An integrated natural disease progression model of nine cognitive and biomarker endpoints in patients with Alzheimer's Disease

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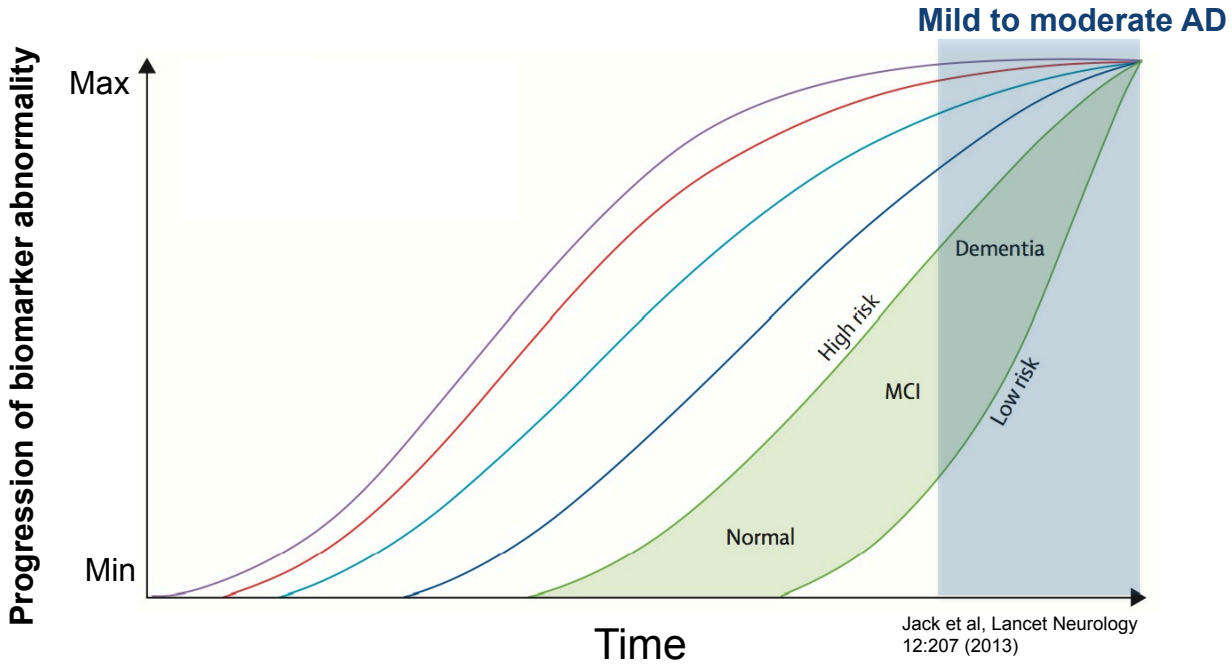
Alzheimer's Disease – a progressive neuro-degenerative disease



- **CSF biomarkers of disease (amyloid)**: ↓$A\beta_{42}$,
- **Brain amyloid load**: ↑ amyloid PET imaging
- **CSF biomarkers of disease (neuro-degeneration):** ↑ t-tau and ↑ p-tau
- **Brain atrophy**: volumetric MRI (↓whole brain volume, ↓hippocampal volume, ↑ventricle size)
- **Cortical activity**: ↓ FDG-PET
- **Cognitive and functional impairment scales**: ↑ ADAS-Cog 12-item, ↑ CDR-SOB, ↓ MMSE
  - Trouble remembering recent events to inability to preform basic tasks and full time care
  - Death within ~ 9 years from diagnosis

Objectives

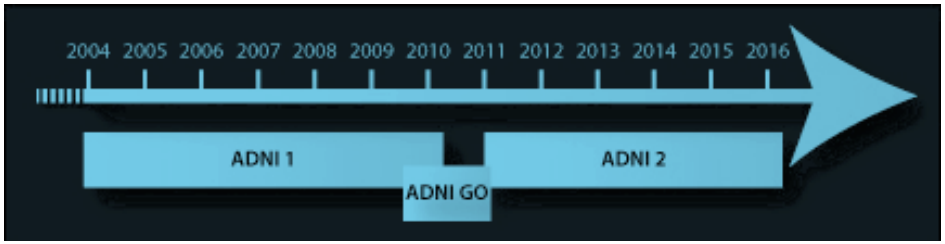
To establish a natural disease progression model integrating multiple biomarkers and endpoints in patients with mild Alzheimer's Disease[1].

➔ An enhanced ability to identify and understand disease progression and impact of covariates and drug treatment effect, rather than within endpoints

➔ Ability to simulate realistic multivariate longitudinal data, to allow assessment of studies with co-primary endpoints

1) Polhamus D et al. AAIC 2013 CDR-SOB, vMRI in MCI

Alzheimer's Disease Neuroimaging Initiative Database



Natural history non-treatment study in USA/Canada

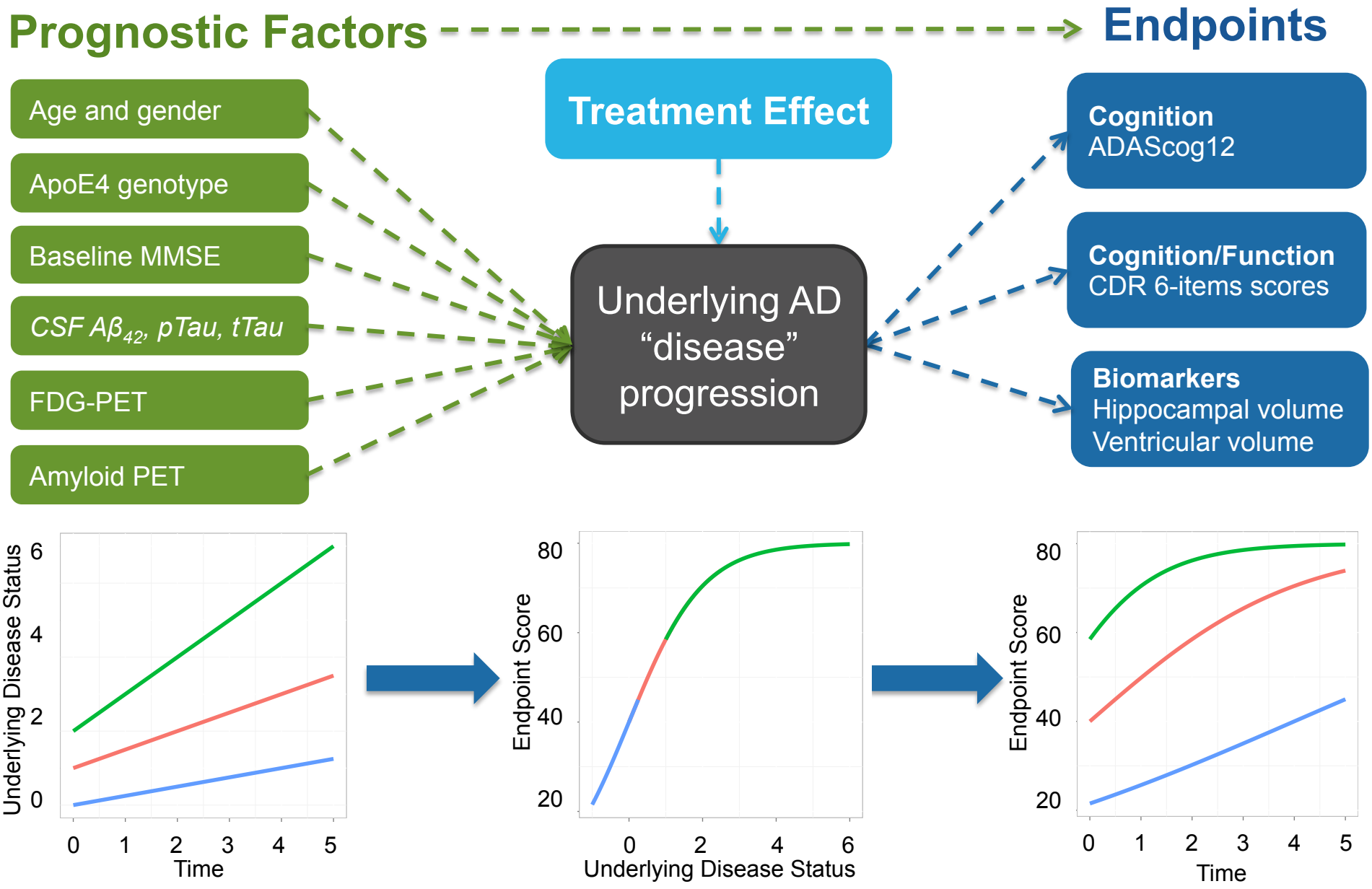
- **298 mild Alzheimer's Disease subjects***
- **Baseline MMSE 20-26**
- **Baseline covariates e.g. age, gender**
- **Up to 3 years longitudinal changes in:**
  - **ADAS-Cog 12-item score**
  - **CDR each of 6 items score**
  - **volumetric MRI (hippocampal, ventricles)**

Software: OpenBUGS v. 3.2.2

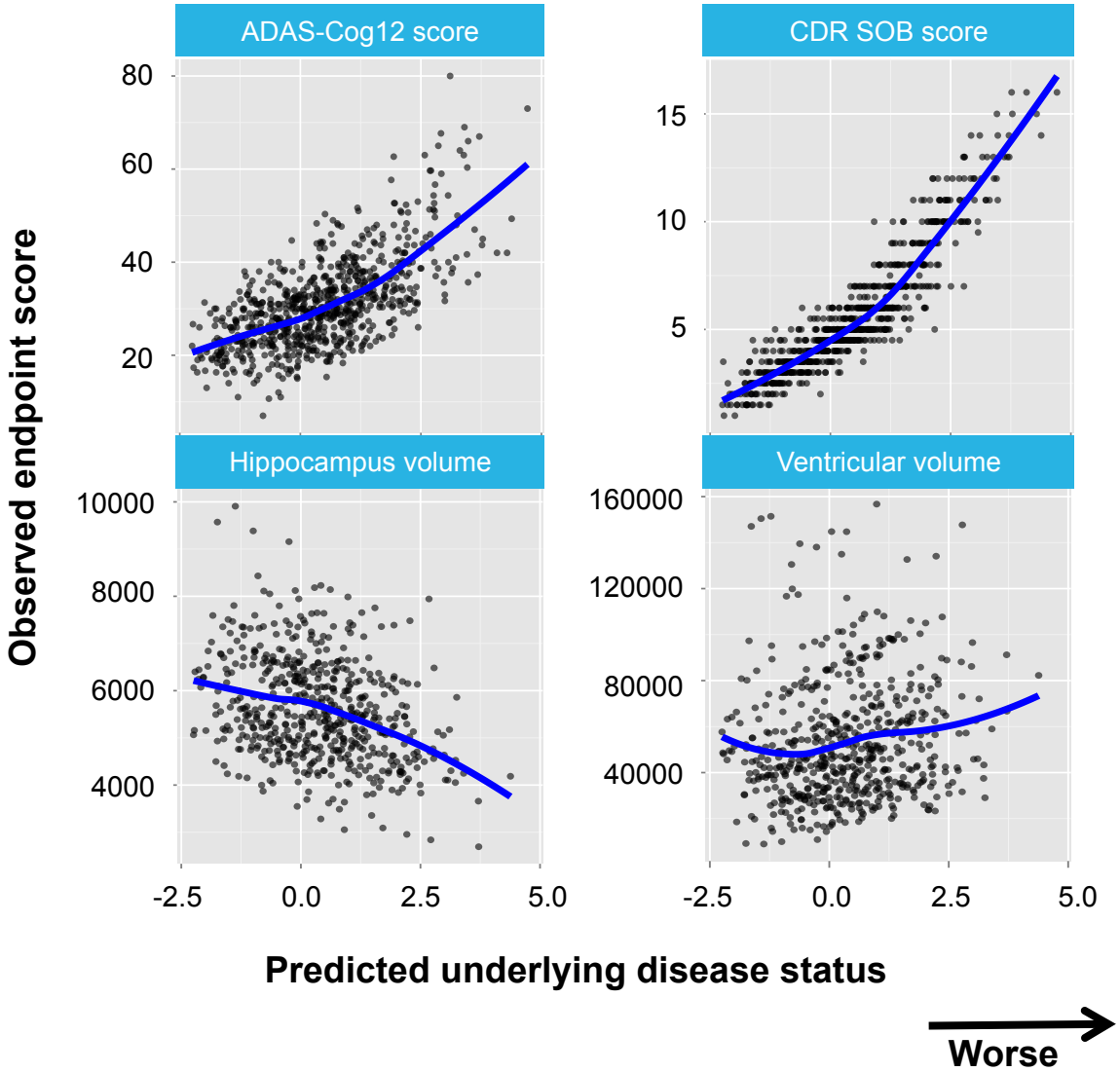
MMSE: Mini-Mental State Examination

* Data in the analysis was from ADNI database extracted on 22 January 2014 : www.loni.ucla.edu/ADNI

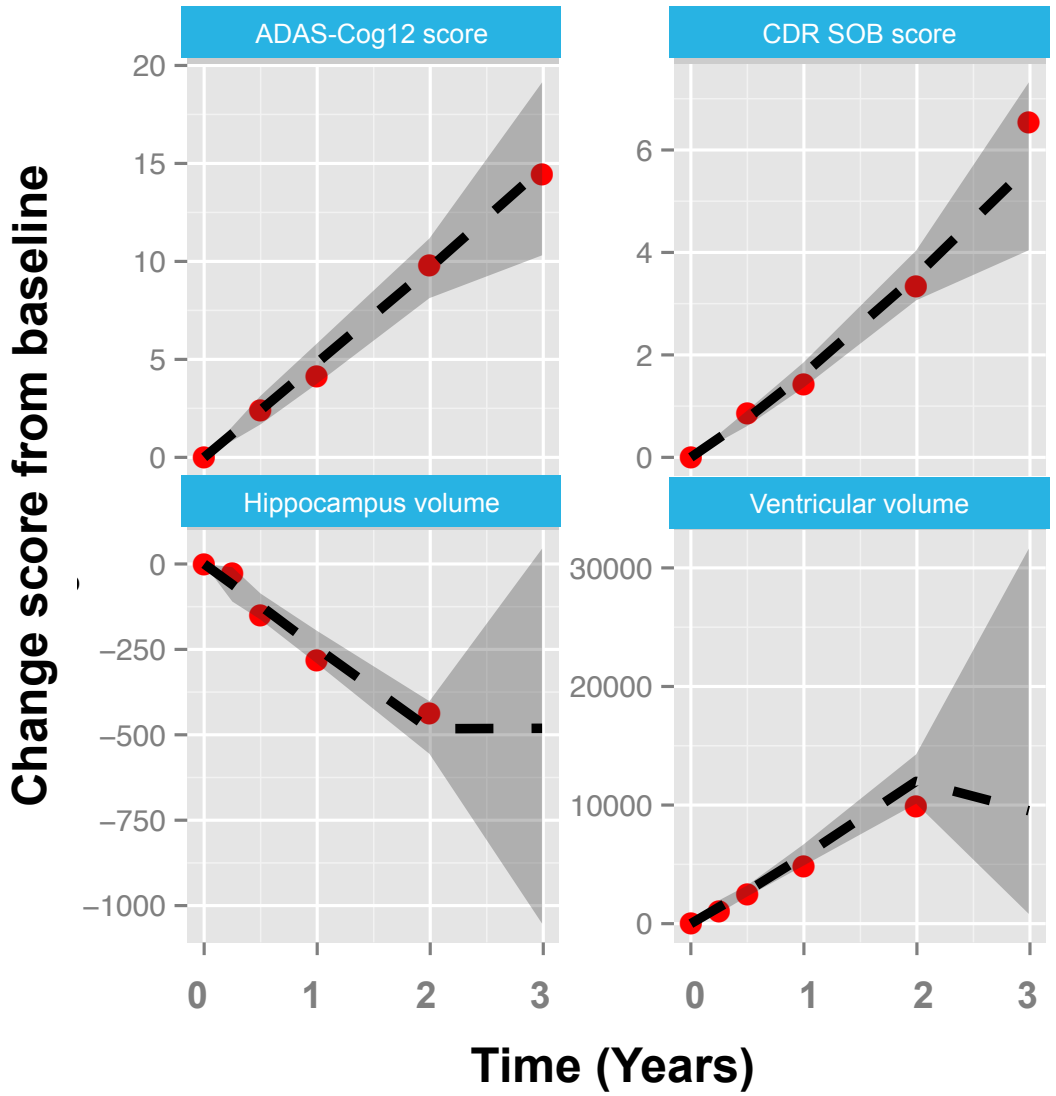
Integrated Longitudinal Alzheimer's Disease Model



Correlation between predicted disease status and observed endpoints

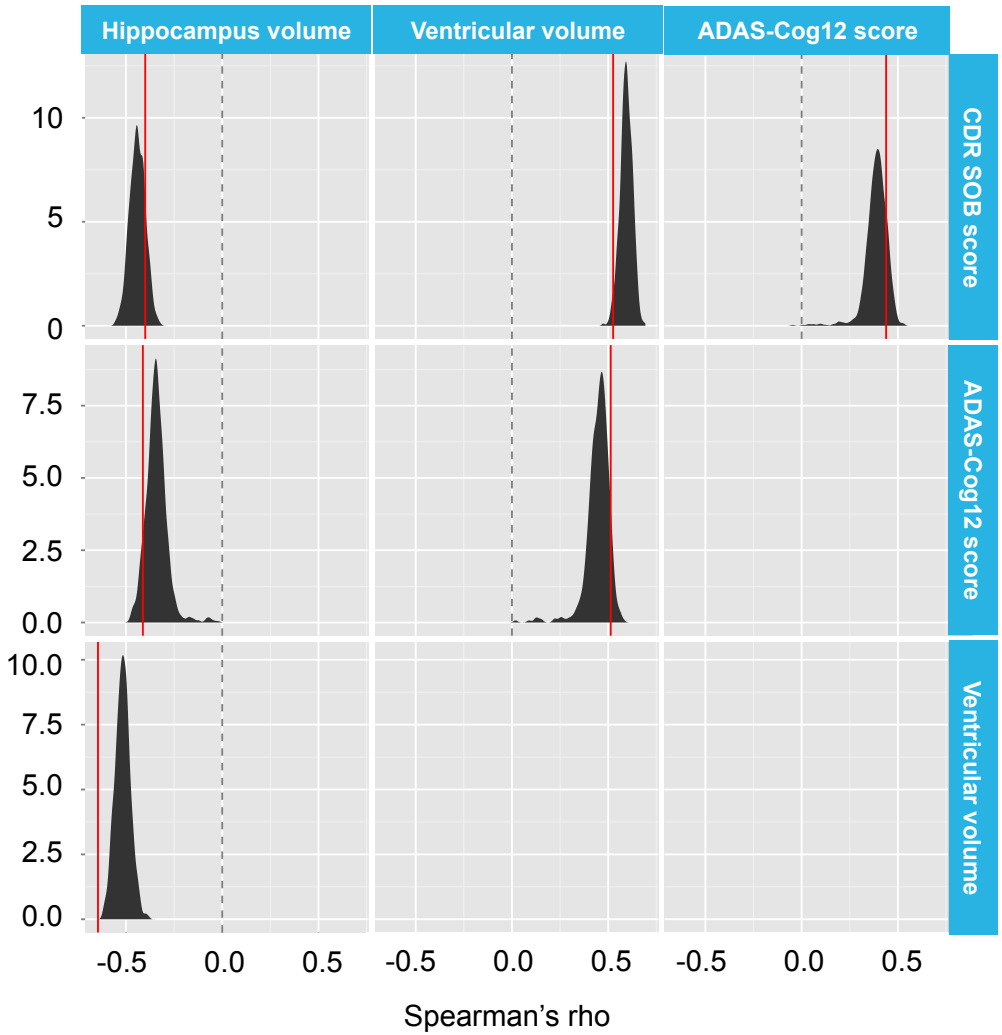


The model accurately captures the central trend of observed data



observed data (red dots) and simulated data (black lines) with 95% credible interval (shaded area)

The model maintains observed correlation between endpoints



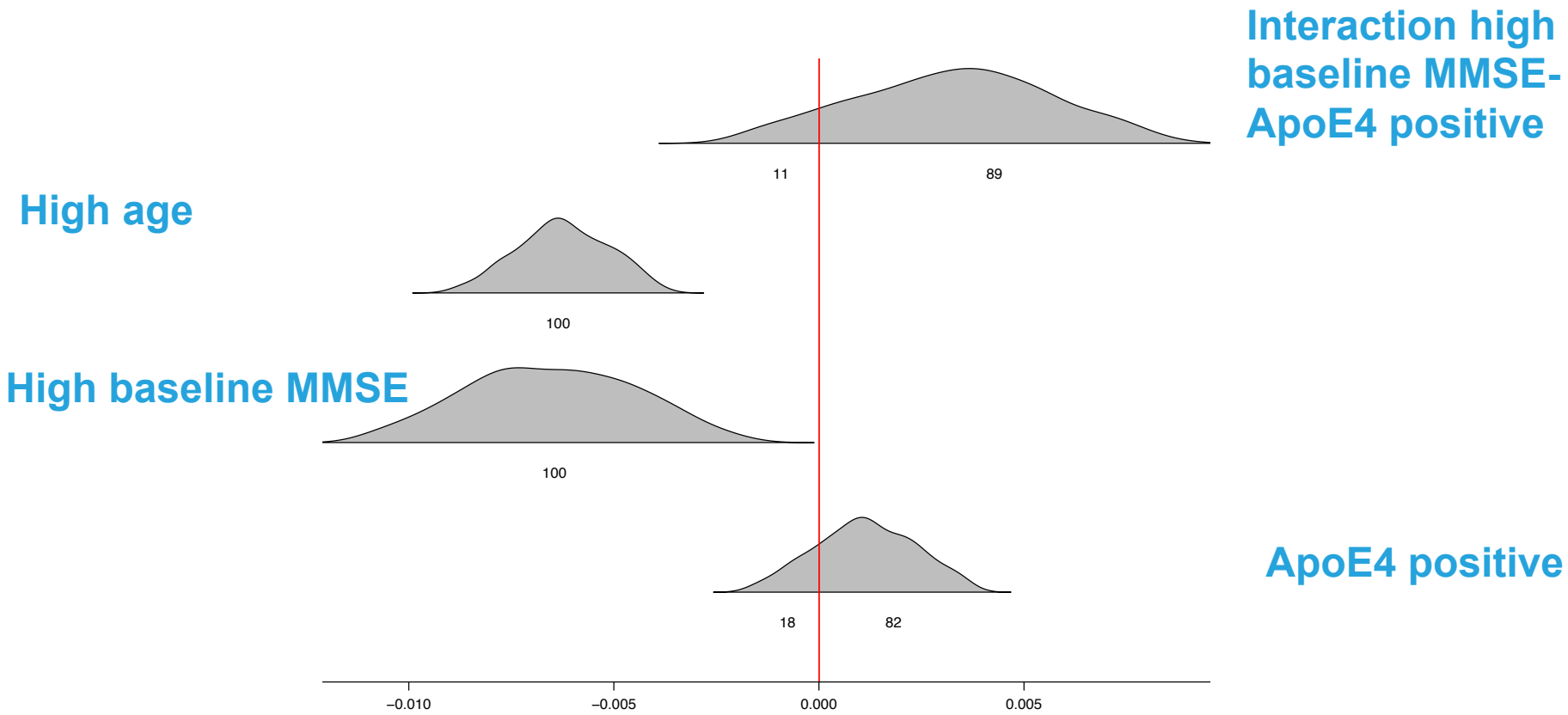
Observed correlation (red line)
Simulated correlation (black distribution)

Impact of prognostic factors on underlying disease progression rate

Slower disease progression | **Faster disease progression**

Reference subject

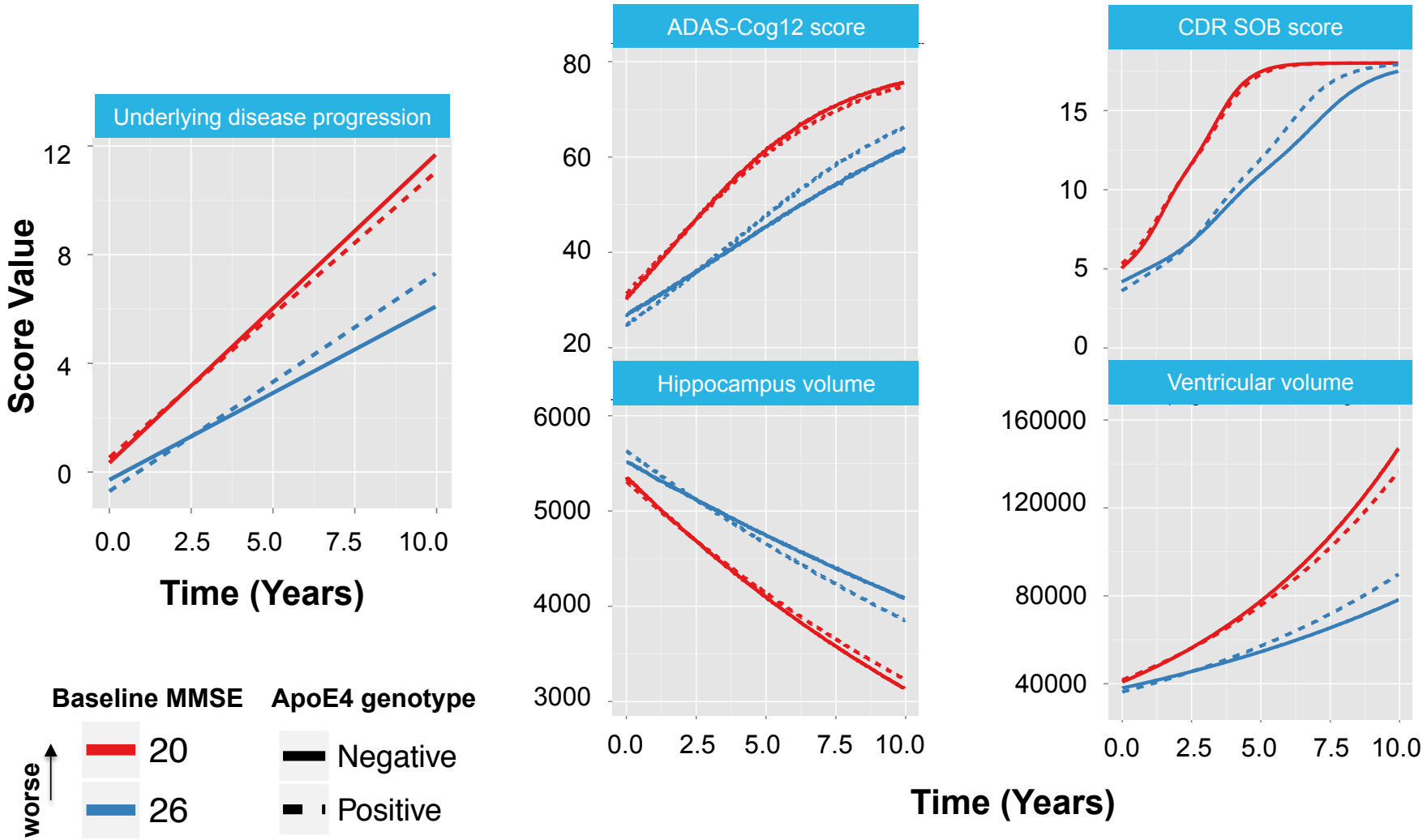
| ApoE4 negative | Baseline MMSE 23 | Age 75 |



Posterior estimated effect of normalized prognostic factors relative to reference subject (with uncertainty)

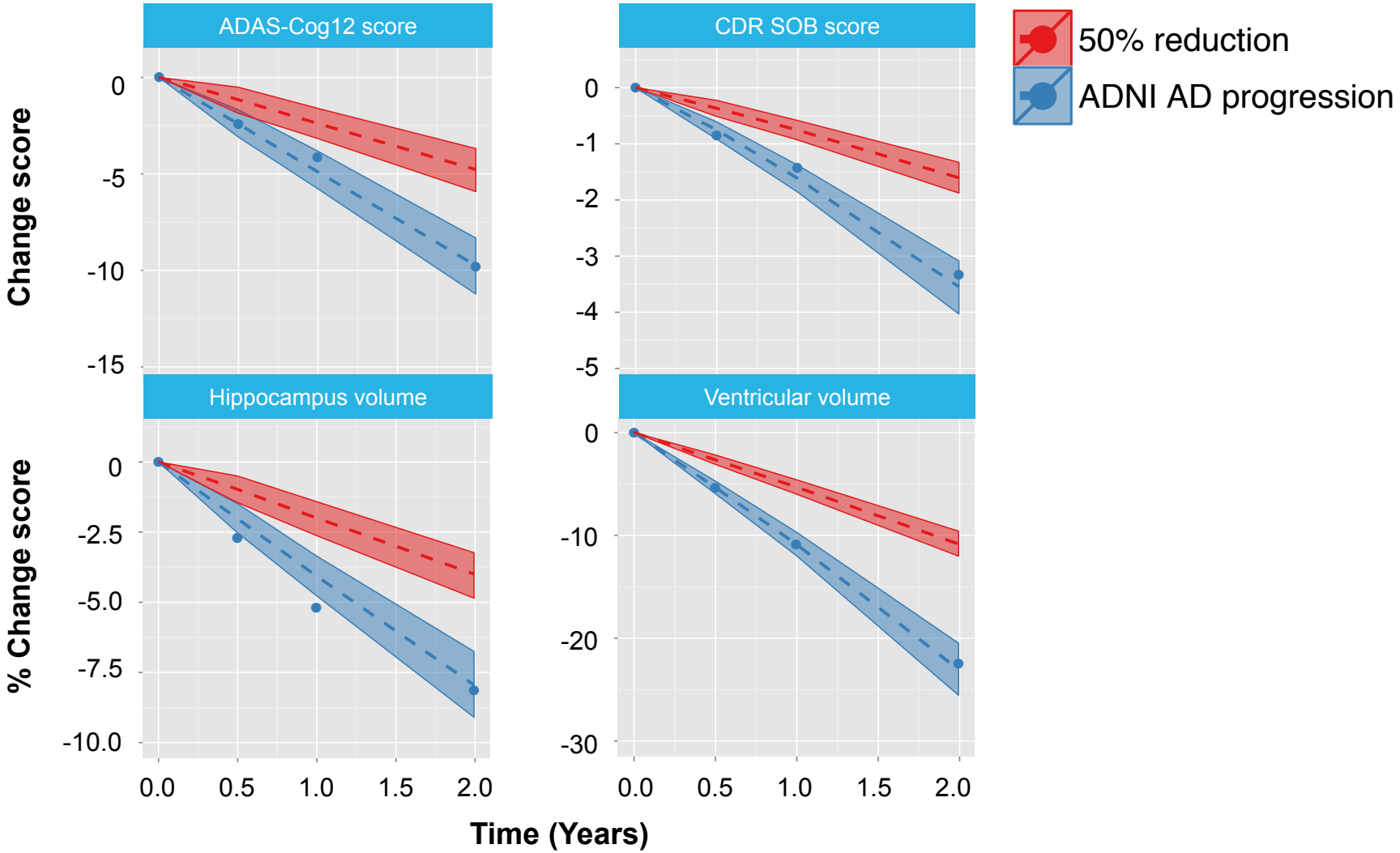
MMSE: Mini-Mental State Examination

Change in disease progression and endpoints for subpopulations



Application

Projected impact of a hypothetical treatment effect across endpoints



Observed unadjusted mean of ADNI data (dots)
Model predictions of a hypothetical treatment effect using baseline covariates (lines and shaded area)

Summary

Longitudinal PKPD model for Alzheimer's Disease

Alzheimer's Disease Model → Placebo Model → Drug Effect Model

Model properties

- Greater insights of disease progression, impact of patient covariates and drug treatment effect
- Allows translation of information across endpoints and biomarkers
- Ability to assess the sensitivity of the different endpoints in subpopulations
- Ability to simulate realistic multivariate longitudinal data

Application

- Comparison of novel-treatment outcomes and placebo response to historical data across endpoints
- Joint analysis of multiple endpoints (e.g. co-primary endpoints)
- Trial design optimization for multiple endpoints

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Alzheimer's Disease Neuroimaging Initiative