Biomarker Values Predictive of Cognitive Decline:
Baseline or Progression?

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Nothing to disclose

Outline of my talk

I. Discuss briefly several statistical approaches useful for longitudinal data analysis

II. Introduce our most recent work in which we aim to identify biomarker values associated with declines in cognitive functions, using ADNI 1 data

# Longitudinal Data Analysis
Why important?

- Knowledge of biomarkers predictive of cognitive and functional decline can facilitate selective recruitment of participants for clinical trials.

- Research efforts are moving towards early identification of high risk subjects and prevention of progression. Identifying biomarkers associated with subtle declines in cognitive functions among asymptomatic subjects is especially critical.

# I. (Some) Statistical Approaches Useful in Longitudinal Data Analysis of Biomarkers and Cognition

➢Change point model

➢Latent trajectory model

Change Point Model

- Developed by Dr. Charles Hall (Einstein School of Medicine)

- Identify the location of changes (acceleration points) in slopes in relation to a specific endpoint (incidence of dementia onset, MCI, death, etc)
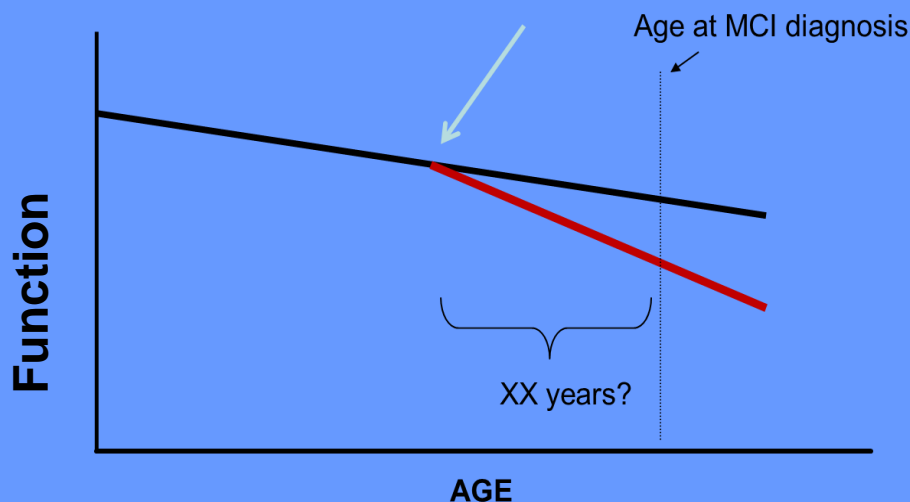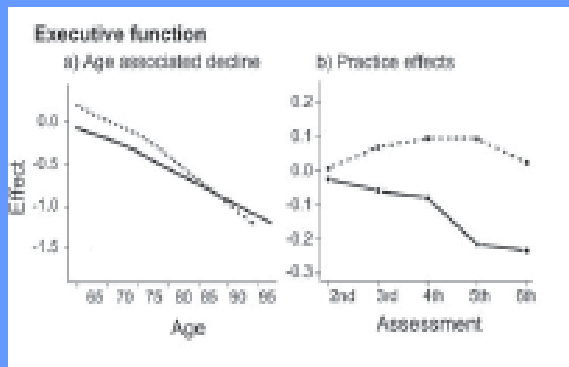
Change Point Models: Examples
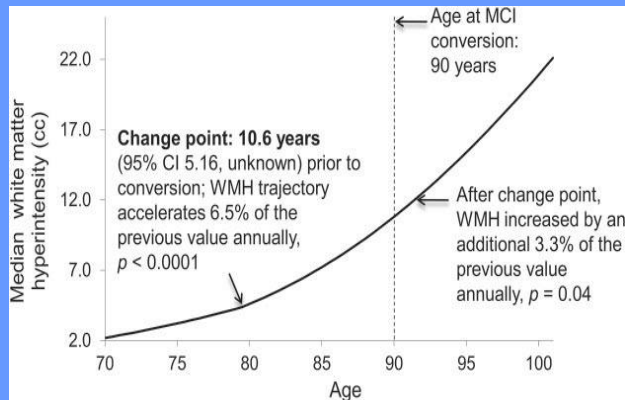
Silbert, Dodge et. al. **Trajectory of white matter hyperintensity burden preceding mild cognitive impairment**. Neurology 2012;79:741-747
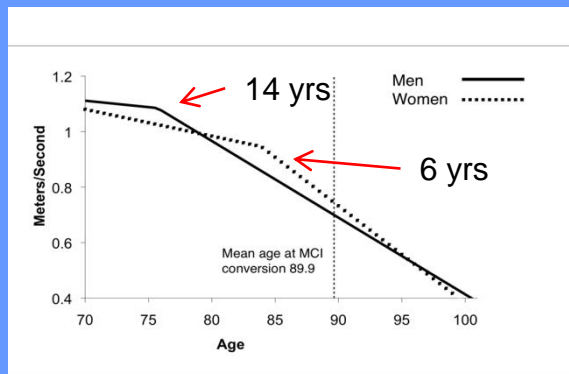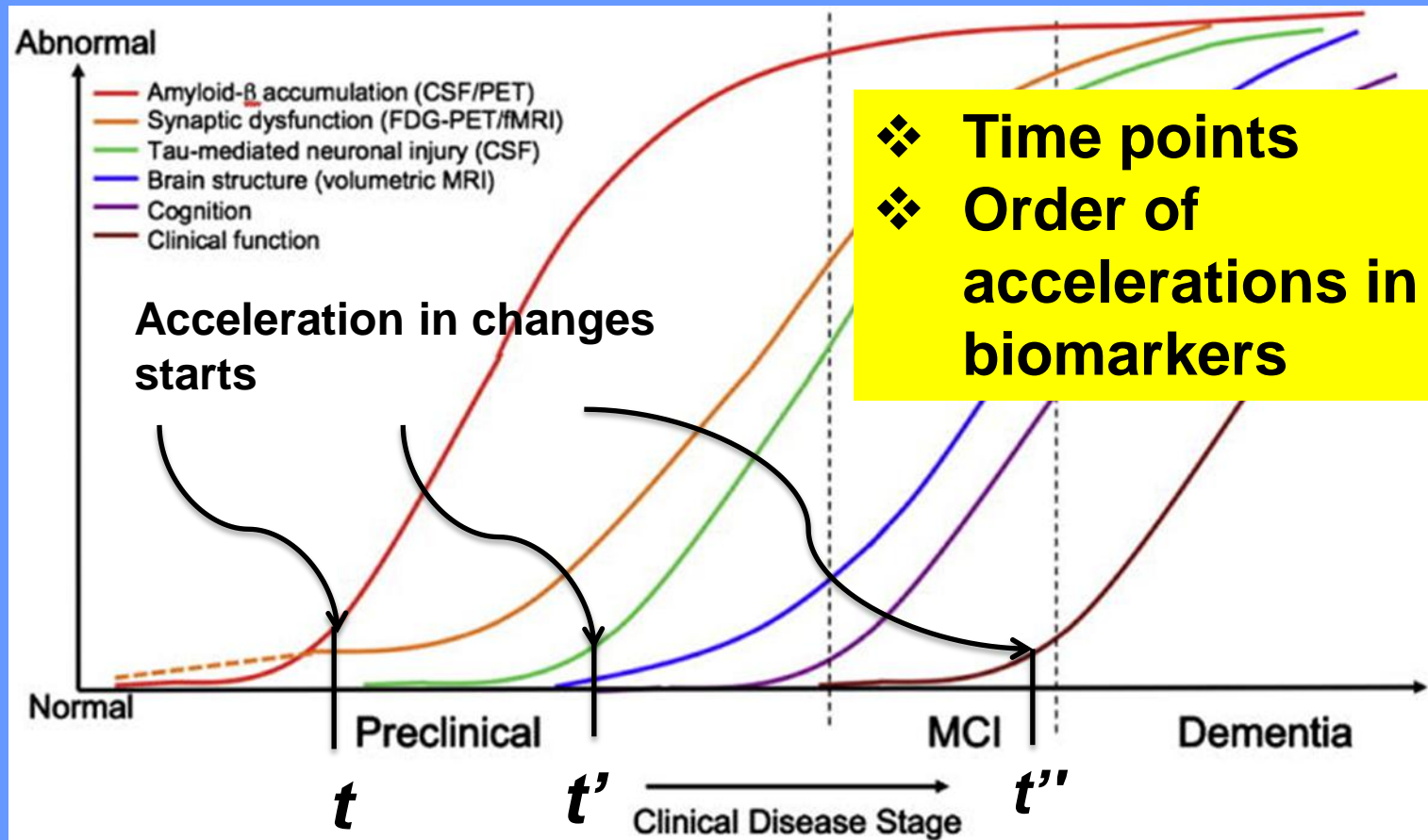

• Buracchio, Dodge et. al**. The trajectory of gait speed preceding MCI**. Archives of Neurology. Archives of Neurology, 2010; 67:980-986

• Dodge, Ganguli**, et al. Terminal decline and practice effects in non-demented older adults.** Neurology, 2011:77;722-730**.**
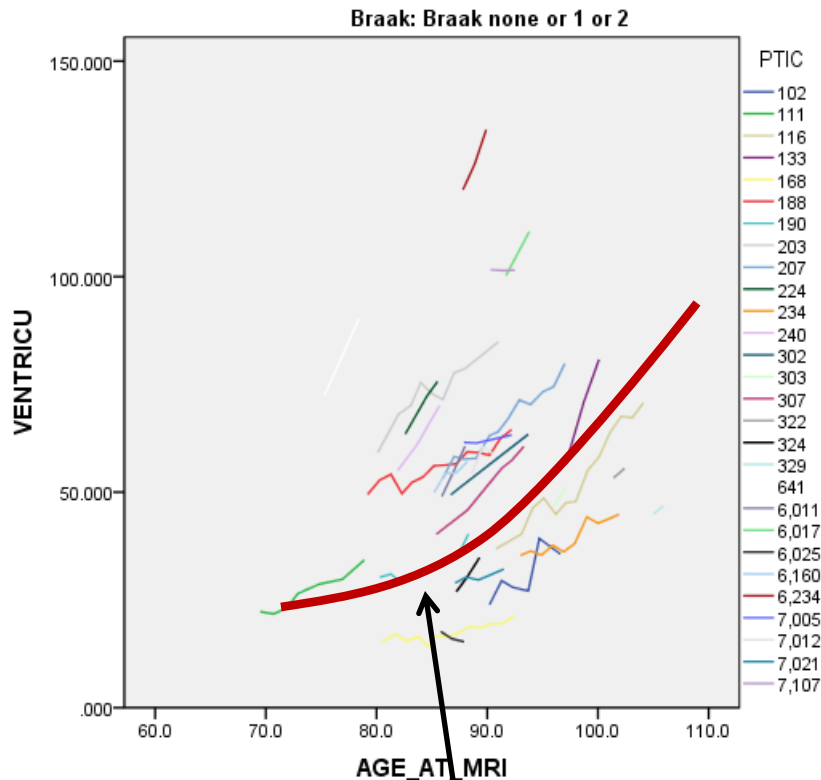
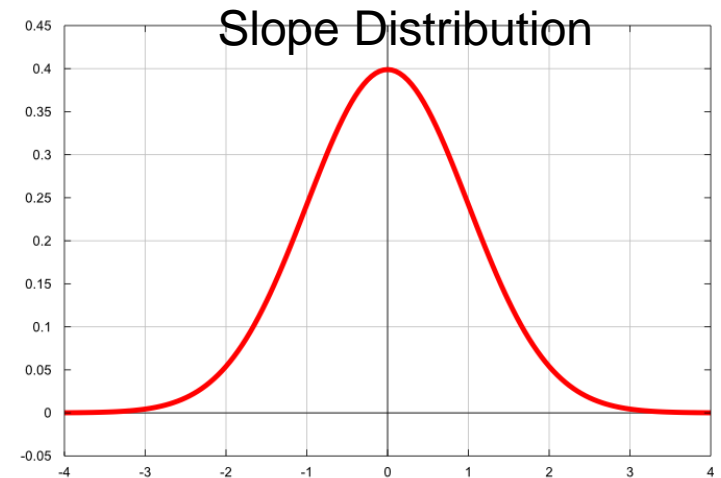# *Application to Biomarker data: Identify Acceleration Points*

Jack et al., (*Lancet Neurol 2010*), Sperling et al., (*Alzheimer's and Dementia 2011*)
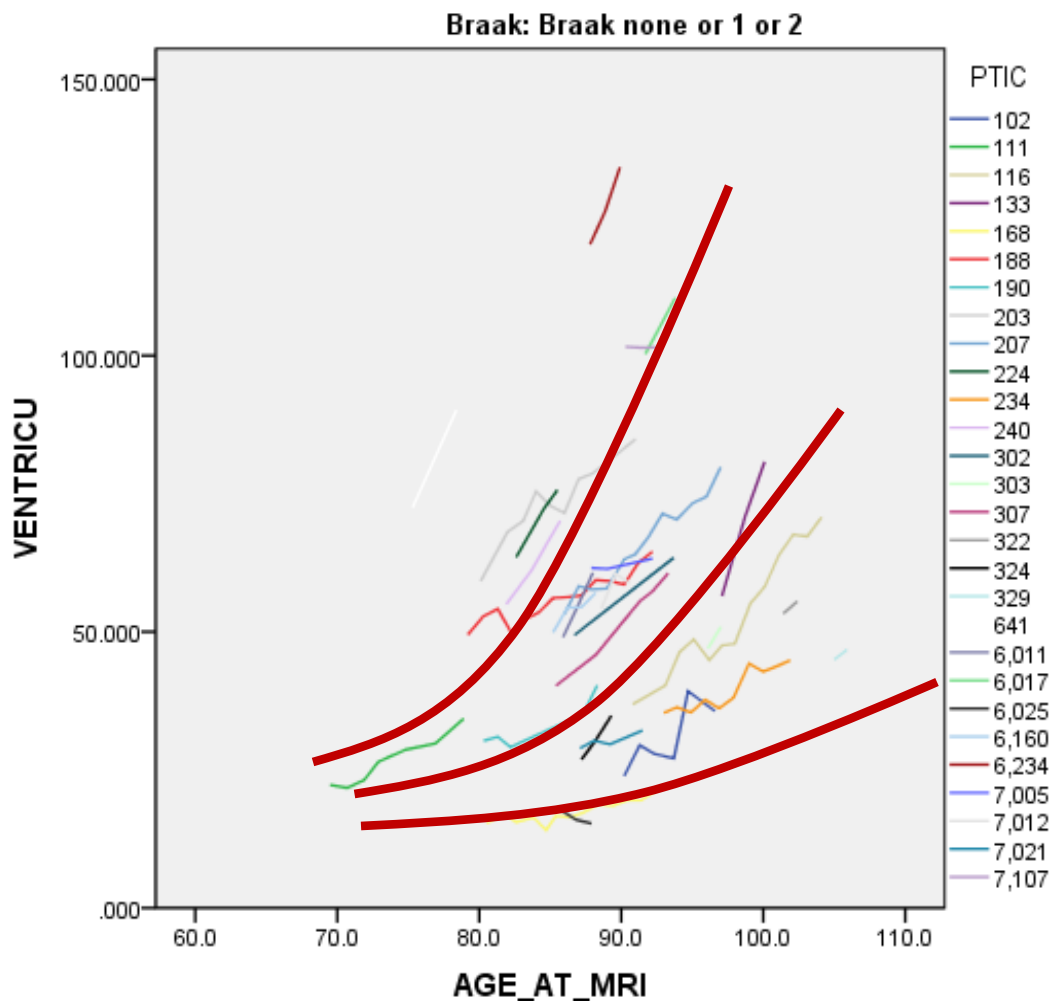
Latent Trajectory Model

Mixed Effects Model: each subject can have a different time slope
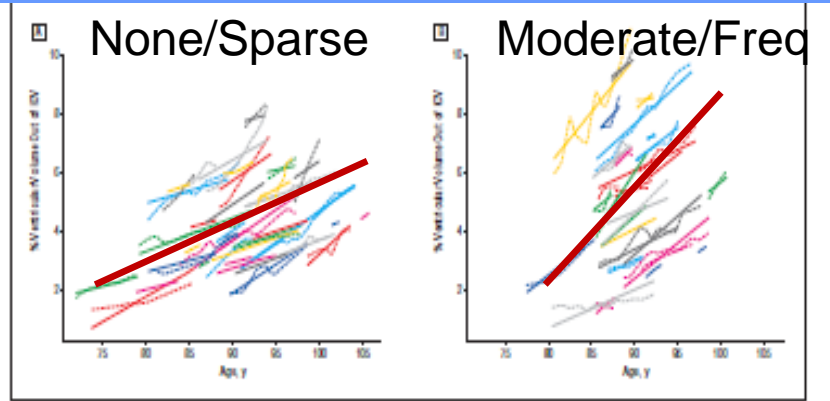
Average Trajectory

Latent Trajectory Model

Identify homogeneous groups in terms of trajectories and estimate characteristics associated with each group simultaneously (mixture modelling)

Mixed Effects Model: Examples

Ventricular Volume Expansion
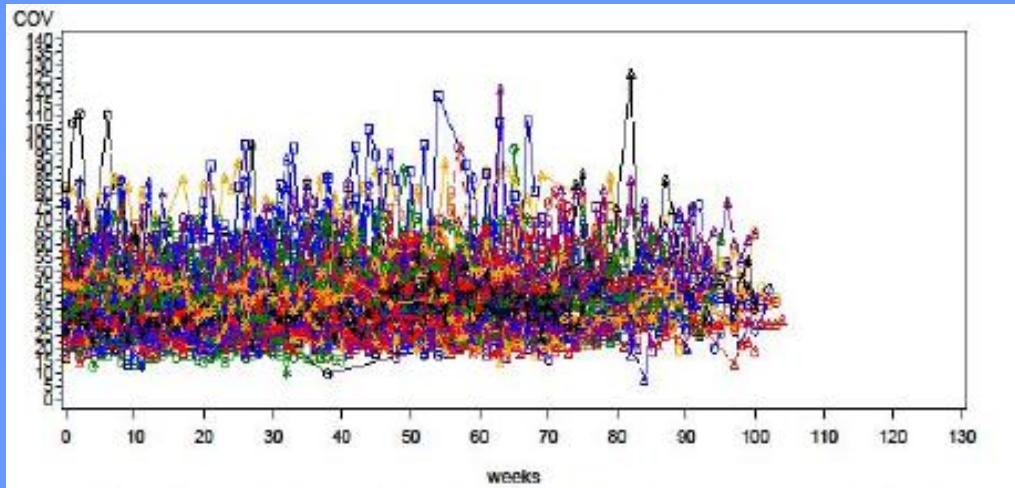by CERAD Neuritic Plaque Categories

Erten-Lyons, Dodge et. al. **Neuropathological basis of age-associated brain atrophy**. JAMA Neurology 70:616-622, 2013.
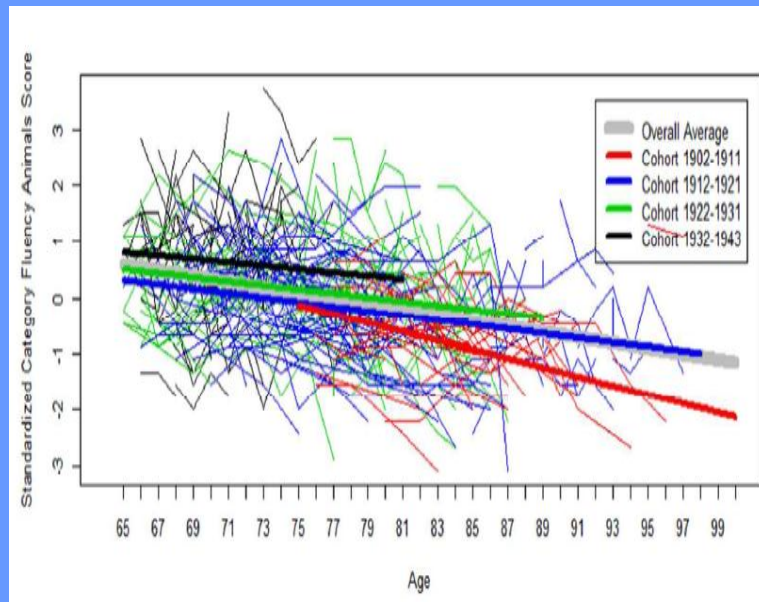
• Dodge, Ganguli et. al. **Cohort Effects in Age-Associated Cognitive Trajectories**. Journal of Gerontology: Medical Sciences. In press.

Latent Trajectory Model: Examples

Dodge, Kaye et. al. **In-home walking speeds and variability trajectories associated with Mild Cognitive Impairment.** Neurology, 2012: 78(24):1946-1952.

Figure 2 Hypothetical trajectory of variability associated with disease progression
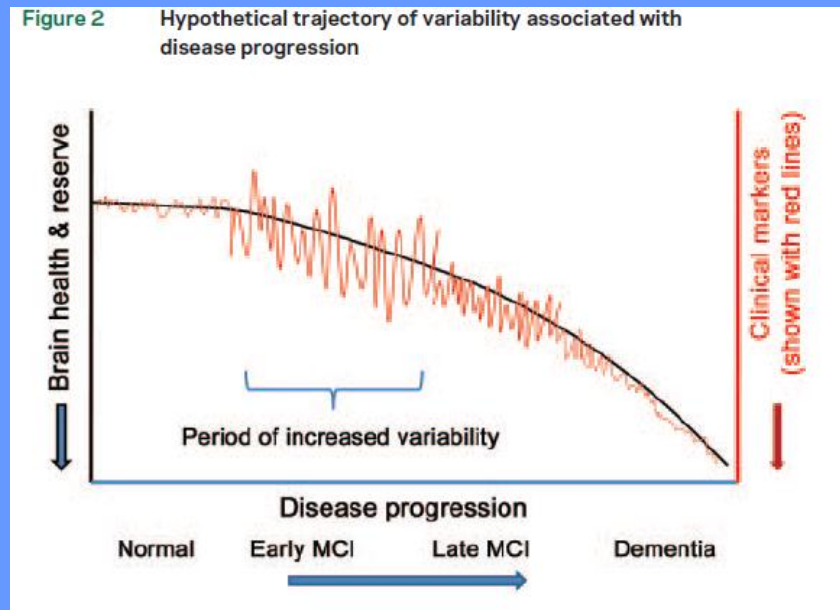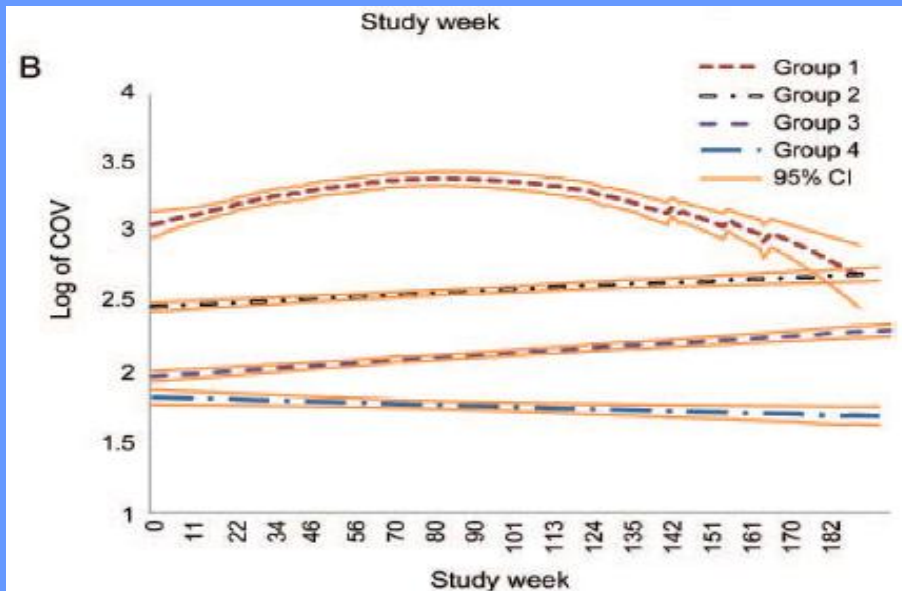
II. Baseline or Progression?- Biomarkers Predictive of Cognitive Declines
(using ADNI 1 data, application of mixed effects model)

Biomarkers vs. cognitive outcomes

Individual Specific Deviations from population mean trajectory (random components)

Cognitive Functions

Population mean/average trajectory

time (age)
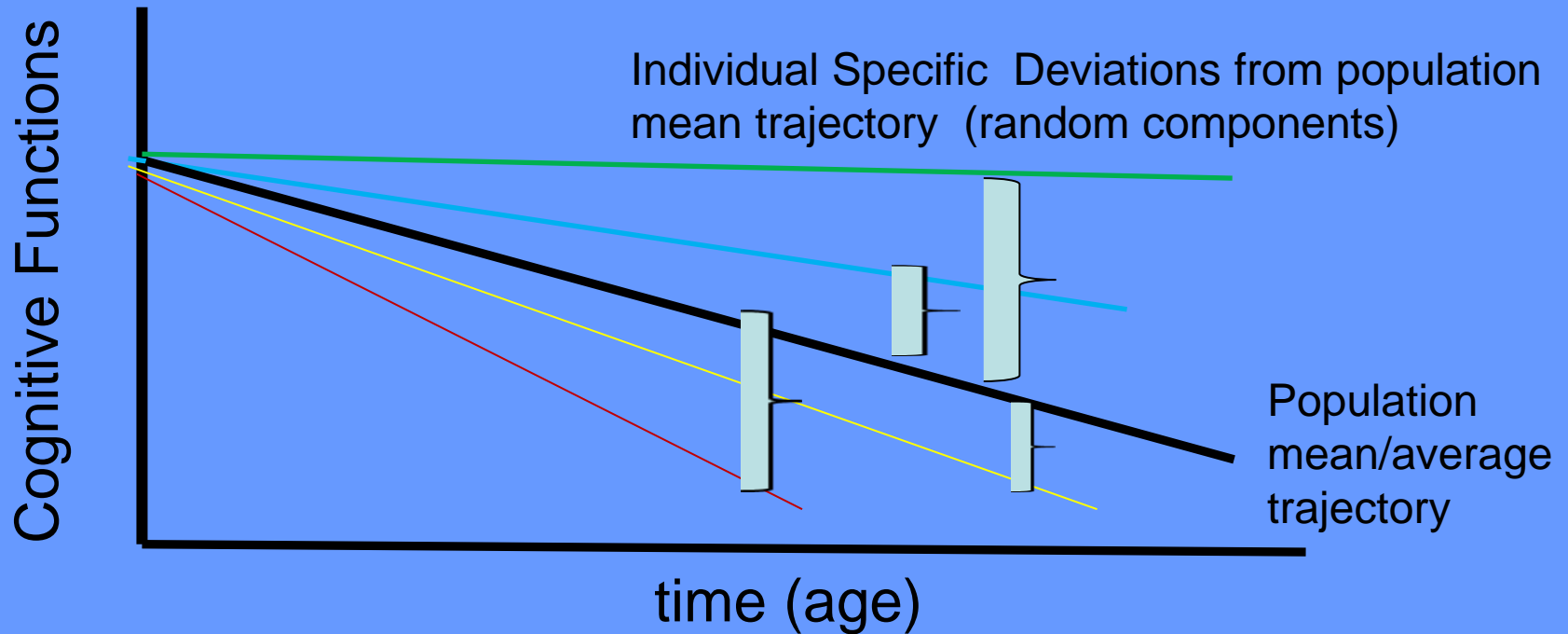
Variability explained by Age, education, (reserve factors)

Baseline biomarker values

Rate of progression in biomarker values

Aim/Data

- To examine which components ---baseline values or biomarker progressions-- explains more variability in cognitive declines in memory and executive functions.

- DATA: the Alzheimer's Disease Neuroimaging Initiative (ADNI 1). 526 subjects with valid data in at least one of our variables of interest were used in this study.

Cognitive Outcomes

- Trajectory (slope) of cognitive functions:

   1. ADNI-memory (ADNI-Mem) and

   2. ADNI-executive (ADNI-Exe).

   (Crane et al., 2012; Gibbons et al., 2012)

The scores are psychometrically optimized composite scores of memory and executive function, derived from items from ADNI neuropsychological tests

Approach: 2-stage

- Stage 1. Individual-specific slope of the longitudinal **trajectory of each biomarker** was estimated using mixed effects models.

Longitudinal trajectories of biomarkers model

$$b_{it} = \beta_{00} + \beta_{0i} + \beta_{10}t + \beta_{1i}t + \gamma_{it},$$

- where $(\beta_{0i}, \beta_{1i})^T \overset{iid}{\underset{\sim}{}} MVN(0, \Sigma_b)$ and $\gamma_{it} \overset{iid}{\underset{\sim}{}} N(0, \sigma_b^2)$.

Approach

- Stage 2. Estimated individual-specific slope of each biomarker and observed baseline values were used as predictors of cognitive declines using mixed effects models.

$$y_{it} = I_i + S_{10} * \left[1_{\{t<0.5\}} * t\right] + S_{2i} * \left[1_{\{t\geq0.5\}} * (t - 0.5)\right] + \varepsilon_{it};$$

- $I_t = \alpha_0 + \alpha_1 * \text{Age at baseline} + \alpha_2 * \text{Sex} + \alpha_3 * \text{Education} + \alpha_4 * \text{Apoe4} + \alpha_5 * b_{i0} + \alpha_{0i};$

- $S_{2i} = s_{20} + s_{21} * \text{Sex} + s_{22} * \text{Apoe4} + s_{23} * \text{Changes in diagnosis} + s_{24} * b_{i0} + s_{25} * \hat{\beta}_{1i}^S + \tau_{2i};$

Approach

- Variability in cognitive declines explained by subject-specific **baseline biomarker values** was compared with variability explained by **biomarker progressions.**

Results

% of Variability in Memory Declines Explained by Biomarkers

BIOMARKERS	Normal Group	Among MCI*	Among AD
CSF ttau baseline	N/A	N/A	N/A
CSF ttau progression	N/A	N/A	N/A
CSF Abeta$_{42}$ baseline	N/A	5.10%	N/A
CSF Abeta$_{42}$ progression	N/A	10.30%	6.60%
FDG-PET baseline	N/A	12.20%	30.00%
FDG-PET progression	1.50%	12.70%	84.00%
Log_wmh/icv baseline	N/A	0.50%	N/A
Log_wmh/icv progression	N/A	N/A	3.00%
Hpcv/icv baseline	N/A	9.00%	4.70%
Hpcv/icv progression	N/A	19.80%	26.00%
Ventricles/icv baseline	N/A	8.70%	4.20%
Ventricles/icv progression	N/A	39.40%	63.80%
Total brain/icv baseline	N/A	2.40%	N/A
Total brain/icv progression	N/A	16.00%	26.00%
Precuneus thickness baseline	4.52%	N/A	12.12%
Precuneus thickness progression	1.29%	4.87%	6.94%
Medial Temporal cortical thickness baseline	N/A	8.14%	N/A
Medial Temporal cortical thickness progression	4.44%	28.68%	34.67%

% of Variability in Executive Function Declines Explained by Biomarkers

BIOMARKERS	Normal Group	Among MCI*	Among AD
CSF ttau baseline	N/A	N/A	N/A
CSF ttau progression	N/A	N/A	N/A
CSF Abeta$_{42}$ baseline	N/A	23.70%	N/A
CSF Abeta$_{42}$ progression	2.50%	14.40%	N/A
FDG-PET baseline	N/A	35.20%	18.20%
FDG-PET progression	6.20%	28.30%	39.50%
Log_wmh/icv baseline	N/A	2.40%	N/A
Log_wmh/icv progression	N/A	N/A	N/A
Hpcv/icv baseline	9.20%	N/A	N/A
Hpcv/icv progression	N/A	9.00%	N/A
Ventricles/icv baseline	N/A	13.00%	11.10%
Ventricles/icv progression	16.90%	44.50%	65.10%
Total brain/icv baseline	N/A	9.50%	3.50%
Total brain/icv progression	N/A	32.20%	18.80%
Precuneus thickness baseline	21.14%	N/A	8.66%
Precuneus thickness progression	9.78%	5.38%	N/A
Medial Temporal cortical thickness baseline	N/A	N/A	N/A
Medial Temporal cortical thickness progression	N/A	21.55%	22.08%

Notes for Table

- Medial Temporal Cortical Thickness: summary variable by adding averaged means for left and right entorhinal (ERC), perirhinal (PRC) and posterior parahipplocampal (PPHC) cortical region thicknesses.

- Controlled variables: age at baseline, sex, education, apoe 4 allele (at least one vs. none) and practice effects

- N/A: Variability increased instead of decreased, or had no changes, after inclusion of the predictors in the model (i.e., including these variables did not explain the variability of cognitive outcomes or caused more estimation errors instead of explaining the variability).

Conclusions

- A number of studies have shown support for the hypothetical AD progression model developed by Jack et al (Jack et al., 2013; Jack et al., 2010).

- Our study results also coincides with the model to some extent; Across diagnostic groups, the percentages of variability in cognitive declines explained by functional (FDG-PET) or structural (brain morphometric) biomarkers (either their baseline values or progressions)   increased significantly as disease progressed from normal to MCI.

- However, our results suggest that structural changes seem to be more closely to or coincided with FDG-PET change than hypothesized.

- Among normal subjects in this dataset, precuneus thickness baseline values and medial temporal cortical thinning progressions explained variability in declines of ADNI-Mem by over 4%. Although this is small, it showed more explanatory ability than CSF Aβ42 and t-tau.

- The relatively poor performance of CSF Aβ42 and t-tau biomarker progression values in explaining the cognitive trajectories could be due to the fact that:
  - ✓ The control group in ADNI is likely to be heterogeneous and include significant numbers of individuals who will not progress to AD
  - ✓ Shorter duration of follow-up of these markers might have reduced precision of trajectory estimate in comparison with other markers in the current study.
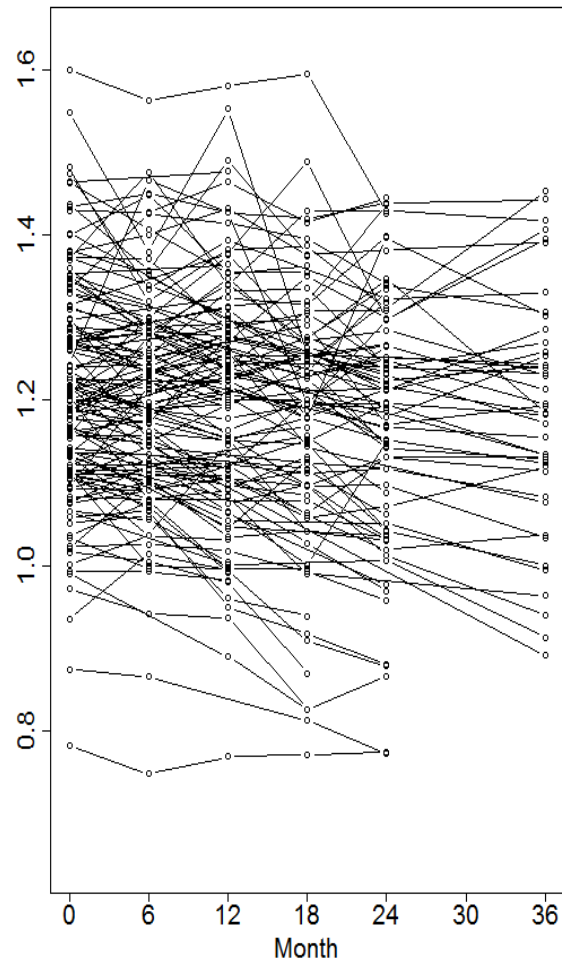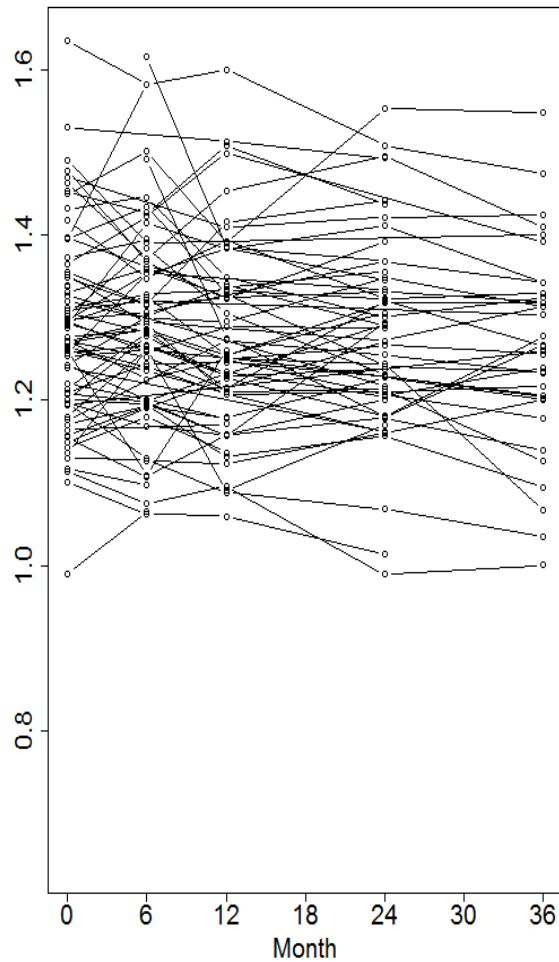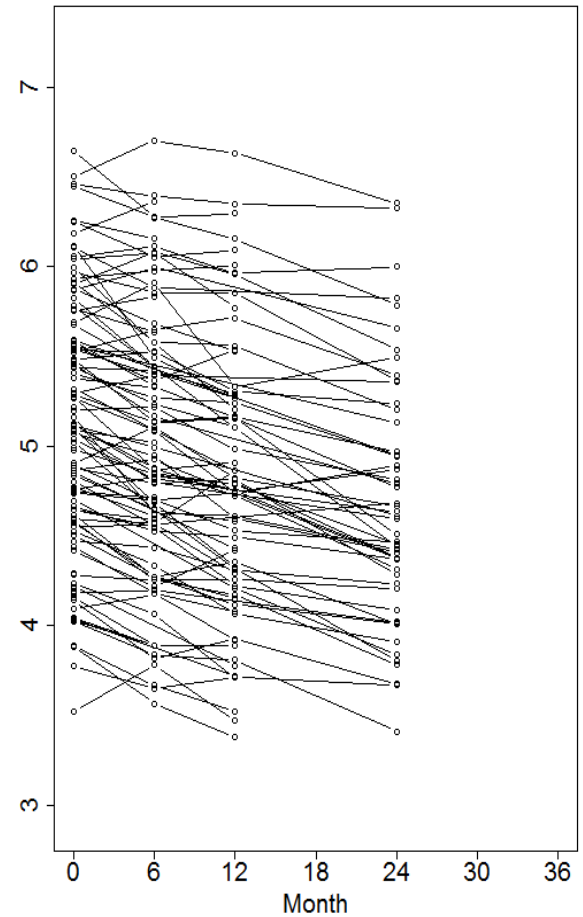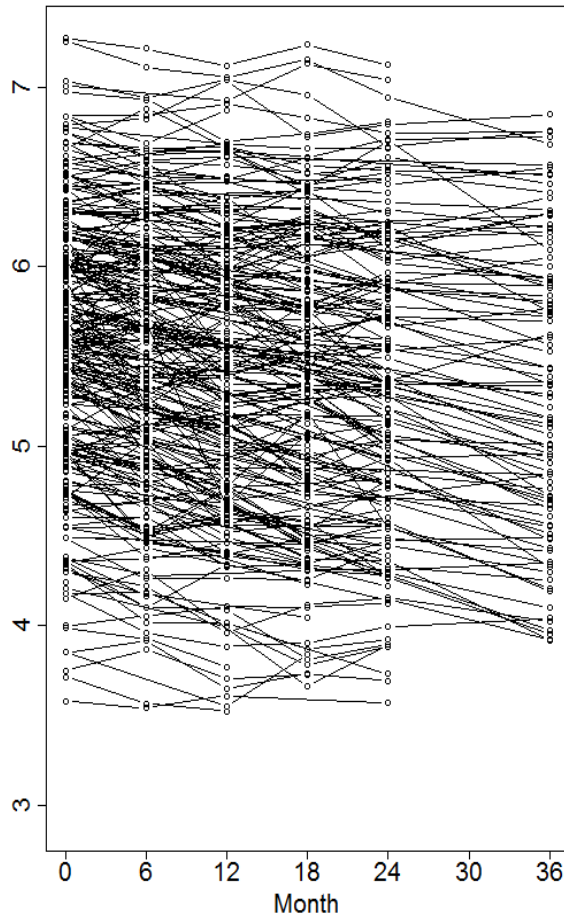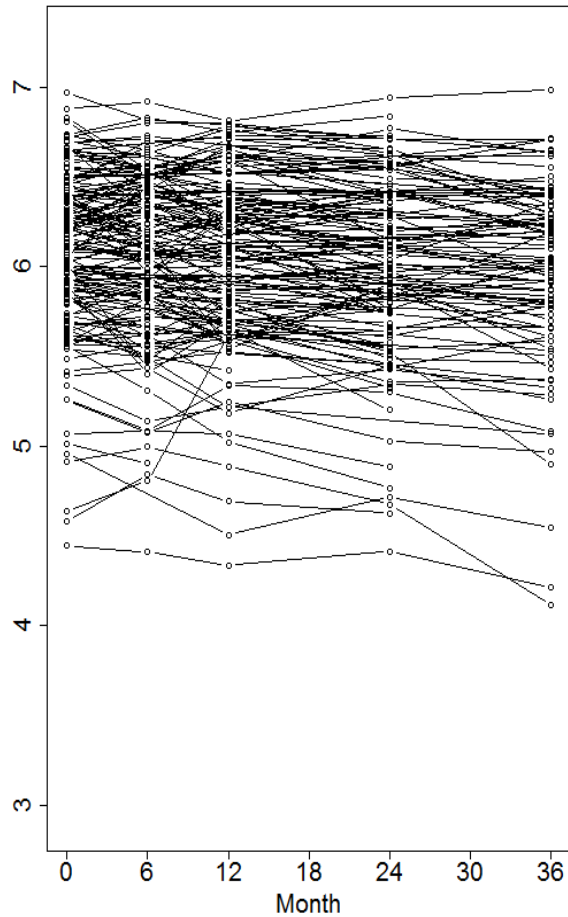
CSF Aβ42 (U2 series) in pg/mL
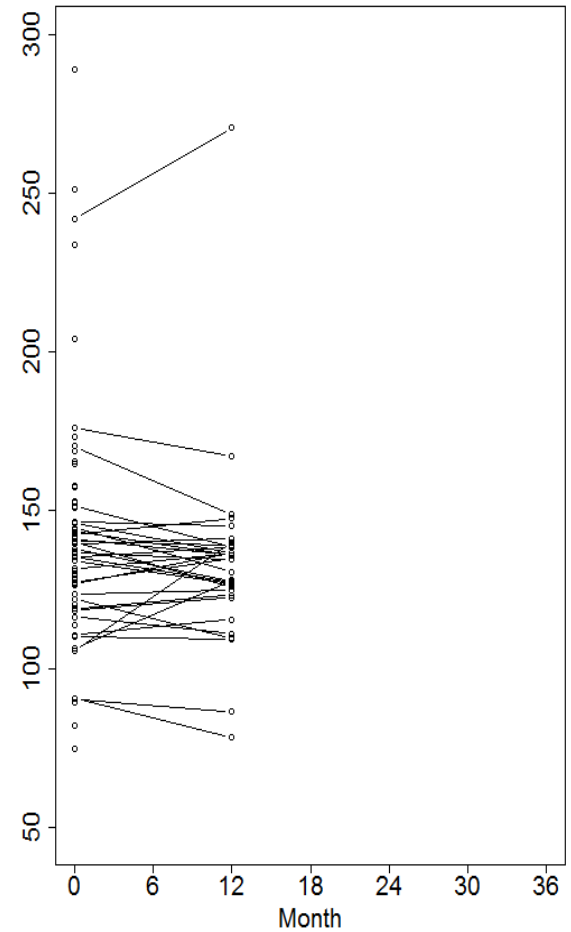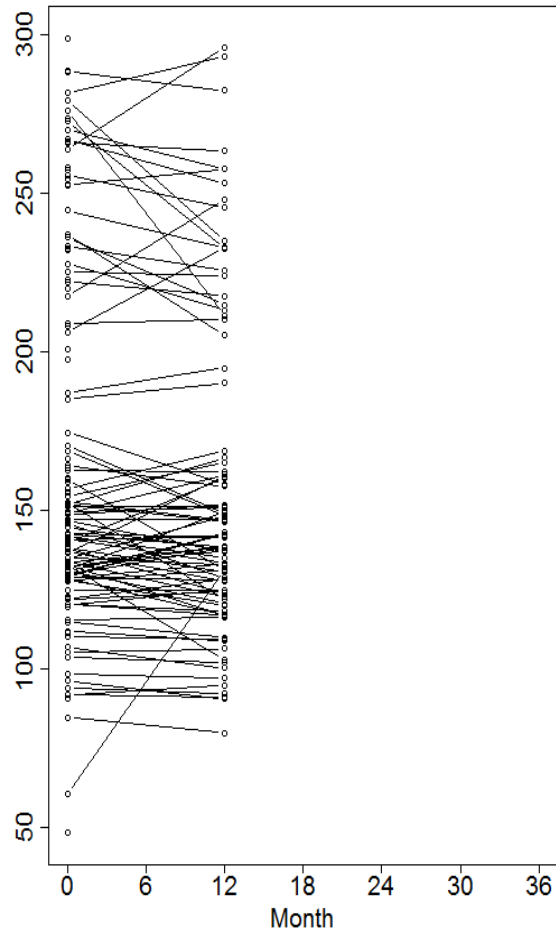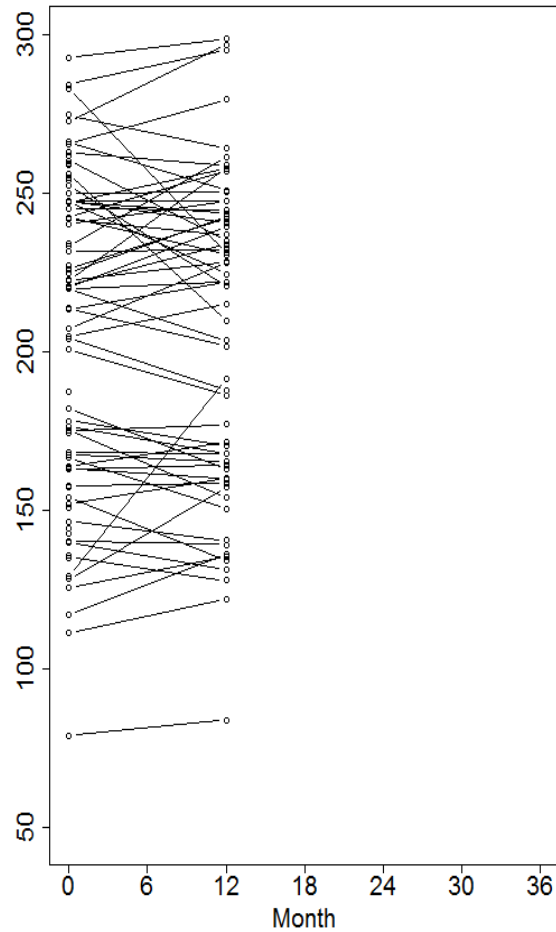
CSF T-tau (U2 series) in pg/mL
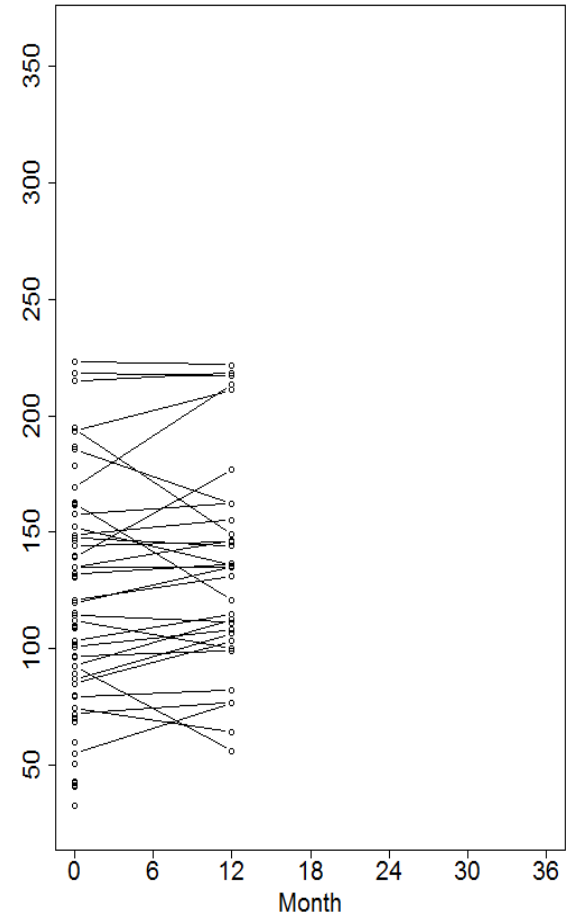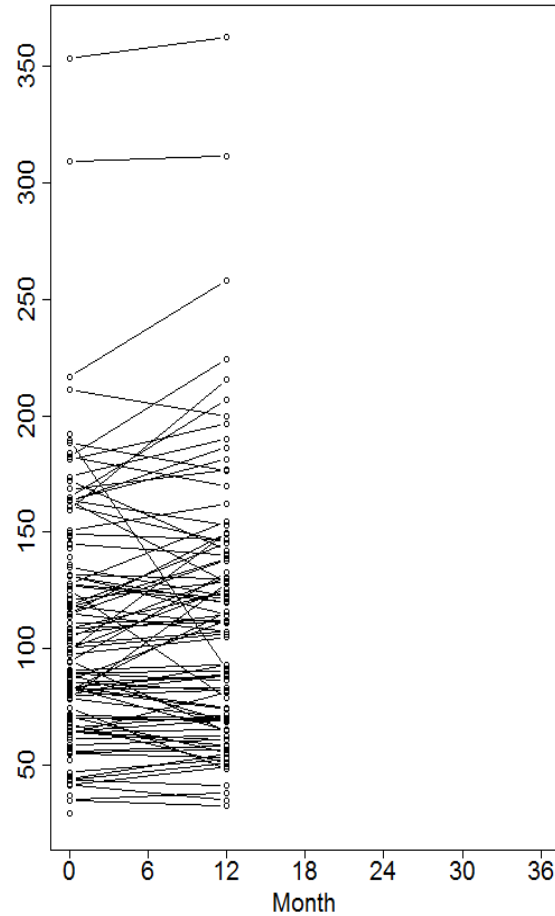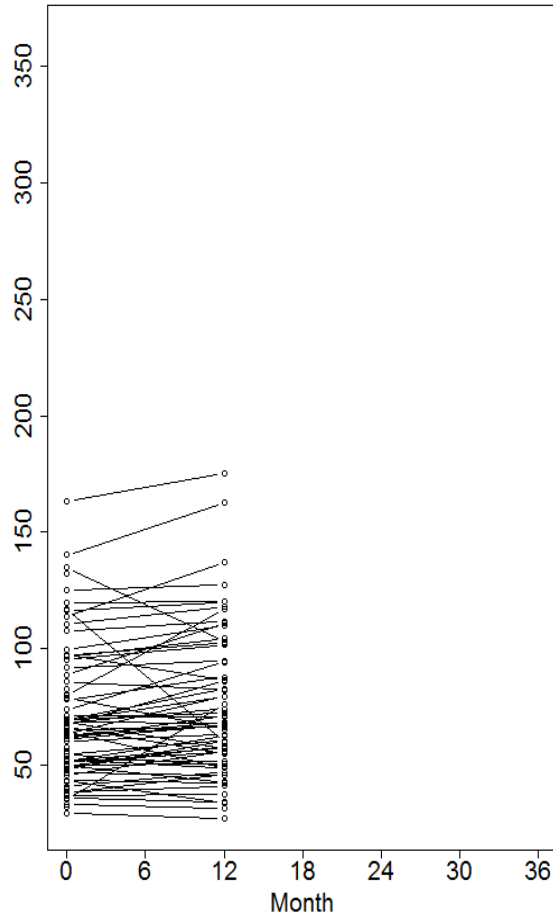
FDG-PET summary score
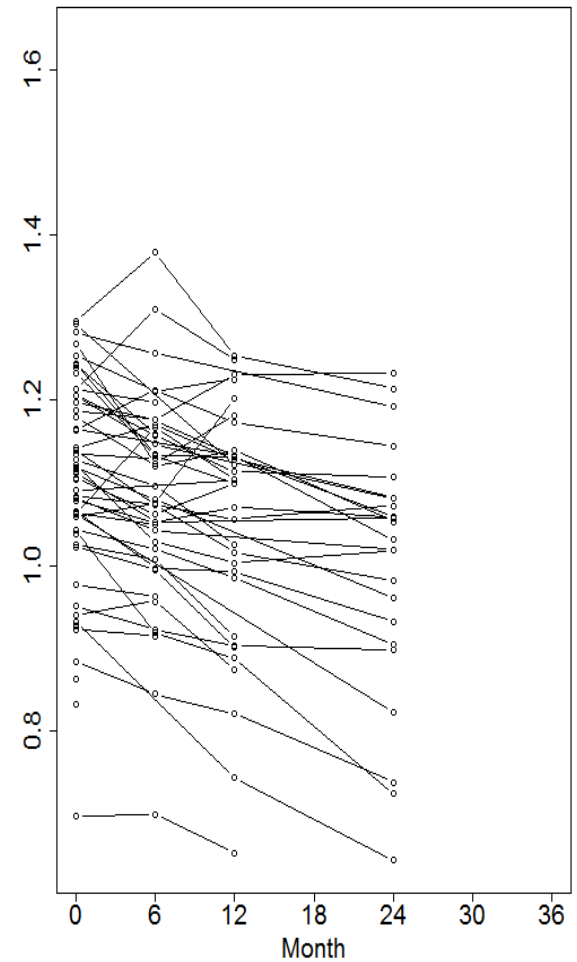
Medial Temporal Cortical Thickness in Millimeters (mm)

Take Home Message

- ✓ For most biomarkers, biomarker progressions were more associated with cognitive decline than baseline values.

- ✓ This suggests that clinical trials which require recruiting at-risk subjects could be improved by using progression rather than baseline values in biomarkers to enrich the study subjects.

- ✓ Future studies are warranted to estimate the incremental effectiveness of improving clinical trial statistical power by using biomarker progression criteria

Special Thanks to:
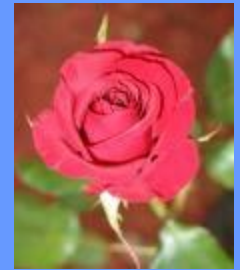
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