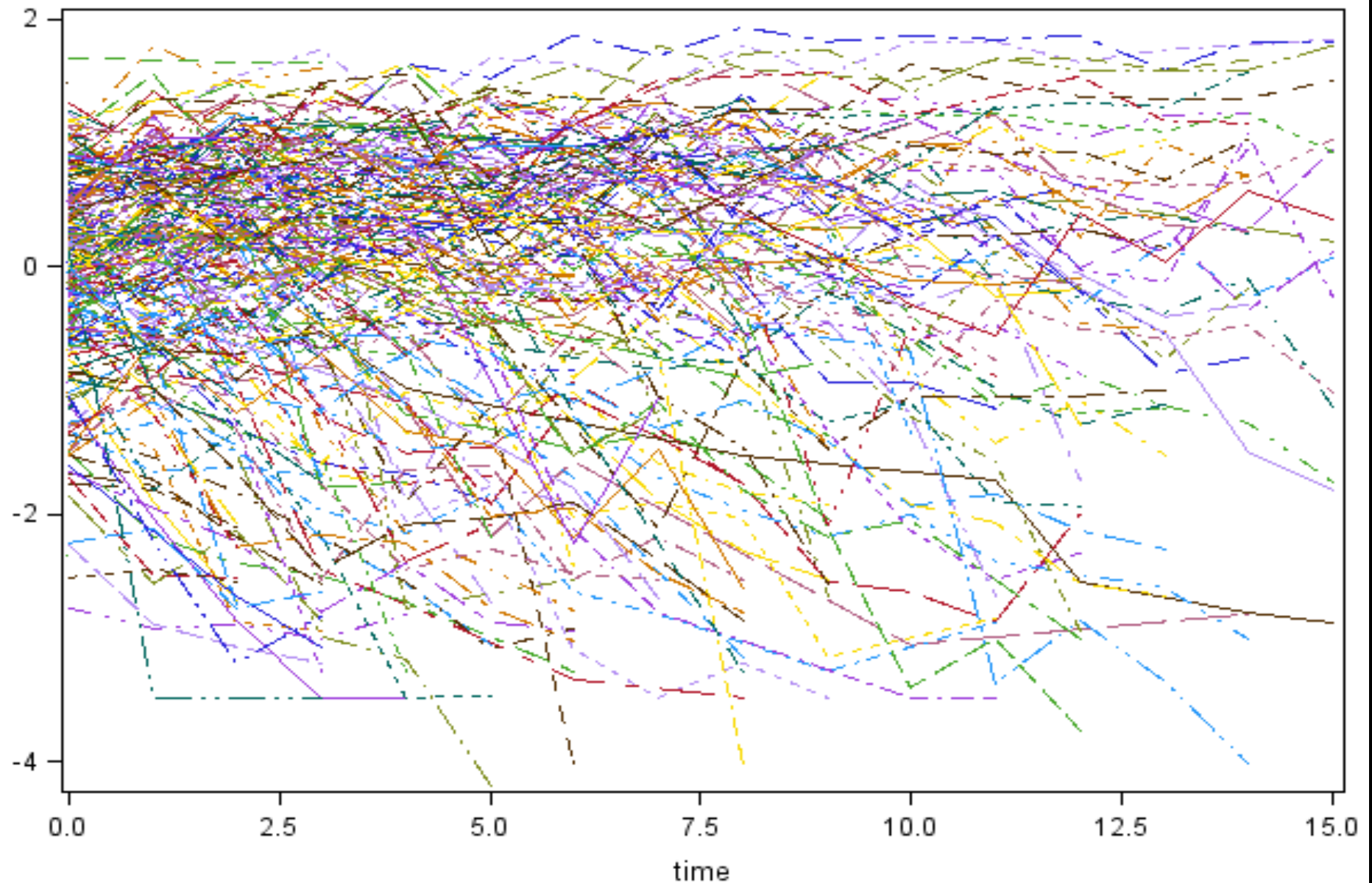
Random Sample of Person-Specific Slopes from Linear Mixed Model

Random Sample of Individual Repeated Measures Before and After AD

A Random Change Point Model for Cognitive Decline in Alzheimer's Disease and Mild Cognitive Impairment

Age: Earlier change point, no effect on slopes

Education: Later change point and faster decline after change point

APOE ε4 allele: No effect on change point, faster decline before and after

Yu L, et al. *Neuroepidemiology.* 2012;39:73-83.

A Random Change Point Model for Cognitive Decline in Alzheimer's Disease and Mild Cognitive Impairment

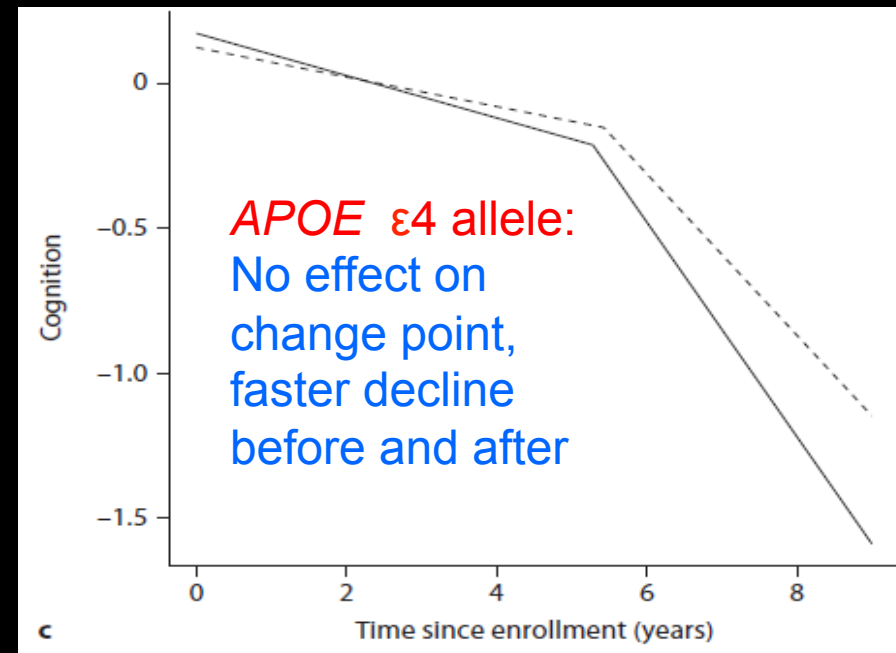Age: Earlier change point, no effect on slopes

Education: Later change point and faster decline after change point

APOE ε4 allele: No effect on change point, faster decline before and after
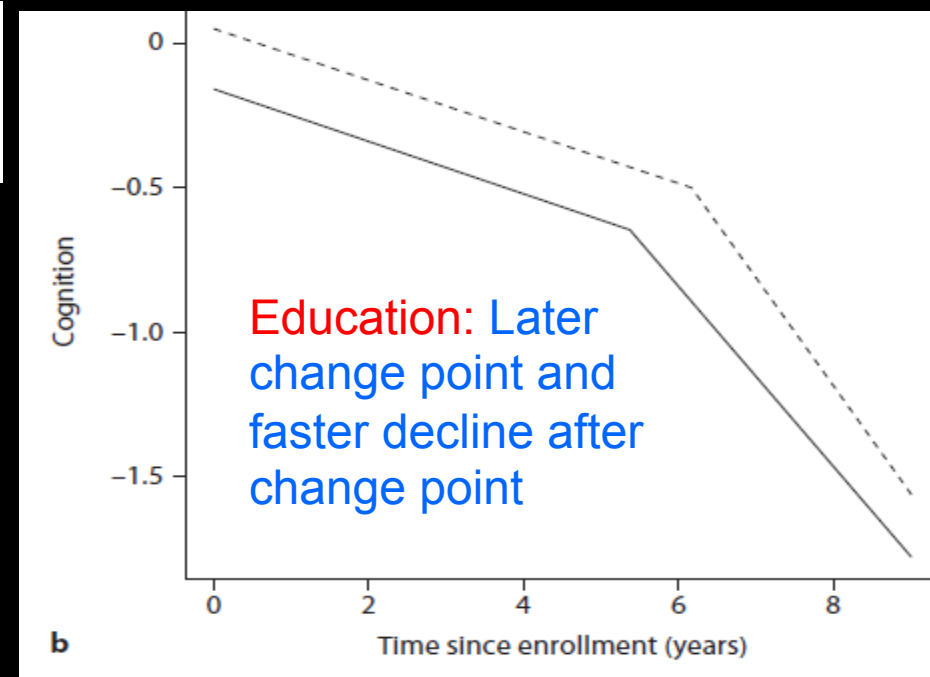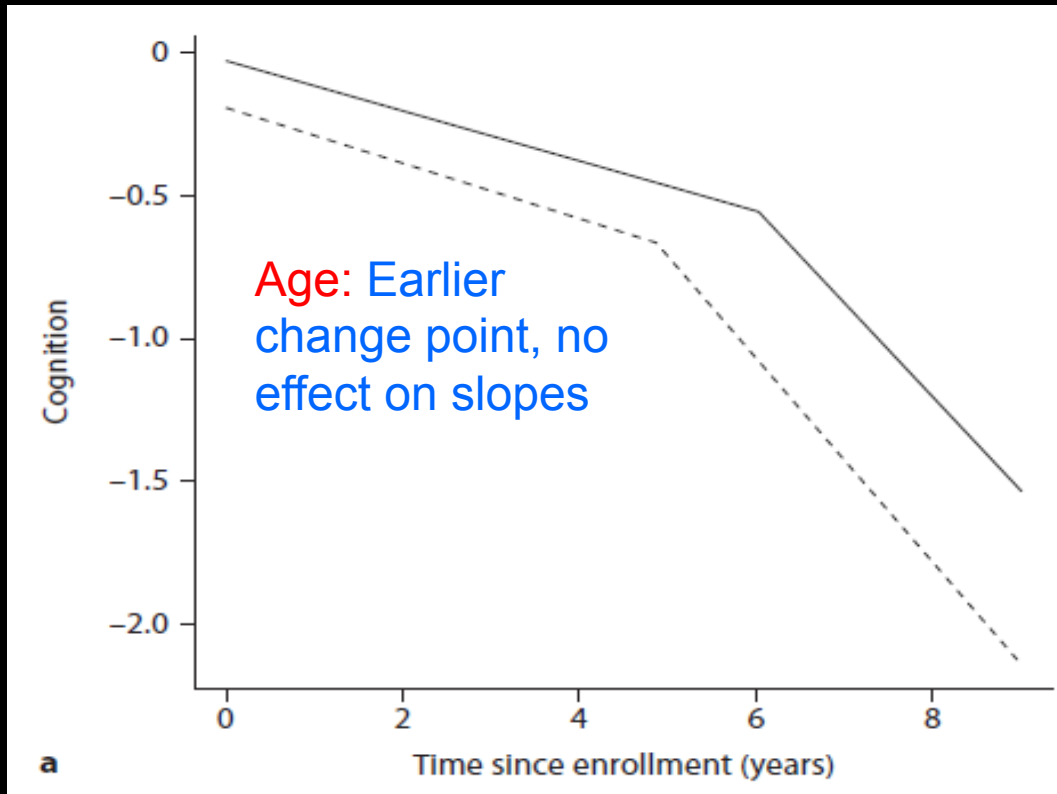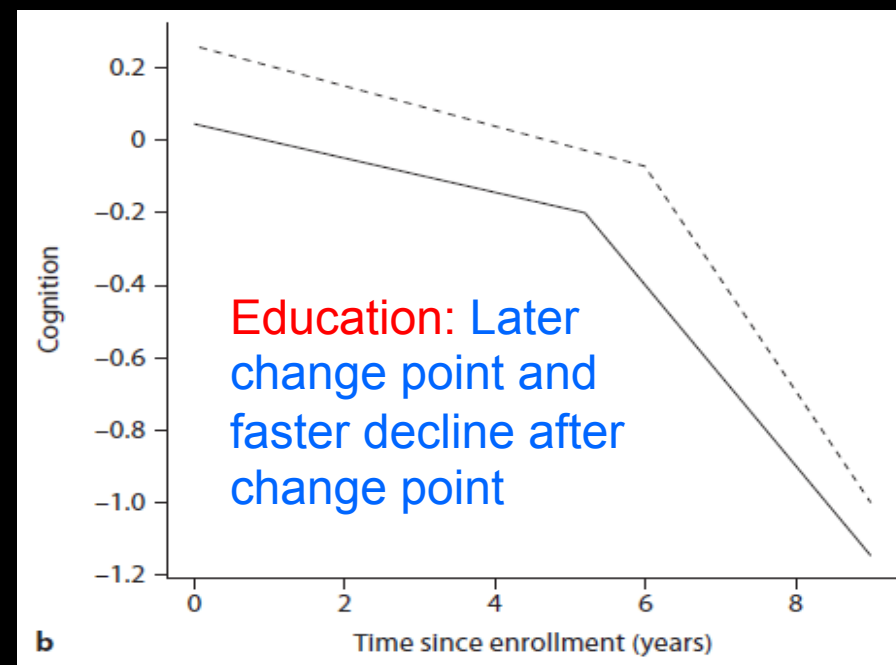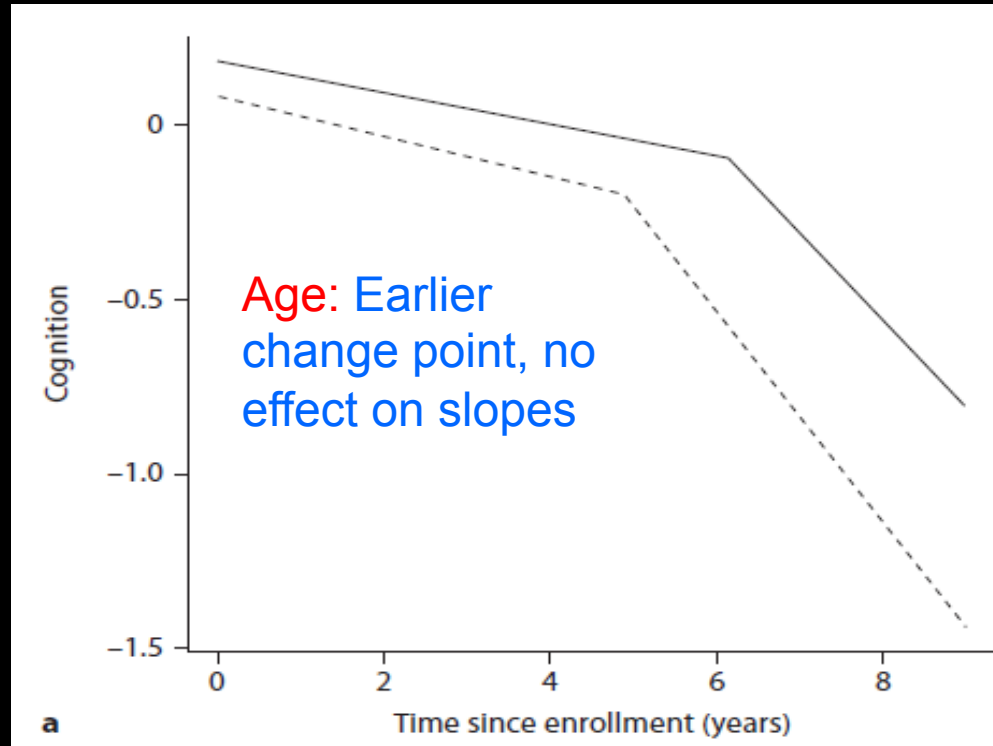
Results for MCI same as AD

Yu L, et al. *Neuroepidemiology.* 2012;39:73-83.

Summary

- Over long follow-up periods, the trajectory of cognitive change can be characterized by change-point models that describe the onset of cognitive decline and the slope prior to and after the onset
- Risk factors are differentially related to these three indices

Objectives

- Change-point models to investigate the relation of risk factors with cognitive decline

- Cross-lagged models to investigate relation of risk factors with cognitive decline and cognitive decline with change in risk factors

- Incorporating neuropathologies into studies of the relation of risk factors to cognitive decline

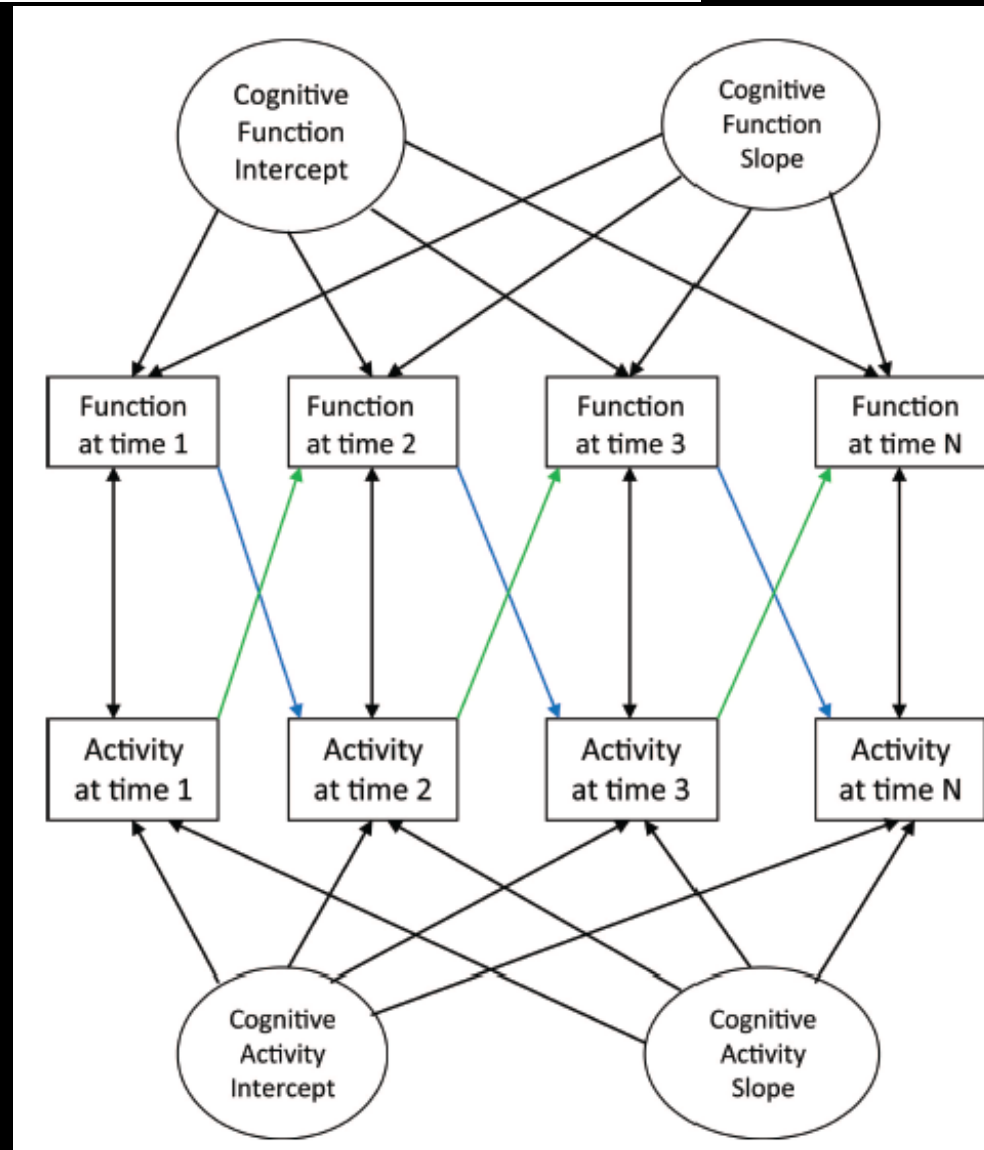# Influence of late-life cognitive activity on cognitive health

Cognitive activity is related to cognitive decline and AD risk. However, cognitive function and cognitive activity both change over time.
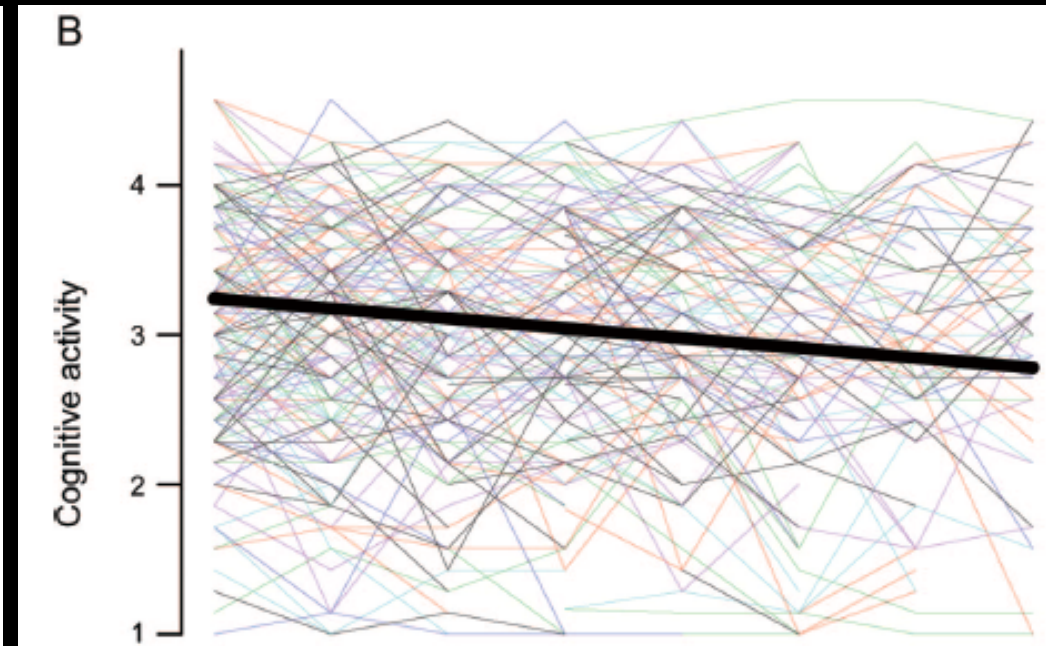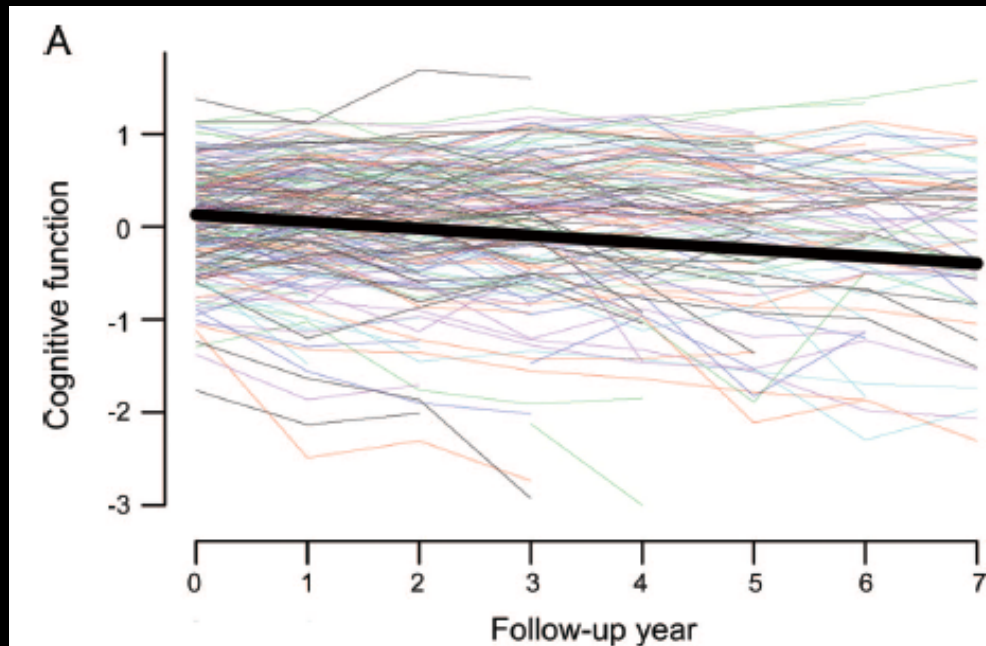
Does cognitive activity predict cognitive subsequent cognitive decline or is loss of cognitive activity and early sign of cognitive decline?

Wilson RS, et al. *Neurology*. 2012;78:1123-1129.

Influence of late-life cognitive activity on cognitive health

Influence of late-life cognitive activity on cognitive health

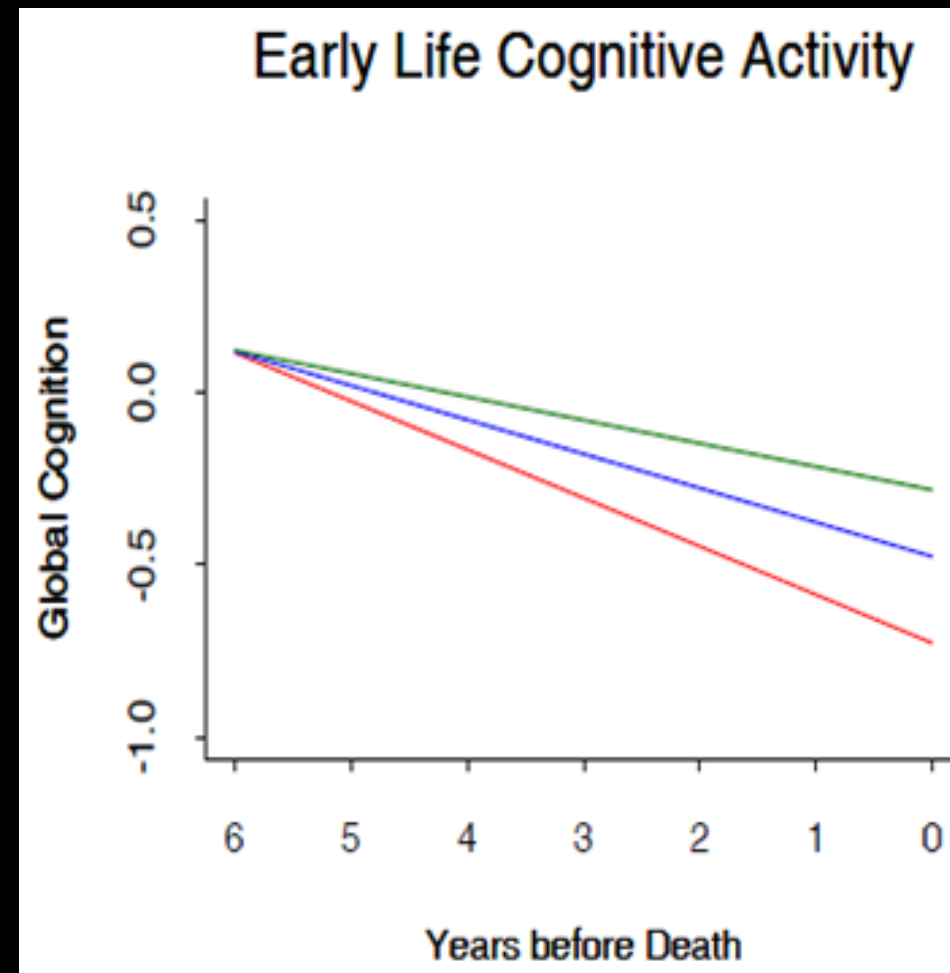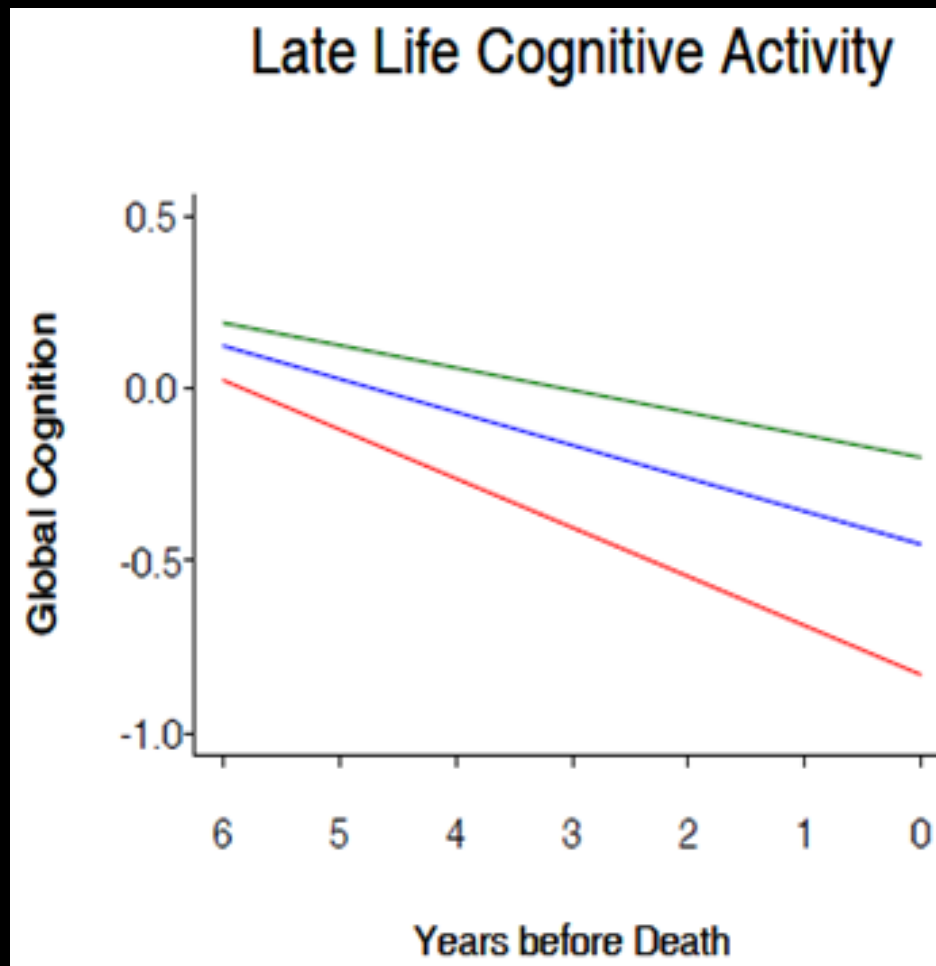| Cognitive function | Correlation between change in cognition and activity | | | Cross-lagged effects[b] | | | | | |
				Activity → function			Function → activity		
	Estimate	SE	p Value	Estimate	SE	p Value	Estimate	SE	p Value
Episodic memory	0.315	0.066	<0.001	0.027	0.004	<0.001	−0.015	0.020	0.450
Semantic memory	0.386	0.065	<0.001	0.020	0.003	<0.001	0.006	0.024	0.789
Working memory	0.227	0.076	0.003	0.015	0.005	0.042	0.042	0.017	0.012
Perceptual speed	0.524	0.058	<0.001	0.019	0.004	<0.001	0.037	0.021	0.081

Summary

- Cross-lagged models can inform on the direction of causality when change in cognition is correlated with change in a risk factor

Objectives

- Change-point models to investigate the relation of risk factors with cognitive decline

- Cross-lagged models to investigate relation of risk factors with cognitive decline and cognitive decline with change in risk factors

- **Incorporating neuropathologies into studies of the relation of risk factors to cognitive decline**

Life Span Cognitive Activity, Neuropathologic Burden, and Cognitive Decline

Effect of Purpose in Life on the Relation Between Alzheimer Disease Pathologic Changes on Cognitive Function in Advanced Age

Purpose in life is the psychological tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness guiding behavior.

Boyle PA, et al. *Arch General Psychiatry.* 2012;69:499-506.
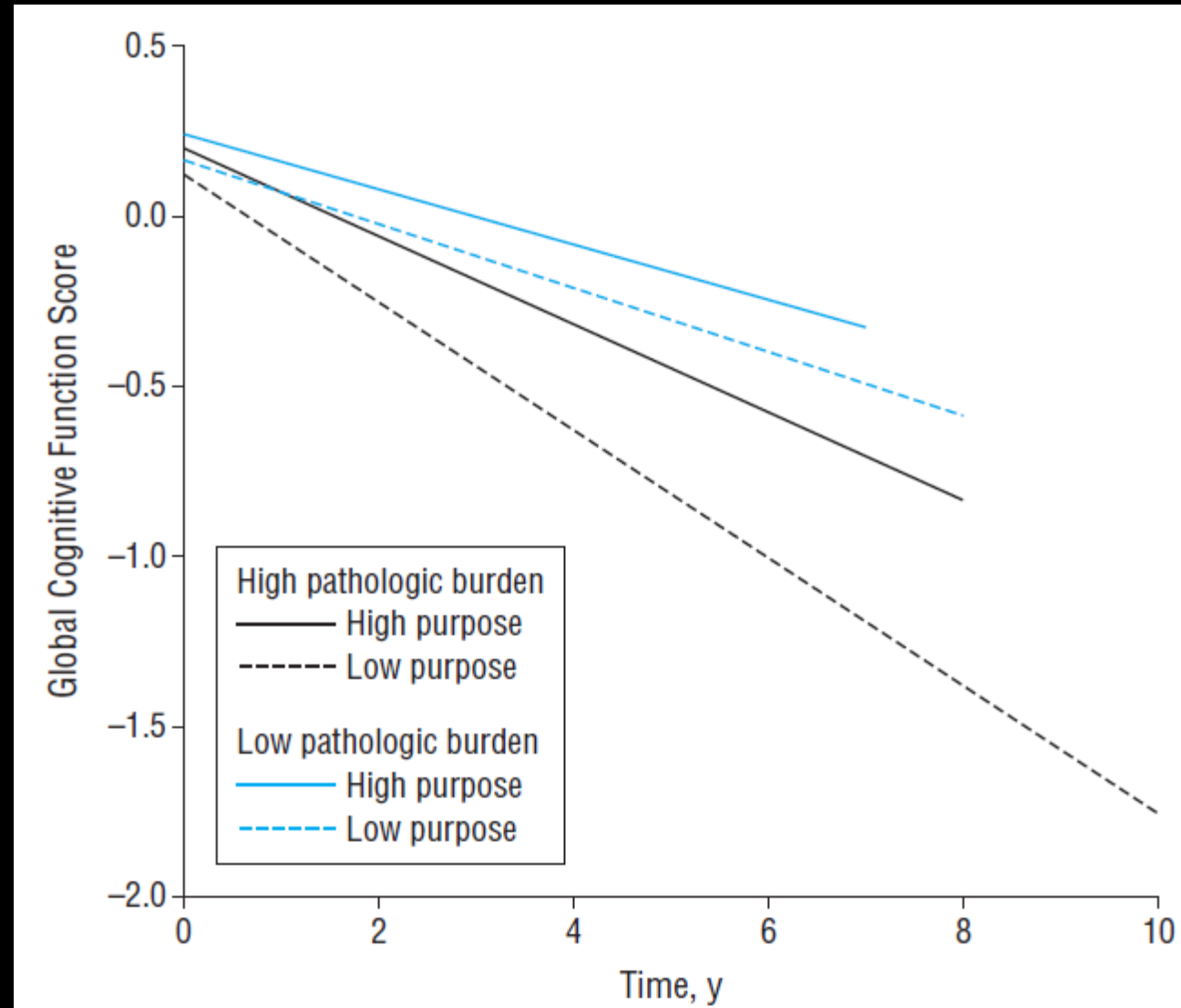
# Random Sample of Individual Repeated Measures Among Deceased
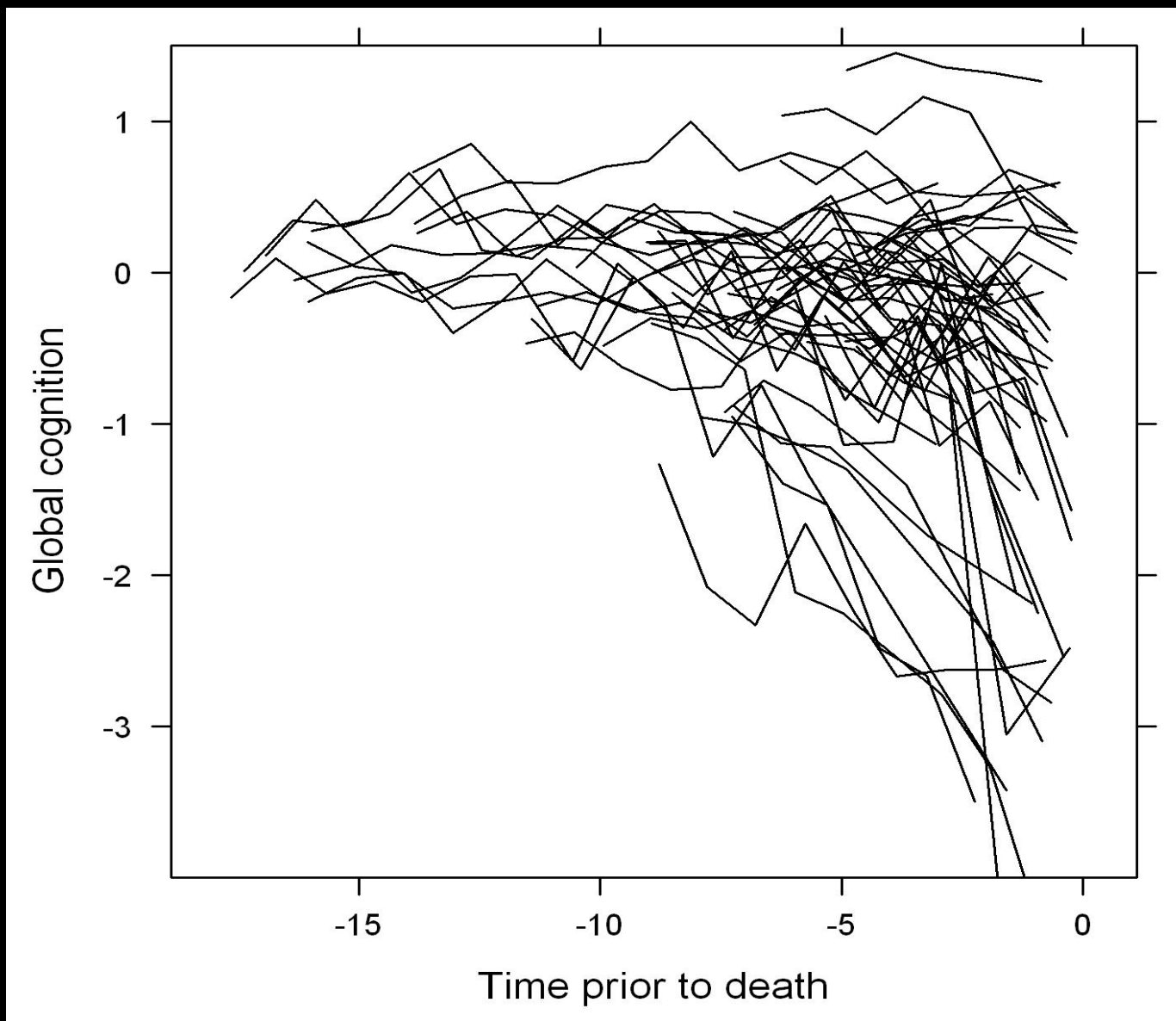
APOE ε4, Alzheimer's disease pathology, cerebrovascular disease, and cognitive change over the years prior to death

## *APOE* associated with an earlier onset of terminal decline, and a faster slope before and after onset

	EST (SD)	95% CI
Mean trajectory for non-carriers		
Onset of terminal decline	**-3.20 (0.16)**	**-3.51, -2.89**
Pre-terminal decline slope	**-0.04 (0.005)**	**-0.05, -0.03**
Terminal decline slope	**-0.30 (0.02)**	**-0.35, -0.27**
Additional burden for carriers		
Onset of terminal decline	**-0.75 (0.22)**	**-1.18, -0.32**
Pre-terminal decline slope	**-0.03 (0.008)**	**-0.05, -0.01**
Terminal decline slope	**-0.12 (0.03)**	**-0.18, -0.06**

APOE ε4, Alzheimer's disease pathology, cerebrovascular disease, and cognitive change over the years prior to death

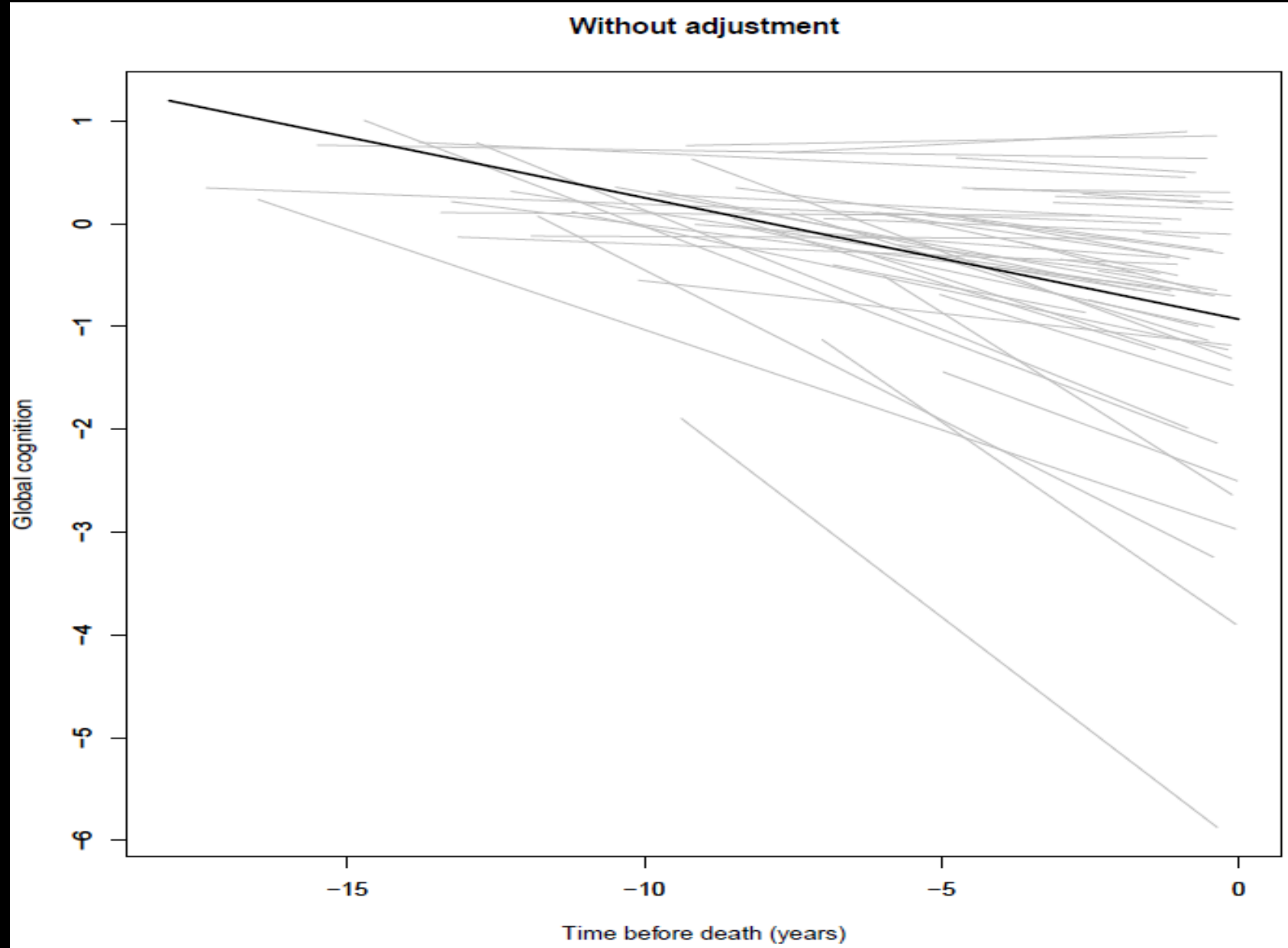APOE not associated with cognitive decline after controlling for amyloid load and PHFtau tangles

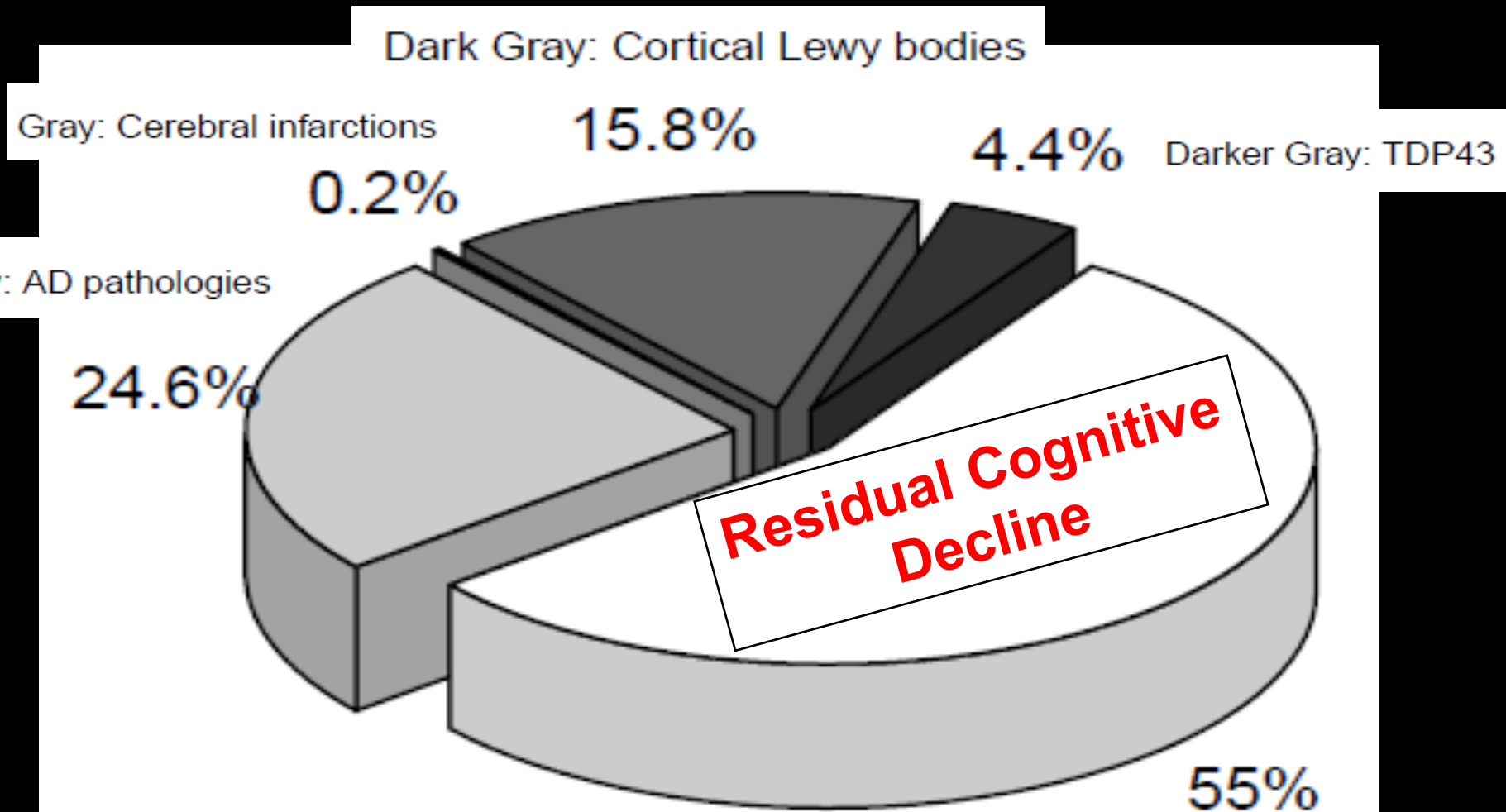Yu L, et al. *Psych & Aging.* In press.
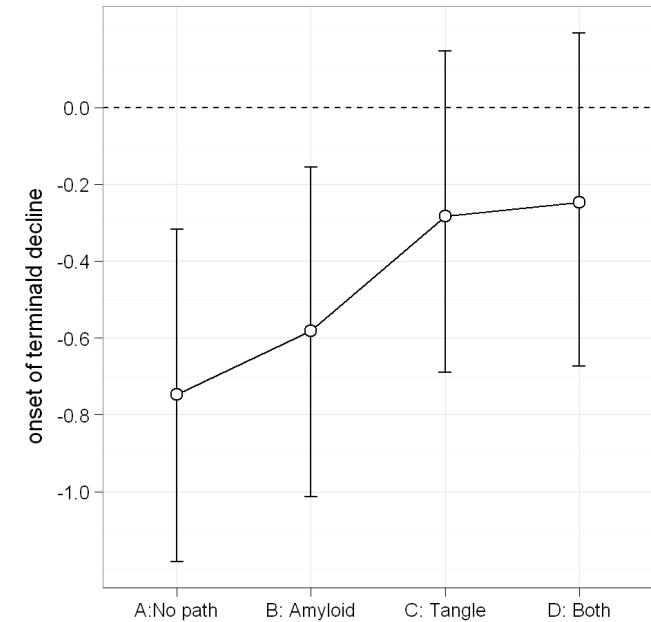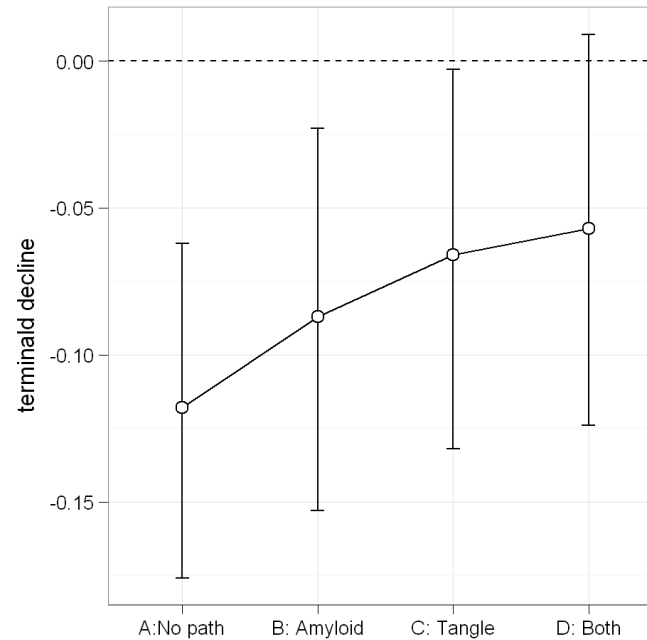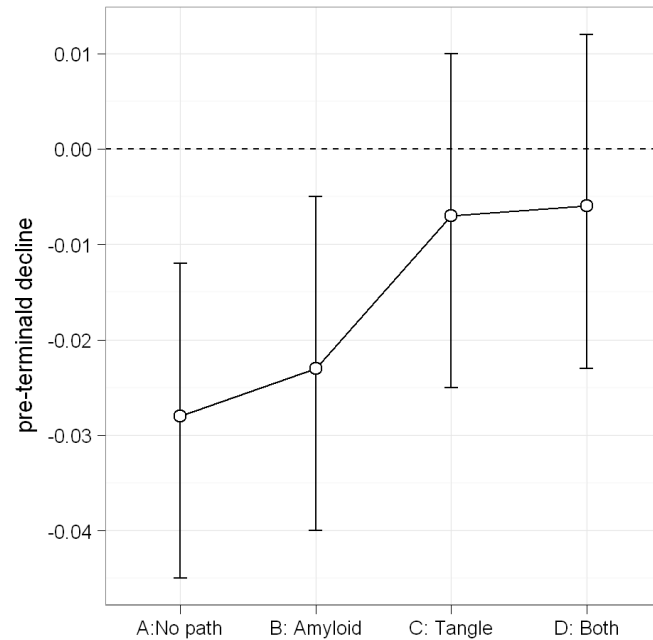
Purpose in life slows the rate of terminal cognitive decline
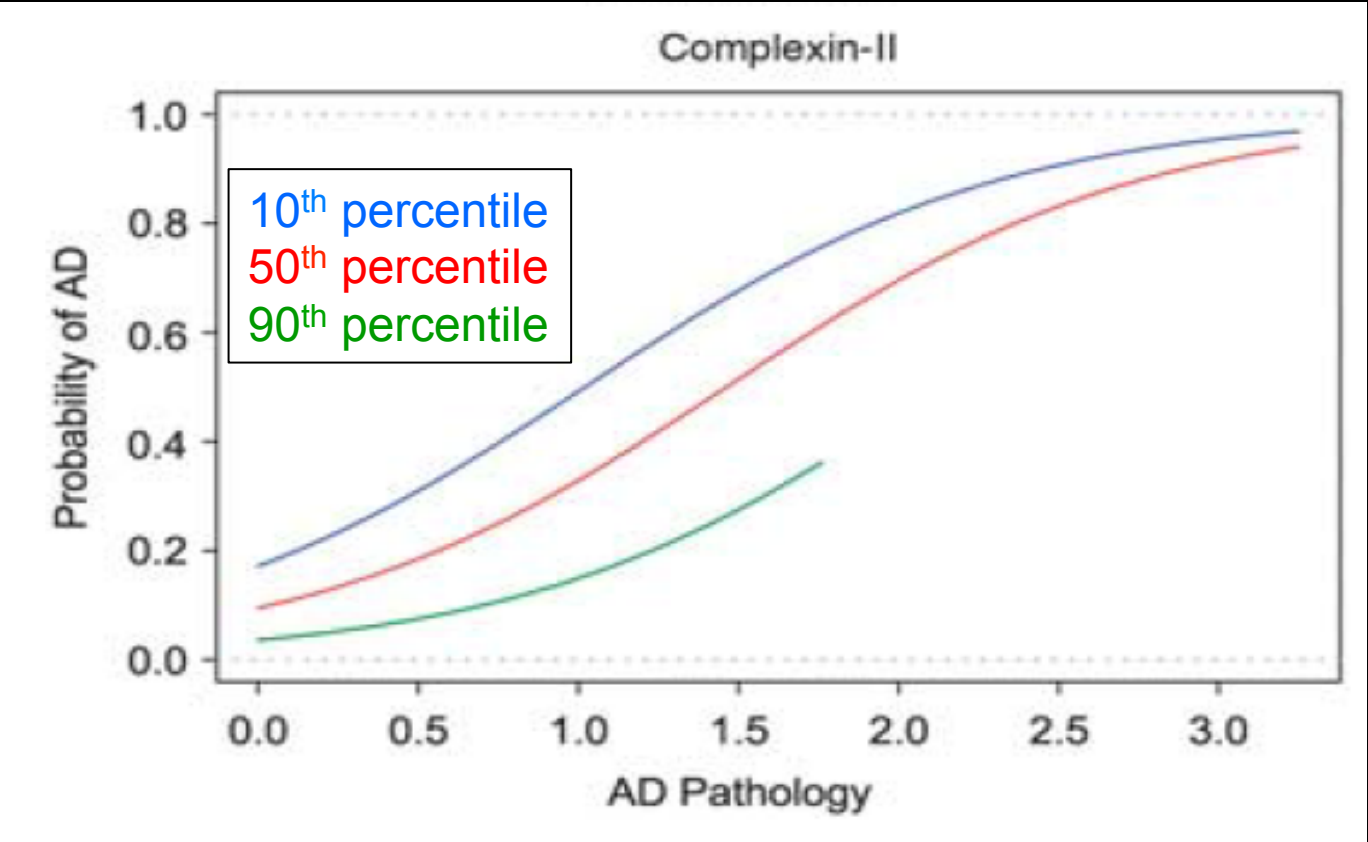

Boyle PA, et al. In preparation.
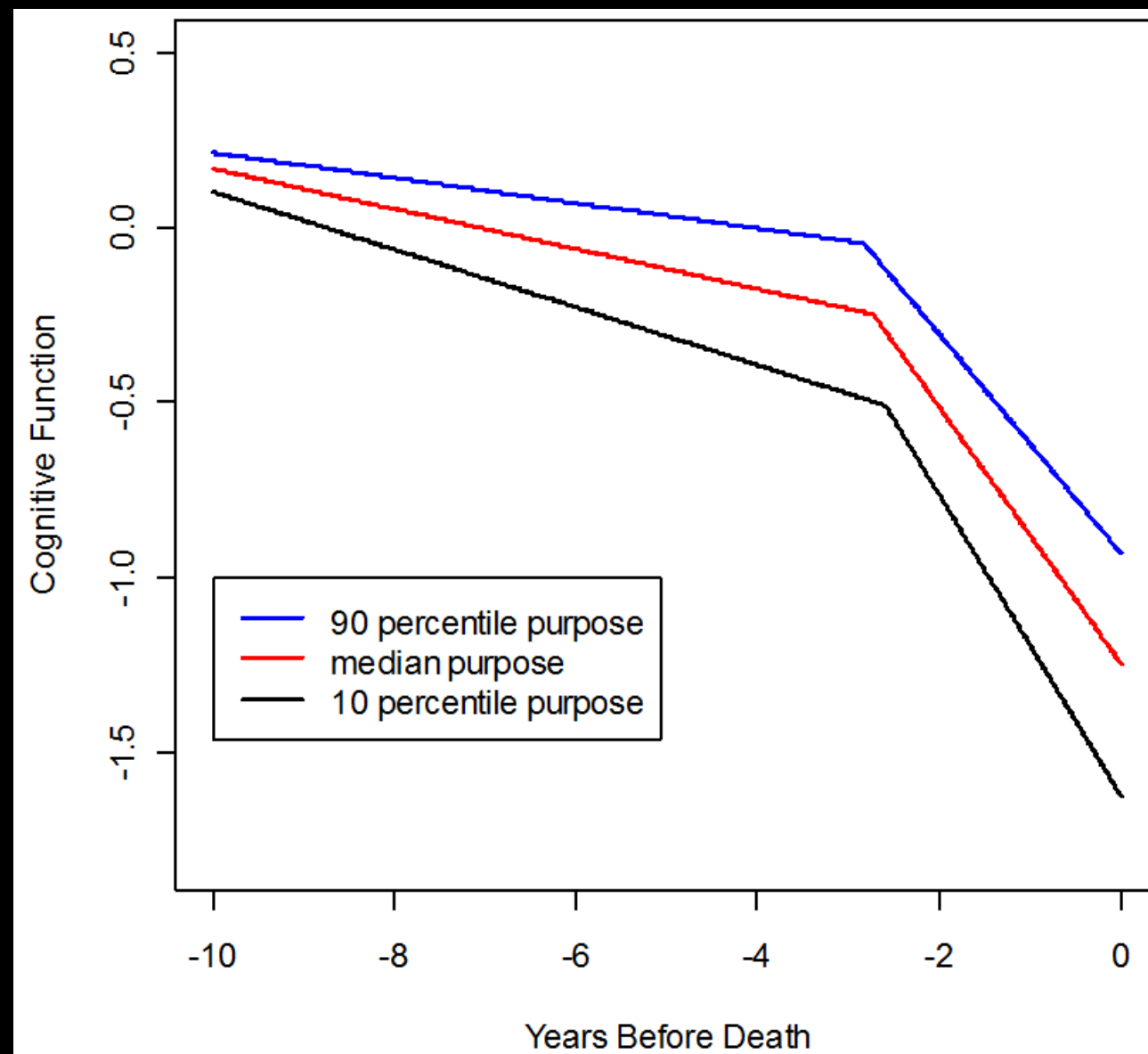
Random Sample of Person-Specific Slopes – Autopsied

Without adjustment

Variance of Cognitive Decline Explained by AD, CVD, LB and TDP-43 Pathology

Dark Gray: Cortical Lewy bodies

Gray: Cerebral infarctions

15.8%

4.4% Darker Gray: TDP43

0.2%

Light Gray: AD pathologies

24.6%

Residual Cognitive Decline

55%

Cognitive reserve, presynaptic proteins and dementia in the elderly

Complexin-II

10th percentile
50th percentile
90th percentile

Probability of AD (y-axis) vs AD Pathology (x-axis)

Honer WG, et al. *Translational Psychiatry*. 2012;2:e114.

Complexin-I (inhibitory)

Global cognition vs Time in study (years)

- 10th percentile (red)
- 50th percentile (black)
- 90th percentile (green)
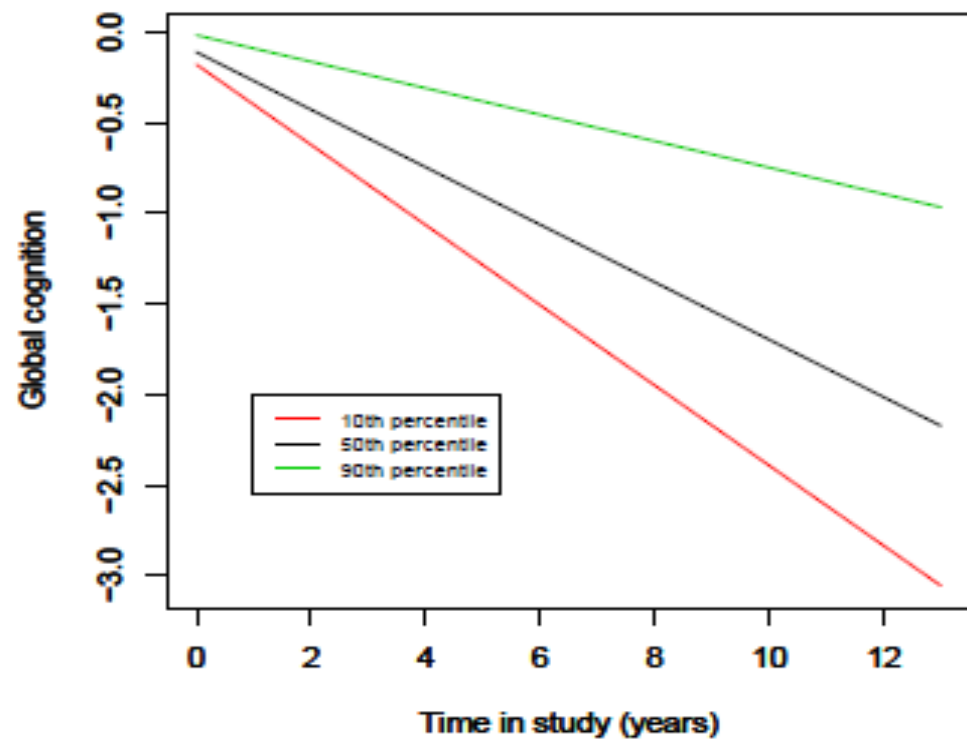
Complexin-II (excitatory)

Global cognition vs Time in study (years)

- 10th percentile (red)
- 50th percentile (black)
- 90th percentile (green)
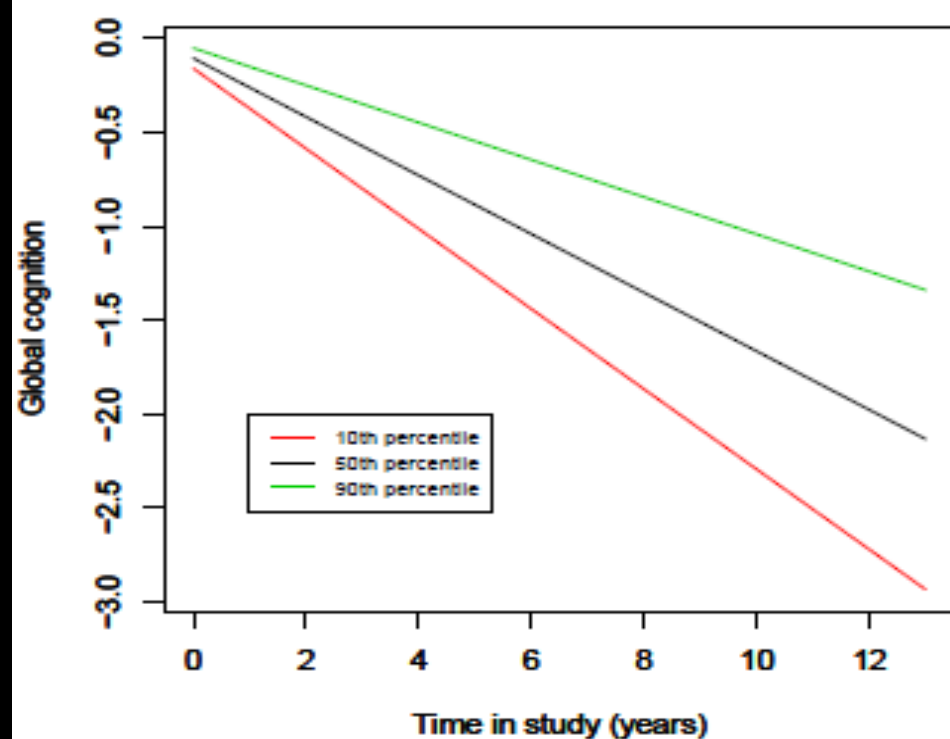
Neural Reserve, Neuronal Density in the Locus Coeruleus, and Cognitive Decline

Wilson RS, et al. *Neurology.* In press.
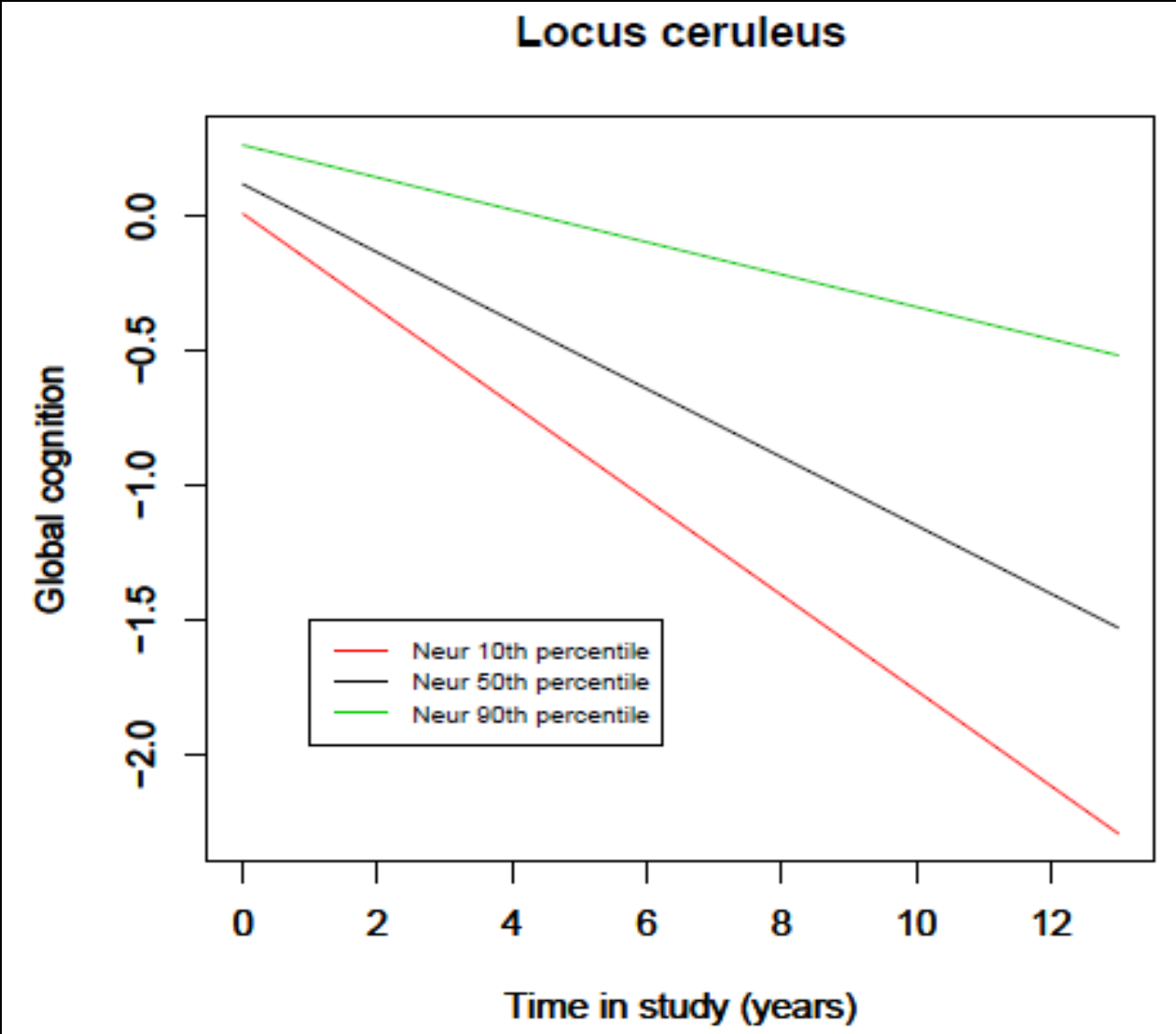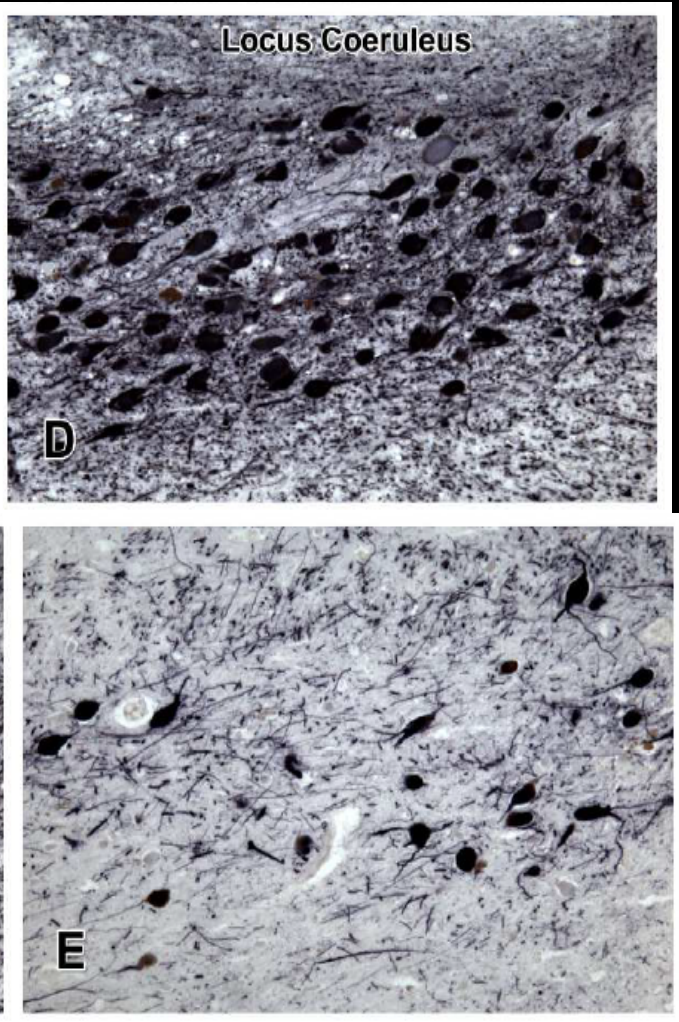
Summary

•Neuropathologies and risk factors, modeled as joint predictors of cognitive decline and terminal decline, reveal complex associations between these variables.
•We can currently explain only about half of the variability of cognitive decline with measures of brain pathology and resilience markers
•The competing effects of neuropathology and resilience markers contribute to important individual differences in the rates of cognitive decline