Joint Modeling of Longitudinal Item Response Data and Survival

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Overview

Introduction

Cross-classified Response Data

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Longitudinal Response Data

Mini-Mental State Examination (MMSE)

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Survival Analysis
- Joint Modeling of Latent Developmental Trajectories and Survival
- Joint (Response, Survival) Analysis Outcomes

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Responses to Test Items

Collection of responses on tests, $i = 1, \dots, N$ persons who answer $k = 1, \dots, K$ items, resulting in $N \times K$ 0/1 responses Y:

$$\mathbf{Y} = \begin{bmatrix} 1 & 0 & 1 & \dots & Y_{1K} \\ 0 & 1 & 1 & \dots & Y_{2K} \\ \vdots & & & \ddots & \vdots \\ Y_{N1} & 0 & 1 & \dots & Y_{NK} \end{bmatrix}$$

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- Develop a model to say something about the structure of this data set
- Structure: person and item effects.

Stage 1: Modeling Success Probabilities

$$
\begin{aligned}
P\left(Y_{ik} = 1 \mid \theta_i, \boldsymbol{\xi}_k\right) &= F\left(a_k\theta_i - b_k\right) \\
\theta_i &\sim N\left(\mu_\theta, \sigma_\theta^2\right)
\end{aligned}
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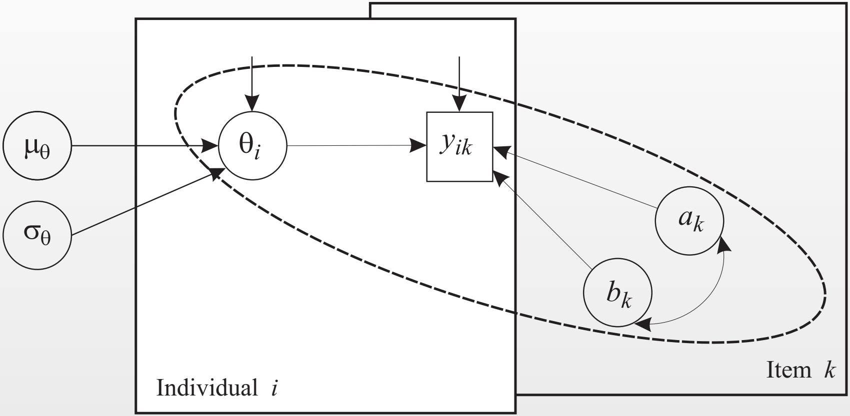
- Response observations k are nested within persons, random person effects (latent variable)
- Response observations k are nested within items, fixed/random item effects.

Two-Parameter Item Response Model



Likelihood-Model

Collection of $N \times K$ responses, N persons and K items

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$$P\left(Y_{ik} = 1 \mid \theta_i, a_k, b_k\right) = \begin{cases} \frac{\exp(d(a_k\theta_i - b_k))}{1+\exp(d(a_k\theta_i - b_k))} & \text{Logistic Model} \\ \Phi(a_k\theta_i - b_k) & \text{Probit Model} \end{cases}$$

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$$p\left(\boldsymbol{y} \mid \boldsymbol{\theta}, \boldsymbol{a}, \boldsymbol{b}\right) = \prod_i \left[\prod_k F\left(\eta_{ik}\right)^{y_{ik}} \left(1 - F\left(\eta_{ik}\right)\right)^{1-y_{ik}}\right]$$

where $\eta_{ik} = a_k\theta_i - b_k$

Population Model for Item Parameters

Stage 2: Prior for Item Parameters

$$(a_k, b_k)^t \sim \mathcal{N}\left(\boldsymbol{\mu}_\xi, \boldsymbol{\Sigma}_\xi\right) I_{\mathcal{A}_k}(a_k),$$

where the set $\mathcal{A}_k = \{a_k \in \mathcal{R}, a_k > 0\}$

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Stage 3: Hyper prior

$$\begin{aligned} \boldsymbol{\Sigma}_\xi &\sim \mathcal{IW}(\nu, \boldsymbol{\Sigma}_0) \\ \boldsymbol{\mu}_\xi \mid \boldsymbol{\Sigma}_\xi &\sim \mathcal{N}(\boldsymbol{\mu}_0, \boldsymbol{\Sigma}_\xi / K_0). \end{aligned}$$

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Respondents are sampled independently and identically distributed.

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$$\begin{aligned} \sigma_\theta^2 &\sim \mathcal{IG}(g_1, g_2) \\ \mu_\theta \mid \sigma_\theta^2 &\sim \mathcal{N}(\mu_0, \sigma_\theta^2/n_0). \end{aligned}$$

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Latent Growth Modeling

- Model Latent Developmental Trajectories:

$$
\begin{aligned}
\theta_{ij} &= \beta_{0i} + \beta_{1i} Time_{ij} + e_{ij} \\
\beta_{0i} &= \gamma_{00} + u_{0i} \\
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2. Number of observations per subject may vary
3. Follow-up times not uniform across subjects (time a continuous variable, individualized schedule)
4. Handle time-invariant and time-varying covariates
5. Estimate subject-specific change across time (average change)

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- Model the covariance structure of the level-1 measurement errors explicitly.
- Model change in several domains simultaneously.

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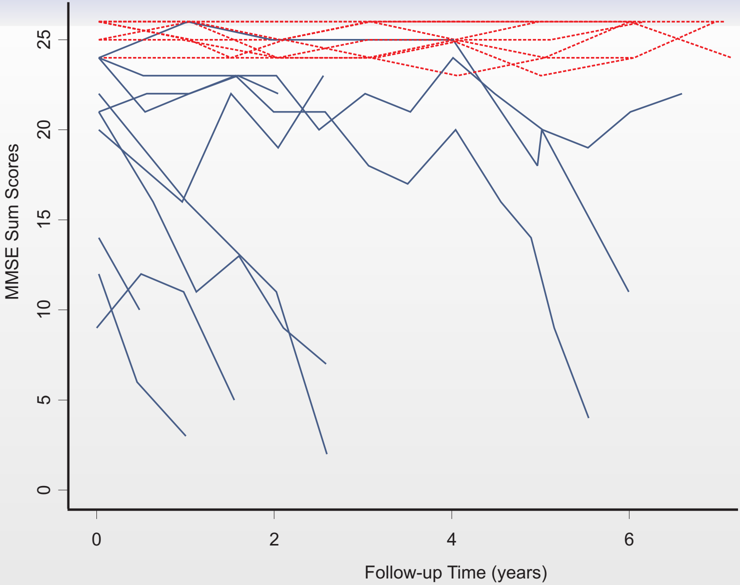
Mini-Mental State Examination (MMSE)

- Data: 4016 measurements of 668 subjects (4-16 measurement occasions)
- 26 MMSE (binary) items;
  - What day of the week is it? (orientation)
  - pencil - What is this? (language)
  - subtract 7 from 100 (attention/concentration)

Demographics

Table: Demographic information of the study participants.

	Participants ($N = 668$)	
Gender	Male 329	Female 339
Age	**start**	**mean**
50-59	55	41
60-69	195	149
70-79	323	315
80-89	149	215
90-100	9	14
Average sum score		
24 – 26	302	
22 – 23	66	
20 – 21	47	
18 – 19	61	
15 – 17	66	
< 14	126	


MMSE Sum Scores
0
5
10
15
20
25
0
2
4
6
Follow-up Time (years)

Modeling of asymmetrical data: Define latent groups g_1 and g_2

$$p\left(\theta_{ij} \mid \boldsymbol{\Omega}\right) = \sum_{g=1}^{2} \pi_{ig} p\left(\theta_{ij} \mid \boldsymbol{\Omega}_g\right)$$

Mixture IRT Modeling

Modeling of asymmetrical data: Define latent groups g_1 and g_2

$$p\left(\theta_{ij} \mid \mathbf{\Omega}\right) = \sum_{g=1}^{2} \pi_{ig} p\left(\theta_{ij} \mid \mathbf{\Omega}_g\right)$$

$$P\left(G_i = 1 \mid \boldsymbol{y}_i, \boldsymbol{\theta}_i\right) = \frac{\pi_{i1} \prod_{j=1}^{n_i} p\left(\boldsymbol{y}_{ij} \mid \theta_{ij}\right) p\left(\theta_{ij} \mid \mathbf{\Omega}_1\right)}{\sum_{g=1,2} \pi_{ig} \prod_{j=1}^{n_i} p\left(\boldsymbol{y}_{ij} \mid \theta_{ij}\right) p\left(\theta_{ij} \mid \mathbf{\Omega}_g\right)}$$

Likelihood-model $\mathcal{M}_1$

Measurement Part $\mathcal{M}_1$

$$P(Y_{ijk} = 1 \mid \theta_{ij}, a_k, b_k) = F\left(a_k\theta_{ij} - b_k\right)$$

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Latent Growth Part $\mathcal{M}_1$

$$\begin{aligned} p\left(\theta_{ij} \mid \gamma_{00}, \tau^2, \sigma^2\right) &= \pi_{i1}\phi\left(\mu_{ij,1}, \sigma^2\right) + \pi_{i2}\phi\left(\mu_{ij,2}, \sigma^2\right) \\ \mu_{ij,1} &= \gamma_{00,1} + u_{i0,1} \\ \mu_{ij,2} &= \gamma_{00,2} + u_{i0,2} \end{aligned}$$

$\left(\gamma^{(2)} < \gamma^{(1)}\right)$

Table: MMSE: Parameter Estimates of Model $\mathcal{M}_1$.

	Mixture MLIRT $\mathcal{M}_1$			
	Decline		Stable	
	Mean	SD	Mean	SD
Fixed Effects				
γ_{00} Intercept	-.998	.037	.689	.030
Random Effects				
Within-individual				
σ^2_θ Residual variance	.133	.003	.133	.003
Between-individual				
τ^2_{00} Intercept	.211	.015	.211	.015

Likelihood-model $\mathcal{M}_2$

Measurement Part $\mathcal{M}_2$

$$P(Y_{ijk} = 1 \mid \theta_{ij}, a_k, b_k) = F\left(a_k\theta_{ij} - b_k\right)$$

Likelihood-model $\mathcal{M}_2$

Measurement Part $\mathcal{M}_2$

$$P(Y_{ijk} = 1 \mid \theta_{ij}, a_k, b_k) = F\left(a_k\theta_{ij} - b_k\right)$$

Latent Growth Part $\mathcal{M}_2$

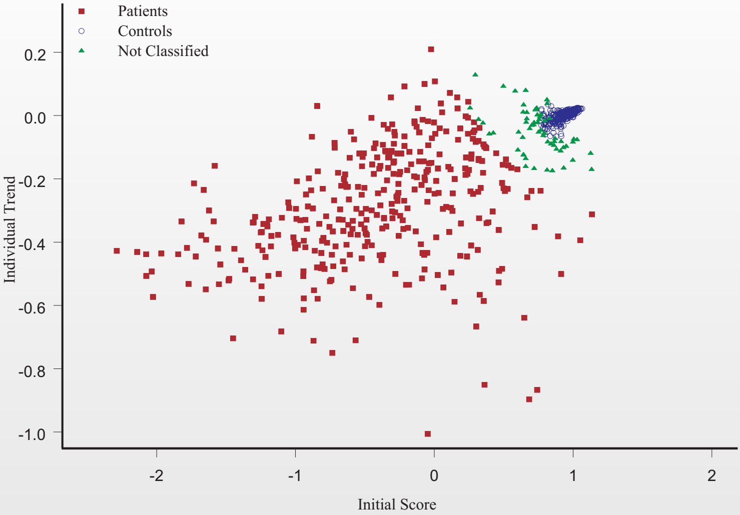
$$\begin{aligned}
p\left(\theta_{ij} \mid \boldsymbol{\gamma}, \boldsymbol{T}, \sigma^2\right) &= \pi_{i1}\phi\left(\mu_{ij,1}, \sigma^2\right) + \pi_{i2}\phi\left(\mu_{ij,2}, \sigma^2\right) \\
\mu_{ij,g} &= \beta_{i0,g} + \beta_{i1,g}Time_{ij} \\
\beta_{i0,g} &= \gamma_{00,g} + u_{i0,g} \\
\beta_{i1,g} &= \gamma_{10,g} + u_{i1,g},
\end{aligned}$$

and $\boldsymbol{u}_{i,g} \sim \mathcal{N}\left(0, \boldsymbol{T}_g\right)$ with $\boldsymbol{T}_g$ a diagonal matrix with elements $\tau^2_{00,g}$ and $\tau^2_{11,g}$ for $g = 1, 2$.

Table: MMSE: Parameter estimates of Model $\mathcal{M}_2$

	Mixture MLIRT $\mathcal{M}_2$			
	Decline		Stable	
	Mean	SD	Mean	SD
Fixed Effects				
γ_{00} Intercept	$-.332$	.037	.913	.012
Time Variables				
γ_{10} Follow-up time	$-.274$	.013	$-.007$	.004
Random Effects				
Within-individual				
σ_θ^2 Residual variance	.043	.001	.043	.001
Between-individual				
τ_{00}^2 Intercept	.471	.038	.016	.003
τ_{11}^2 Follow-up time	.047	.004	.002	.000

Estimated random effects of cognitive impairment



Survival Time Data

- Time to certain (non-repeatable) events (e.g., death, response, failure time)

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- Persons were followed to death or (right-)censored in a study

$$\text{survival time } v_i = \begin{cases} t_i & t_i \leq c_i \text{ observed} \quad\quad \text{(uncensored)} \\ c_i & t_i > c_i \text{ not observed} \quad \text{(censored)} \end{cases}$$

Distribution of Survival Times

- Survivor function: probability survives longer than t

$$S(t) = P(T > t) = 1 - F(t)$$

- Probability density function

$$f(t) \geq 0, t \geq 0$$

- Hazard function: conditional failure rate

$$h(t) = \frac{f(t)}{1 - F(t)} = \frac{f(t)}{S(t)}$$

Right-Censored Observations

Joint probability of observing data $\boldsymbol{v}$:

$$f(\boldsymbol{v} \mid \boldsymbol{\eta}) = \prod_{i=1}^{r} f(t_i, \boldsymbol{\eta}) \prod_{i=r+1}^{n} S(c_i, \boldsymbol{\eta})$$

Problems in Survival Modeling

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- Censoring: data missingness, subject does not undergo the event
- Unobserved between-individual variation in the probability to experience the event
- Presence of time-varying covariates (e.g., prognostic factors)

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$$\frac{h(t \mid \boldsymbol{x}_1)}{h(t \mid \boldsymbol{x}_2)} = \text{constant}$$

$$\begin{aligned} h(t \mid \boldsymbol{x}) &= h_0(t) g(\boldsymbol{x}) \\ &= h_0(t) \exp(\boldsymbol{\eta}^t \boldsymbol{x}) \end{aligned}$$

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- Violate proportional hazards assumption when using time-varying covariates

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Joint Modeling Approach

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- Patients and controls with different (latent, time-continuous) backgrounds may have different survival prognosis
- Longitudinal factor/covariates are measured infrequently and with measurement error
- Subjects enter the study at different time-points, measured at different times, different number of measurements

Joint Modeling: Two-stage procedure

- Survival information not used in modeling the covariate process.

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- Survival information not used in modeling the covariate process.
- New growth curves are estimated at each new event (interpretability)
- Handle measurement error in time-dependent (latent) covariate(s) survival model

Joint Modeling

- Joint distribution (survival data, response data):

$$
\begin{aligned}
p\left(\boldsymbol{t}, \boldsymbol{y} \mid \boldsymbol{x}\right) &= \int p\left(\boldsymbol{t}, \boldsymbol{y} \mid \boldsymbol{\eta}, \boldsymbol{x}\right) p\left(\boldsymbol{\eta} \mid \boldsymbol{x}\right) d\boldsymbol{\eta} \\
&= \int\int p\left(\boldsymbol{t} \mid \boldsymbol{\eta}, \boldsymbol{x}\right) p\left(\boldsymbol{y} \mid \boldsymbol{\eta}\right) p\left(\boldsymbol{\eta} \mid \boldsymbol{\Omega}, \boldsymbol{x}\right) p(\boldsymbol{\Omega}) d\boldsymbol{\eta} d\boldsymbol{\Omega} \\
&= \int\int p\left(\boldsymbol{t} \mid \boldsymbol{\eta}, \boldsymbol{\Omega}, \boldsymbol{x}\right) p\left(\boldsymbol{y} \mid \boldsymbol{\eta}\right) p\left(\boldsymbol{\eta} \mid \boldsymbol{\Omega}, \boldsymbol{x}\right) p(\boldsymbol{\Omega}) d\boldsymbol{\eta} d\boldsymbol{\Omega}
\end{aligned}
$$

Time Density Function

- Define $v_i = \min(t_i, c_i)$,

$$D_i = \begin{cases} 1 & \text{Event observed} \\ 0 & \text{Censored observation} \end{cases}$$

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$$\begin{aligned} f\left(v_i, d_i \mid \boldsymbol{\eta}, \boldsymbol{\Omega}\right) &= h\left(v_i \mid \boldsymbol{\eta}, \boldsymbol{\Omega}\right)^{d_i} S\left(v_i \mid \boldsymbol{\eta}, \boldsymbol{\Omega}\right) \\ &= h\left(v_i \mid \boldsymbol{\eta}, \boldsymbol{\Omega}\right)^{d_i} \exp\left[-\int_0^{v_i} h\left(u \mid \boldsymbol{\eta}(u), \boldsymbol{\Omega}\right) du\right] \end{aligned}$$

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- Define subject-specific time-intervals, $t_{il} - t_{i(l+1)}$;

$$f_{il}\left(d_i, t_{i(l+1)}, t_{il} \mid \eta_l\right) = \frac{S\left(t_{i(l+1)} \mid \eta_l\right)^{1-d_i} f\left(t_{i(l+1)} \mid \eta_l\right)^{d_i}}{S\left(t_l \mid \eta_l\right)}$$

Time Density Function

- For subject i

$$
\begin{aligned}
f_i\left(d_i, \boldsymbol{t}_i \mid \boldsymbol{\eta}\right) &= \prod_{l=0}^{l=L_i-1} f_{il}\left(d_i, t_{il}, t_{i(l+1)} \mid \eta_l\right) \\
&= \prod_{l=0}^{l=L_i-1} \frac{S\left(t_{i(l+1)} \mid \eta_l\right)^{1-d_i} f\left(t_{i(l+1)} \mid \eta_l\right)^{d_i}}{S\left(t_l \mid \eta_l\right)}
\end{aligned}
$$

Overview

Estimated Parameters Mixture Model

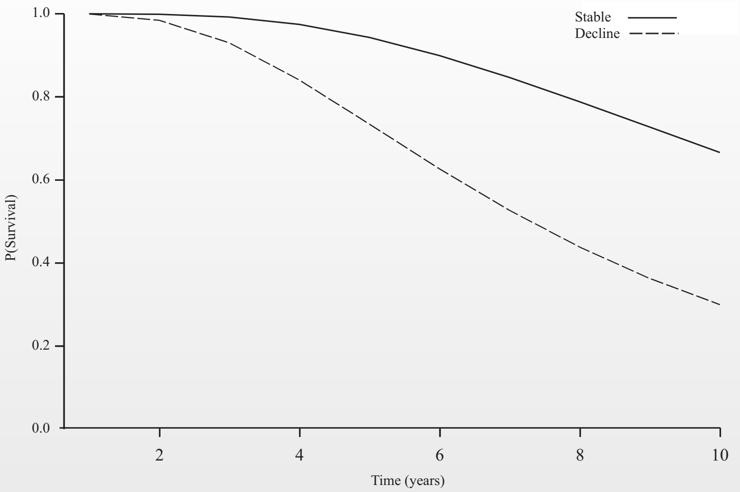
	Decline		Stable	
	EAP	SD	EAP	SD
Fixed Effects				
γ_{00} Intercept	-.709	.031	.776	.036
γ_{01} Time Slope	-.112	.012	-.009	.006
Variance Components				
τ^2 Between Individual	.244	.124	.134	.118
σ^2 Residual	.219	.029	.219	.029
Mixture Proportion				
π	.432	.020	.568	.020

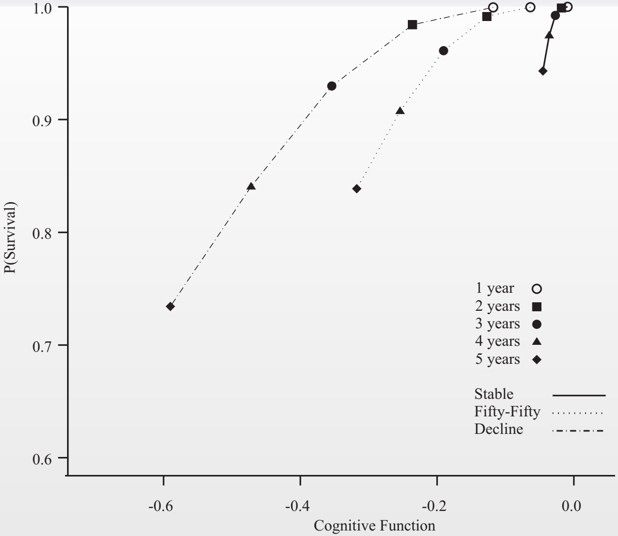
Results: Comparing Models

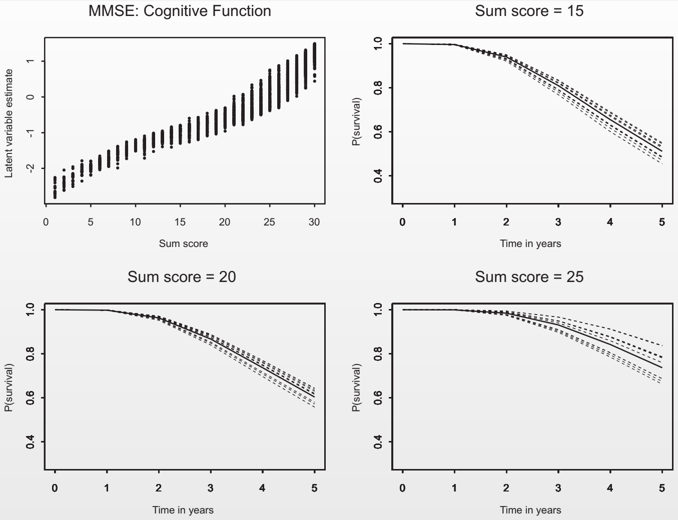
Model	Density	Covariates	Groups	DIC
M_1	Exponential	1	2	2146.0
M_2	Weibull	1	2	1872.3
M_3	Lognormal	1	2	1905.4
M_4	Exponential	$1, \theta$	2	2041.7
M_5	Weibull	$1, \theta$	2	1836.0
M_6	Lognormal	$1, \theta$	2	1816.1
M_7	Weibull	$1, \theta$, Male, Age	2	1775.0
M_8	Lognormal	$1, \theta$, Male, Age	2	1768.1
M_9	Weibull	$1, \theta$, Male, Age	1	1856.3
M_10	Lognormal	$1, \theta$, Male, Age	1	1858.3

Stratified Lognormal Survival Model M_{10}

	Decline (g=2)		Stable (g=1)	
	EAP	SD	EAP	SD
Fixed Effects				
$\beta_{0,g}$ Intercept	1.986	.072	2.561	.081
$\beta_{1,g}$ Male	-.270	.064	-.282	.076
$\beta_{2,g}$ Age (standardized)	-.179	.080	-.212	.090
Λ_g Cognitive Function	.369	.041	.254	.046
Variance Components				
σ_S^2 Residual	.362	.031	.362	.031


Stable
Decline
1.0
0.8
0.6
0.4
0.2
0.0
P(Survival)
2
4
6
8
10
Time (years)


1.0
0.9
0.8
0.7
0.6
P(Survival)
-0.6
-0.4
-0.2
0.0
Cognitive Function
1 year
2 years
3 years
4 years
5 years
Stable
Fifty-Fifty
Decline


MMSE: Cognitive Function
Latent variable estimate
Sum score
Sum score = 15
P(survival)
Time in years
Sum score = 20
P(survival)
Time in years
Sum score = 25
P(survival)
Time in years

Discussion

- Mental health (individual trajectory of cognitive impairment) serves as a time-varying covariate

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- Making inferences at the level of individuals (patients) and their disease trajectories
- Combine cognitive test outcomes with other indicators to serve as a diagnostic tool