# Exploring the use of biomarkers for predicting Alzheimer's disease progression status

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# Objectives

Study AD related biomarkers in order to improve early detection

- What's their accuracy?
- How to choose a threshold?
- Do we need to make it individualized?
- How do we combine the information?

# Challenge and Considerations

- Ideal evaluation requires comparing the biomarker values to a gold standard
  - The underlying AD pathophysiology process cannot be observed directly
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  - Risk factors
  - Covariates that may affect biomarker levels

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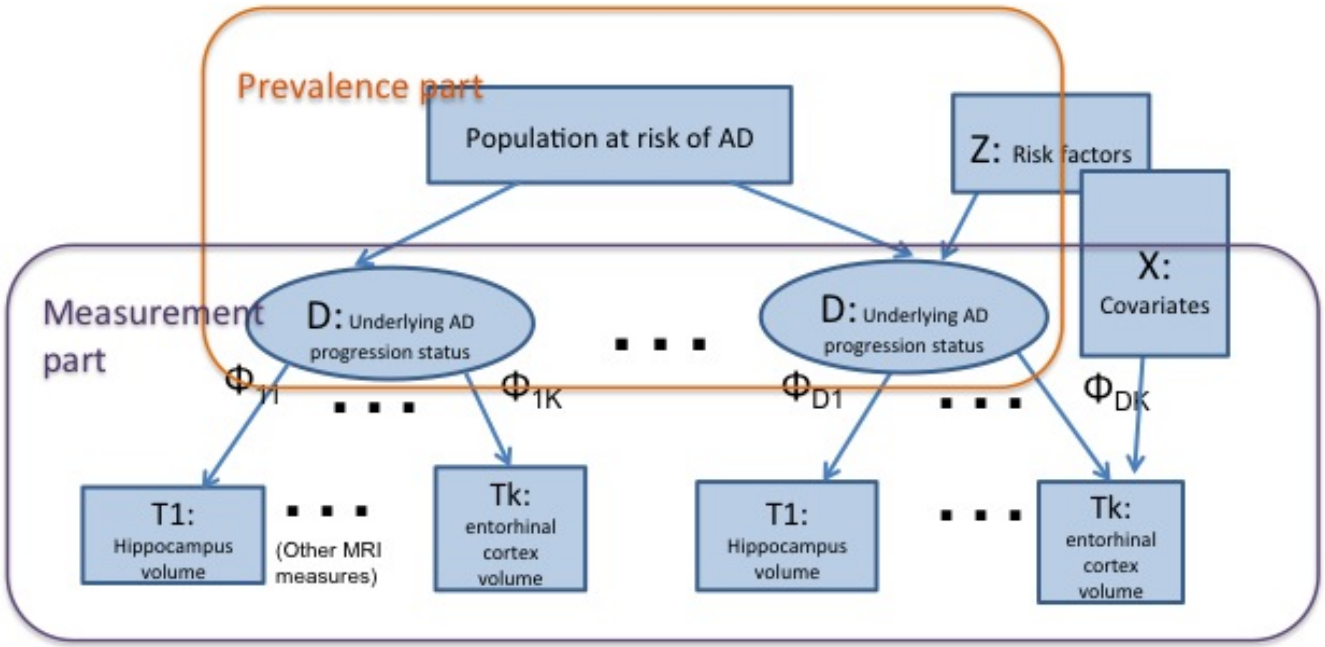
- Structure
  - Observed: biomarkers, risk factors, additional covariates
  - Unobserved: the underlying AD pathophysiology progression status

# A Latent Variable Model

- First level: latent structural model $P(D|Z)$
  - prevalence varies with subjects with different characteristic.
- Second level: measurement model $P(T|D,X)$
  - study covariate effect on biomarker levels
- R package "latentreg"



# Analysis: MRI biomarkers in NACC UDS

- Examine MRI biomarkers +/- CDR tests
  - Subjects may be more willing to use MRI as a monitoring tool
  - More realistic population
- Population:
  - UDS subjects who had at least one MRI evaluation
  - had volumetric MRI biomarkers calculated
  - had a UDS visit within 2 years of the MRI visit (CDR test compatible)
  - Complete covariate information
  - N=359: 166 normal cognition, 29 impaired but not MCI, 123 MCI of any type, and 41 AD

# Analysis: Model specifications

- Risk factors considered: Age, number of ApoE4
- CDR Tests:
  - memory, orientation, judgment and problem solving, community affairs, home and hobbies, exclude personal care
  - collapsed scores of 1, 2, and 3 into one category
- MRI biomarkers: volumes of hippocampus, white matter hyperintensities and temporal lobe gray matter
- Covariates:
  - For CDR Test: D, age, education, depression
  - For MRI biomarkers: D, age, whole brain volume

# Analysis: Results

Table: Estimates and 95% CI in parentheses based on 2000 bootstrap replicates (estimates in bold indicate a significant effect).

| Prevalence model $P(D \mid Z)$ | | | |
|---|---|---|---|
| | (Intercept) | Age×10 | ApoE4 |
| $D = 1$ | **-5.27** (-8.08, -2.73) | **0.57** (0.24, 0.92) | **0.82** (0.42, 1.22) |

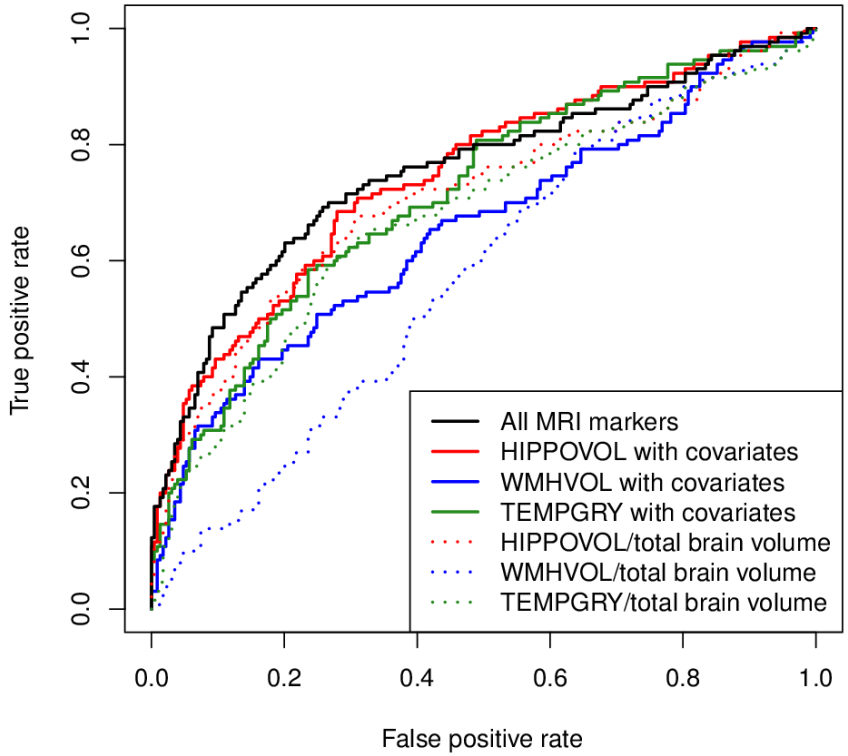
| Biomarker model $P(T \mid D, X_\beta)$ | | | |
|---|---|---|---|
| | HIPPOVOL | WMHVOL | TEMPGRY×10 |
| (Intercept) | 2.39 (-0.33, 4.68) | **-3.68** (-5.73, -1.69) | -7.50 (-39.9, 0.68) |
| $D = 1$ | **-0.89** (-2.09, -0.33) | 0.13 (-0.10, 0.38) | **-1.19** (-4.21, -0.33) |
| Age×10 | **-0.28** (-0.79, -0.07) | **0.68** (0.48, 0.89) | 0.02 (-0.49, 0.58) |
| BRNV×100 | **0.75** (0.28, 1.80) | 0.07 (-0.04, 0.17) | **2.92** (0.88, 9.39) |
| $\lambda$ | 1.33 (0.79, 1.81) | 0.06 (-0.02, 0.14) | 1.42 (0.92, 1.90) |
| $\sigma$ | 1.13 (0.43, 2.61) | 1.10 (0.92, 1.27) | 2.19 (0.65, 6.98) |

| Test model $P(T \mid D, X_\gamma)$ | | | | | |
|---|---|---|---|---|---|
| | MEMORY | ORIENT | JUDEMENT | COMMUN | HOMEHOBB |
| (Intercept1)* | 1.8 (-0.6, 4.5) | 3.1 (-0.2, 6.8) | 2.7 (-0.5, 5.9) | **7.7** (3.9, 27) | **5.2** (1.9, 9.4) |
| (Intercept2)** | **6.0** (3.5, 9.2) | **5.8** (2.6, 9.7) | **5.1** (2.0, 8.4) | **9.7** (5.9, 29) | **7.5** (4.1, 12) |
| $D = 1$ | **-4.8** (-6.3, -4.0) | **-5.0** (-6.2, -4.3) | **-4.2** (-5.1, -3.6) | **-6.7** (-23, -5.3) | **-5.1** (-6.6, -4.4) |
| Age×10 | -0.2, (-0.6, 0.1) | **-0.3** (-0.7, 0.2) | -0.2 (-0.6, 0.2) | **-0.5** (-1.1, -0.0) | -0.4 (-0.9, 0.0) |
| EDUC | **0.1** (0.0, 0.1) | **0.2** (0.1, 0.2) | **0.1** (0.0, 0.2) | **0.2** (0.1, 0.3) | **0.1** (0.0, 0.2) |
| DEP2YRS | **-1.0** (-1.5, -0.5) | -0.6 (-1.4, 0.0) | -0.35, (-1.0, 0.3) | -0.5 (-1.3, 0.3) | -0.5 (-1.2, 0.3) |

* Intercept for having test score 0 vs. $\geq 0.5$

** Intercept for having test score $\leq 1$ vs. $> 1$

# Analysis: Results




AUC before and after accounting for subjects' characteristics:

- Hippocampal volume:
  0.71 (95% CI: 0.64 to 0.78) increases to 0.74 (95% CI: 0.67 to 0.81)
- Volume of white matter hyperintensities:
  0.57 (95% CI: 0.49 to 0.63) to 0.65 (95% CI: 0.55 to 0.73)
- Volume of temporal gray:
  0.67 (95% CI: 0.61 to 0.76) to 0.72 (95% CI: 0.62 to 0.79)

# Analysis: Results

Table: Comparison between prediction based on baseline MRI biomarkers and CDR tests versus cognitive status at latest follow-up

| Baseline[♭] | Not normal | | Any type of MCI | | Normal | |
|---|---|---|---|---|---|---|
| Last follow-up[♭] | Normal | MCI or AD | no MCI no AD | AD | Normal | Not normal |
| Number of subjects | $N$ =30 | $N$ =160 | $N$ =12 | $N$ =55 | $N$ =141 | $N$ =25 |
| Prognostic accuracy | Specificity | Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity |
| CDR+covariates[†] | 0.93 (28[♮]) | 0.65 (105) | 0.83 (10) | 0.65 (36) | 0.90 (128) | 0.24 (7) |
| CDR+MRI+covariates | 0.93 (28) | 0.67 (108) | 0.83 (10) | 0.69 (38) | 0.91 (129) | 0.24 (6) |

[♭] Based on clinician diagnosis

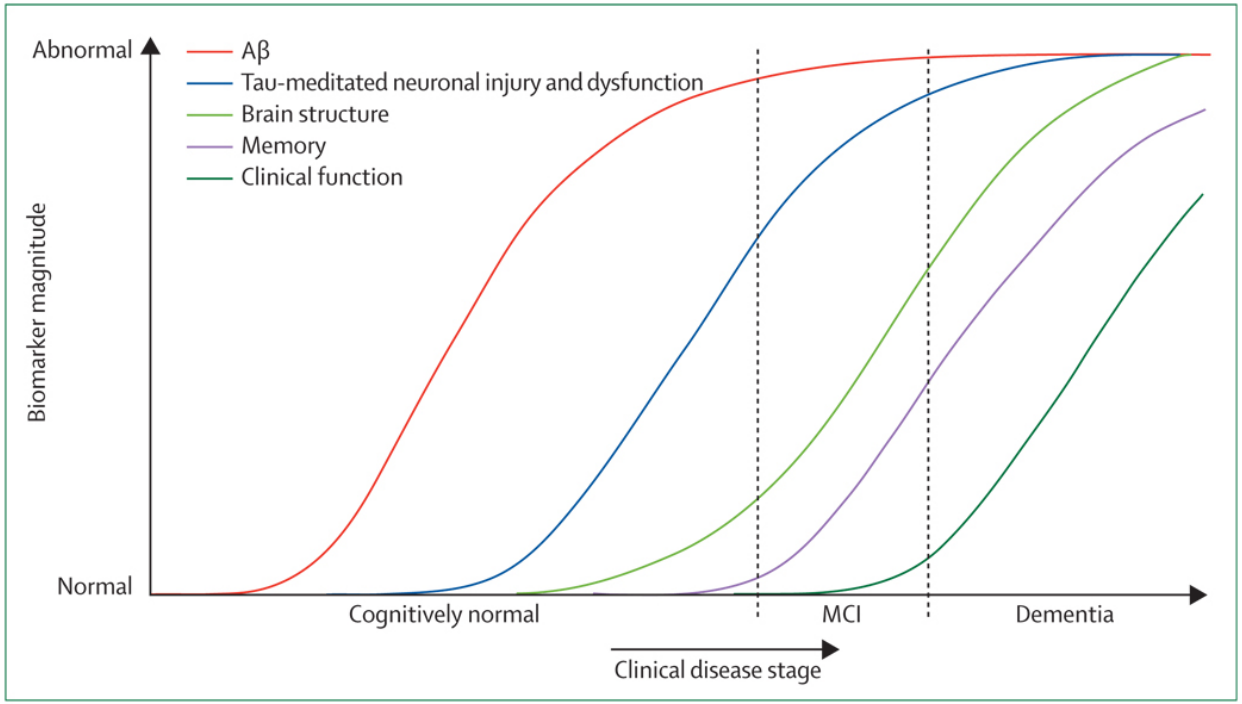
[♮] Number of subjects with correct prognosis

[†] Based on a model excluding MRI markers and related covariates

# Discussion: Next Steps

- Prospective validation with BIOCARD data
- Longitudinal model of repeated biomarker measurements

# Discussion: longitudinal models



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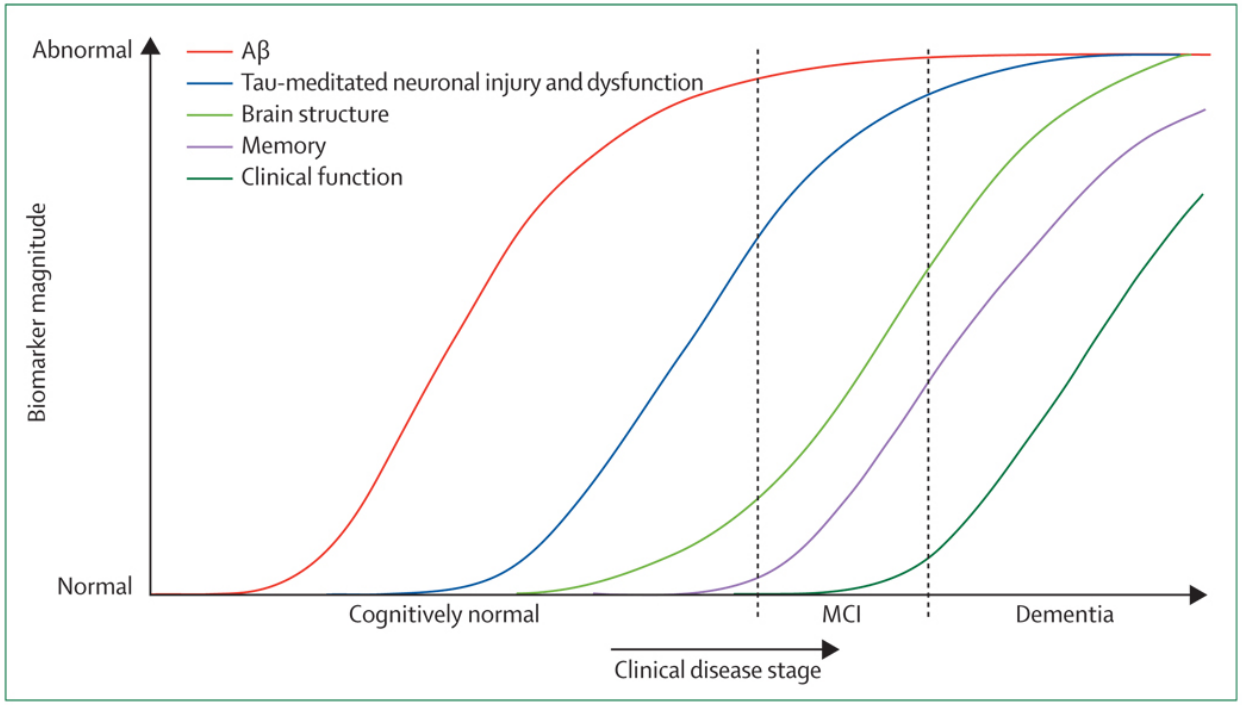


- Biomarker valus $y_{imt}$ vs. latent disease progression $d_{it}$

$$y_{imt} \sim \mathbf{X}_i^T \beta_{im} + f_m(d_{it})$$

  - $f_m$ is a "S" shaped function (Jack et. al)
  - $f_m$ differs for different biomarkers
  - Covariates $X$ shift the curve: increase/decrease biomarker levels

# Discussion: longitudinal models

- Latent disease progression vs. time: quadratic function

$$d_{it} = \gamma_{1i} + \gamma_{2i} Z_i + \gamma_{3i} t + \gamma_{4i} t^2$$

  - Disease may progress slowly at the beginning and get worse very quickly afterwards
  - Risk factors $Z$ affect disease progression
- Any suggestion are welcome!

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