

Gerontologic Biostatistics: Modeling Longitudinal Ordinal Data in Aging



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Acknowledgments



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Disclosure

Dr. Allore has no conflicts of interest.



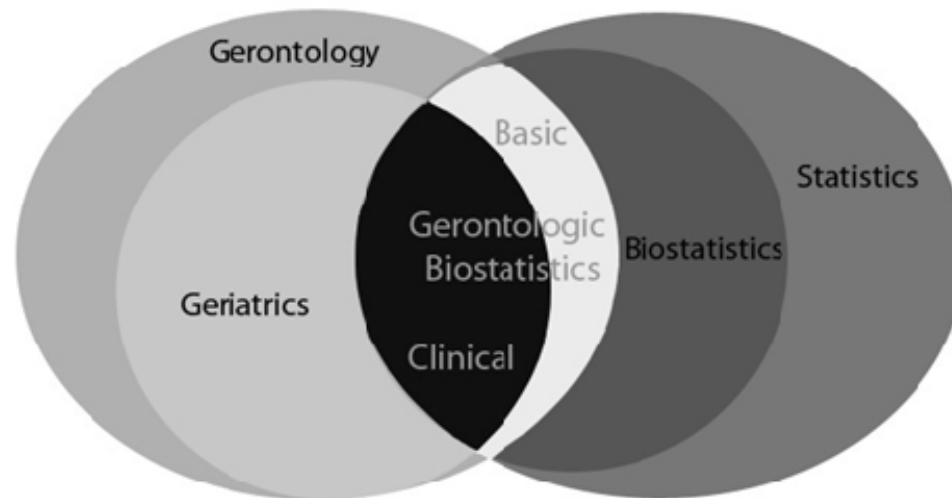
**KEEP
CALM
AND
LOVE
BIOSTATISTICS**



Gerontologic Biostatistics

- Gerontologic biostatistics distinctiveness originates in the multifactorial etiologies of geriatric health syndromes and the multiple morbidities accruing with aging at the end of life

Figure 1: Gerontologic Biostatistics and its Relationships with Kindred Disciplines



Van Ness et al, Gerontologic Biostatistics: The statistical Challenges of Clinical research with Older Study Participants. J am Geriatr Soc. 2010; 58(7):1386-1392

Gerontologic Biostatistics

- Develop and extend methods to address clinically-relevant aging research
- Distinctiveness originates in the multifactorial etiologies of geriatric health syndromes and the social dynamics of later life.
- **Statistical challenges:** design and analytical strategies for multicomponent interventions, multiple outcomes, state transition models, floor and ceiling effects, missing data - mortality, and mixed methods

Outline

- 1st disability event time-dependent intervening events
- Dynamic process of disability / multistate model with intervening events
- Trajectories of disability at the end of life
- Trajectories of disability over 18 years
- Bayesian joint models

Let's enter the world of functional disability

- Functional disability is when a person is unable to independently to perform Activities of Daily Living (ADLs).



Precipitating Events Project

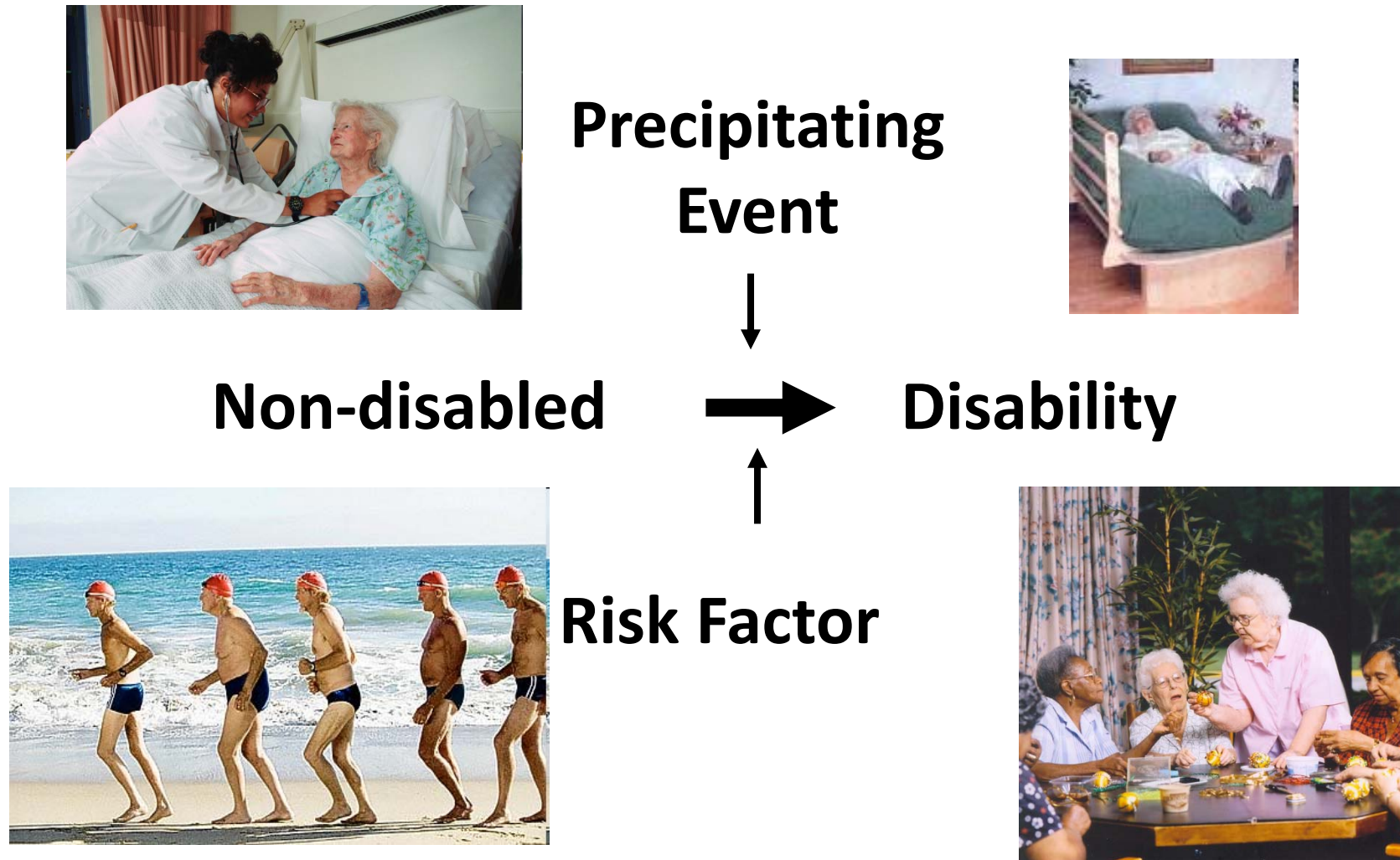
Thomas M. Gill, MD

Humana Professor of Medicine (Geriatrics) and Professor of Epidemiology (Chronic Diseases) and of Investigative Medicine; Director, Yale Center for Disability and Disabling Disorders, Yale Program on Aging, Yale OAIC



- Prospective cohort study of 754 nondisabled, community-living persons aged 70 years or older assembled in 1998-99
- Overall research objectives
 - to rigorously evaluate the natural history of disability among community-living older persons
 - to elucidate the mechanisms underlying the development of, and recovery from, functional decline and disability among community-living older persons

Vulnerability Model of Disability



Yale Precipitating Events Project (PEP)

- 754 community-dwelling adults aged ≥ 70 at enrollment
- No disability with four basic activities of daily living (ADL)
— bathing, dressing, walking and chair transferring
- Comprehensive assessments every 18 months ongoing
- Telephone interview monthly still ongoing
- Frail elders over-sampled
- Minimum 2 year life expectancy
- 224 monthly interviews (18+ yrs)
- 12 comprehensive assessments (216 mn)
- 662 decedents, 92 survivors



Statistical Methods

- Time-dependent Cox proportional hazards
- Exact method was used to handle tied event times.
- The hazard ratios refer to the risk of developing disability at month $t+1$ based on exposure to hospitalization or restricted activity only during the preceding month (t).
- The reference group was participants who had no hospitalization or restricted activity during the preceding month.
- Exposure for the prior events was defined as the number of months with hospitalization and the number of months with restricted activity only

Association Between New Intervening Events and Disability According to Physical Frailty at Baseline

Table 4. Association Between New Intervening Events and Disability According to Physical Frailty at Baseline

Intervening Event†	Hazard Ratio (95% Confidence Interval)*		
	Any Disability	Persistent Disability	Disability With Nursing Home Admission
Hospitalization‡			
Physically frail at baseline	31.8 (22.5-45.0)	29.5 (20.2-43.1)	191 (102-357)
Not physically frail at baseline	122 (82.4-180)	76.5 (47.3-124)	312 (141-691)
Restricted activity only§			
Physically frail at baseline	4.13 (2.87-5.95)	2.76 (1.39-5.46)	4.52 (1.95-10.5)
Not physically frail at baseline	6.45 (4.06-10.3)	3.30 (2.15-5.07)	1.71 (0.35-8.29)

*Hazard ratios are adjusted for age, sex, race/ethnicity, living alone, years of education, chronic conditions, cognitive impairment, depressive symptoms, and prior intervening events.

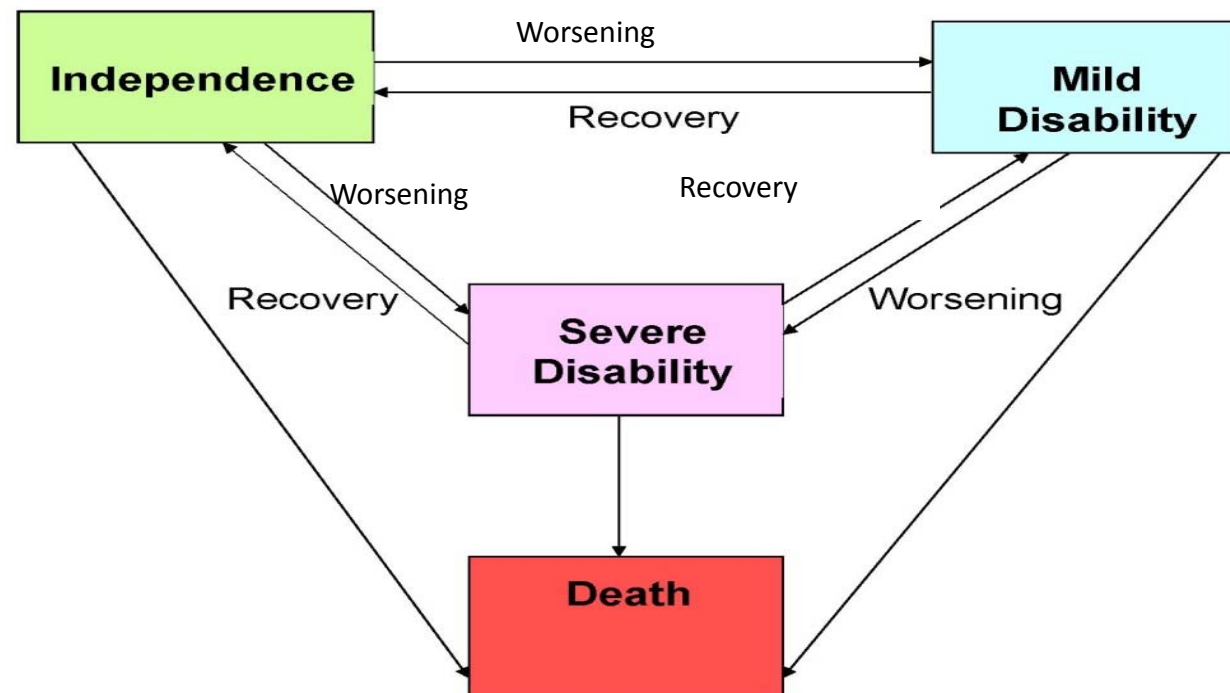
†The exposure period was the month prior to the assessment of disability. The comparison group included participants without an acute hospital admission or restricted activity.

‡There was a statistical interaction with physical frailty for any disability ($P < .001$) and persistent disability ($P = .002$), but not for disability with nursing home admission ($P = .22$).

§There were no statistical interactions with physical frailty for any of the 3 disability outcomes.

Dynamic Process of Disability: Longitudinal multistate transition model

- Modeling the transition rate/intensity among the different states of ADL and death.



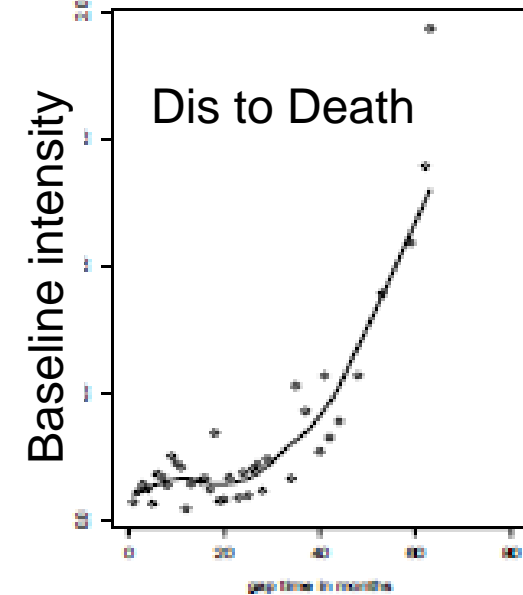
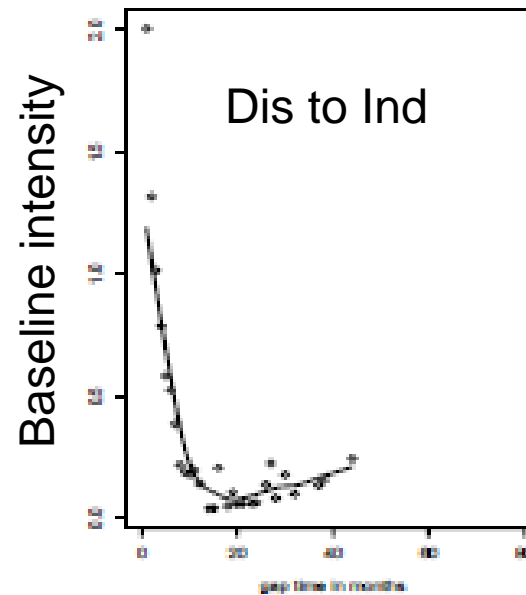
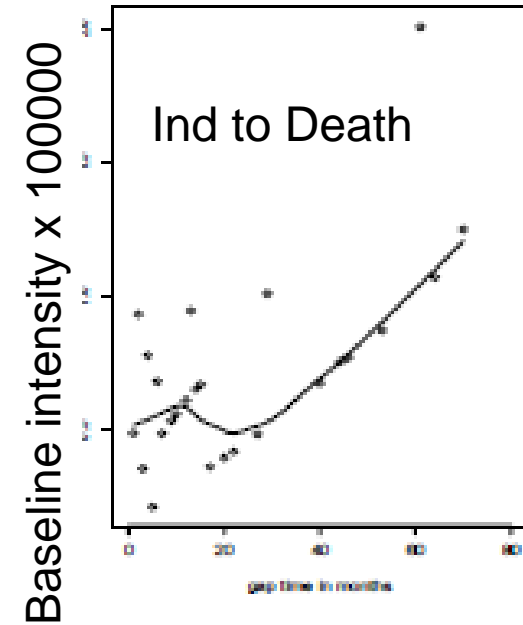
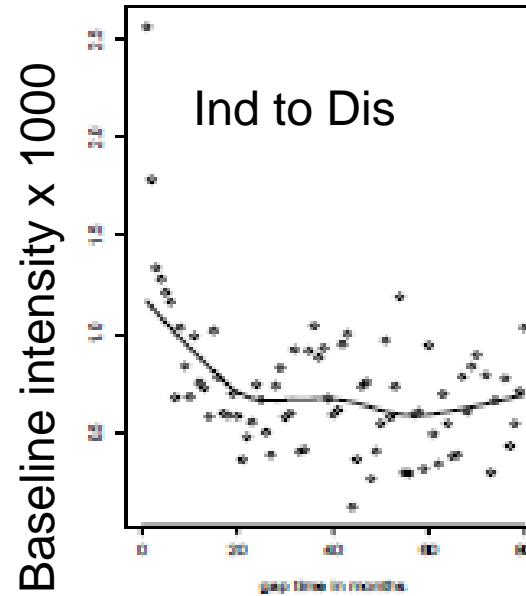
A Semiparametric Transition Model with Latent Traits for Longitudinal Multistate Data

Lin, Guo, Peduzzi, Gill, Allore Biometrics 2008. 64(4):1032-42

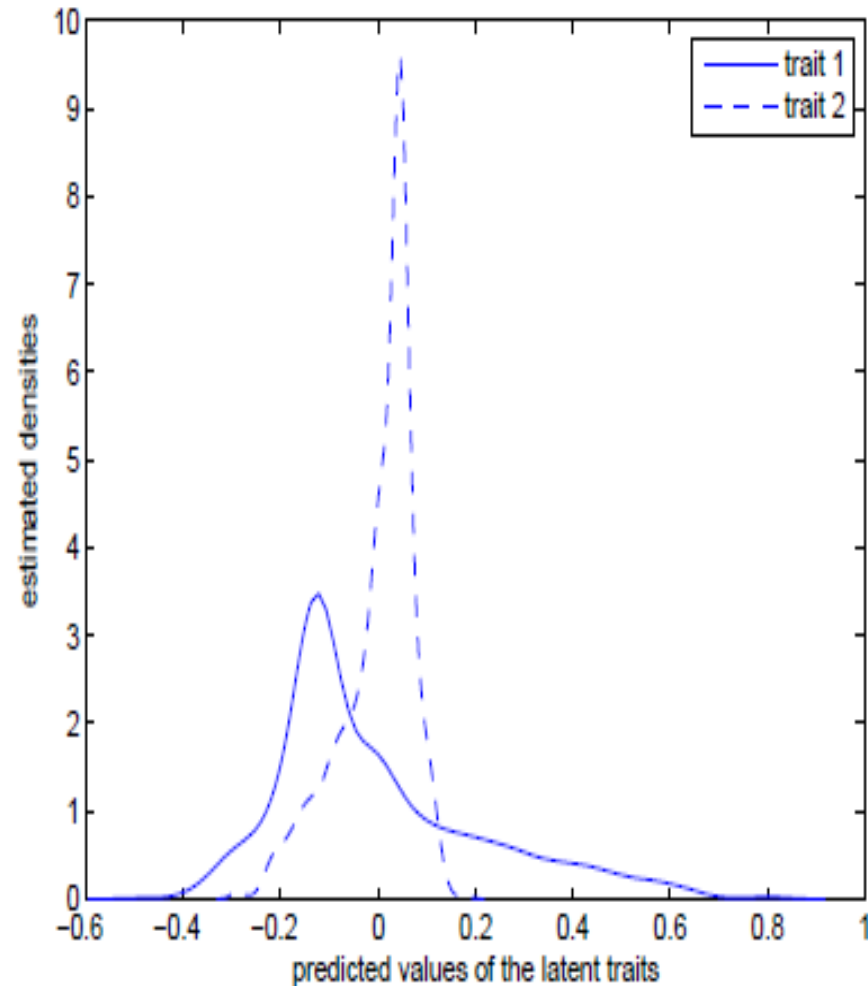
- General multistate transition model developed for the analysis of repeated episodes of multiple states
- Transitions among multiple states are modeled jointly using multivariate latent traits with factor loadings.
- Different types of state transition are described by flexible transition-specific nonparametric baseline intensities.

Plots of the Baseline Intensities

Circles are non-parametric estimates of the baseline intensities. Lines are the loess smoothed estimates.

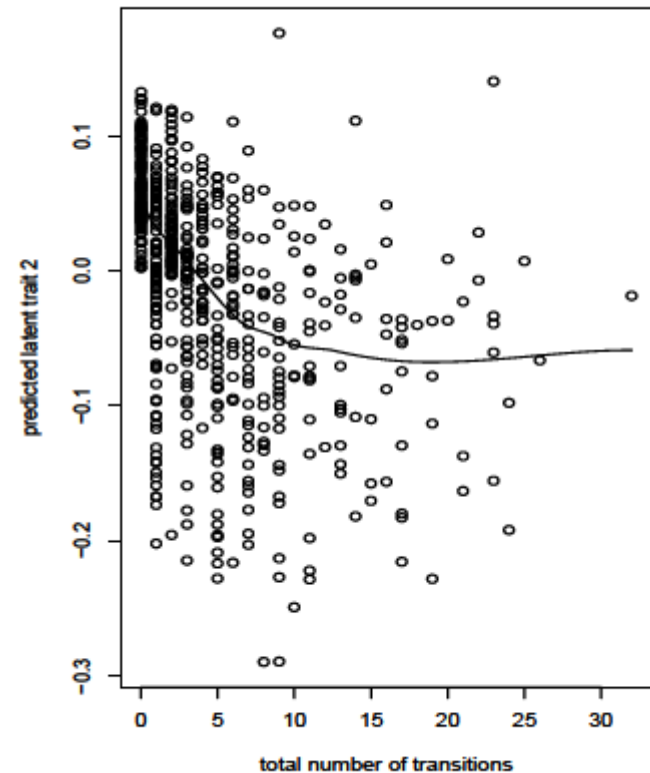
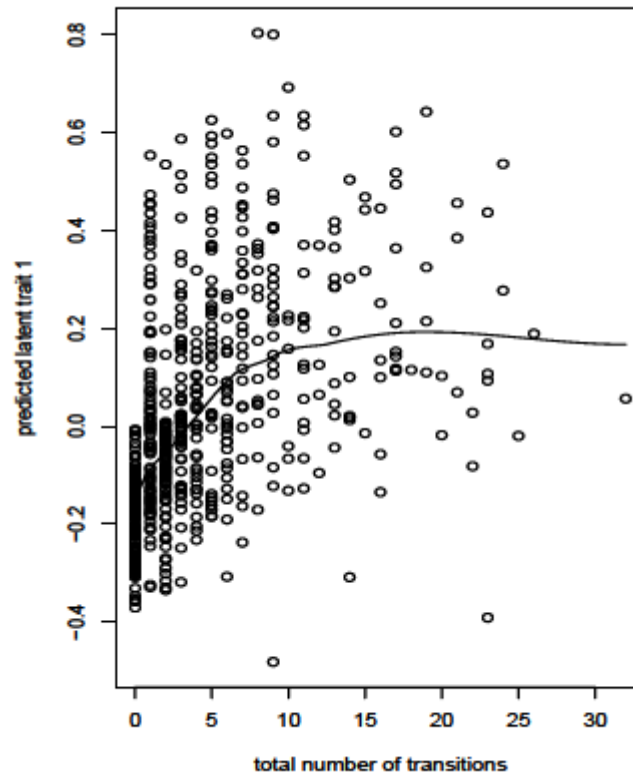


Predicted latent traits for independent state (1) and for disability state (2) denote the intrinsic individual tendency of transitioning out of a particular state (or sojourn in that state) that cannot be explained by the measured covariates and captures dependence between repeated sojourns in the same state within an individual.



Correlation among sojourns across different states within an individual is accounted for by the correlation between the different latent traits.

Significant covariance between the two latent traits means the likelihood of a transition from ADL independence to disability state is negatively correlated with the reverse transition.



Interpretation

An older person who tends to stay longer in an independence state (i.e., whose value of latent trait 1 is smaller) will be more likely to recover (if she happens to be disabled), and one who tends to stay longer in a disability state (i.e., whose latent trait 2 value is smaller) will be more likely to transit from an independence state (if she happens to be in it) back to a disability state.

Factor loadings for latent traits allow for dependence of the transitions to different competing states

$\hat{\gamma}_{22}$, is highly significant indicating that recovery and dying in disability are two associated competing events

Loading [‡]	$\hat{\gamma}_{11}$ Standard Error			$\hat{\gamma}_{12}$ Standard Error		
	Estimate	Bootstrap	Asymptotic	Estimate	Bootstrap	Asymptotic
	1	NA	NA	-0.4855	1.4860	0.4938

Loading [‡]	$\hat{\gamma}_{21}$ Standard Error			$\hat{\gamma}_{22}$ Standard Error		
	Estimate	Bootstrap	Asymptotic	Estimate	Bootstrap	Asymptotic
	1	NA	NA	5.3678	1.1854	0.8820

[‡]: We use $k = 1$ and 2 to index the states of independence and disability, respectively. We use $l = 1$ and 2 denote the states of disability and death that can be transited to from the state of independence (state 1). We use $l = 1$ and 2 to denote the states of independence and death that can be transited to from the state of disability (state=2).

Clinical research question

- Estimate longitudinal process of ADLs accounting for mortality.
- Concern: ignoring death or simply treating death as a cessation of measurement results in underestimation of population level ADL disability and its rate of change over time.



Excellent health statistics - smokers are less likely to die of age related illnesses.'

Physical Frailty, Intervening Events And Functional Transitions In Older Persons

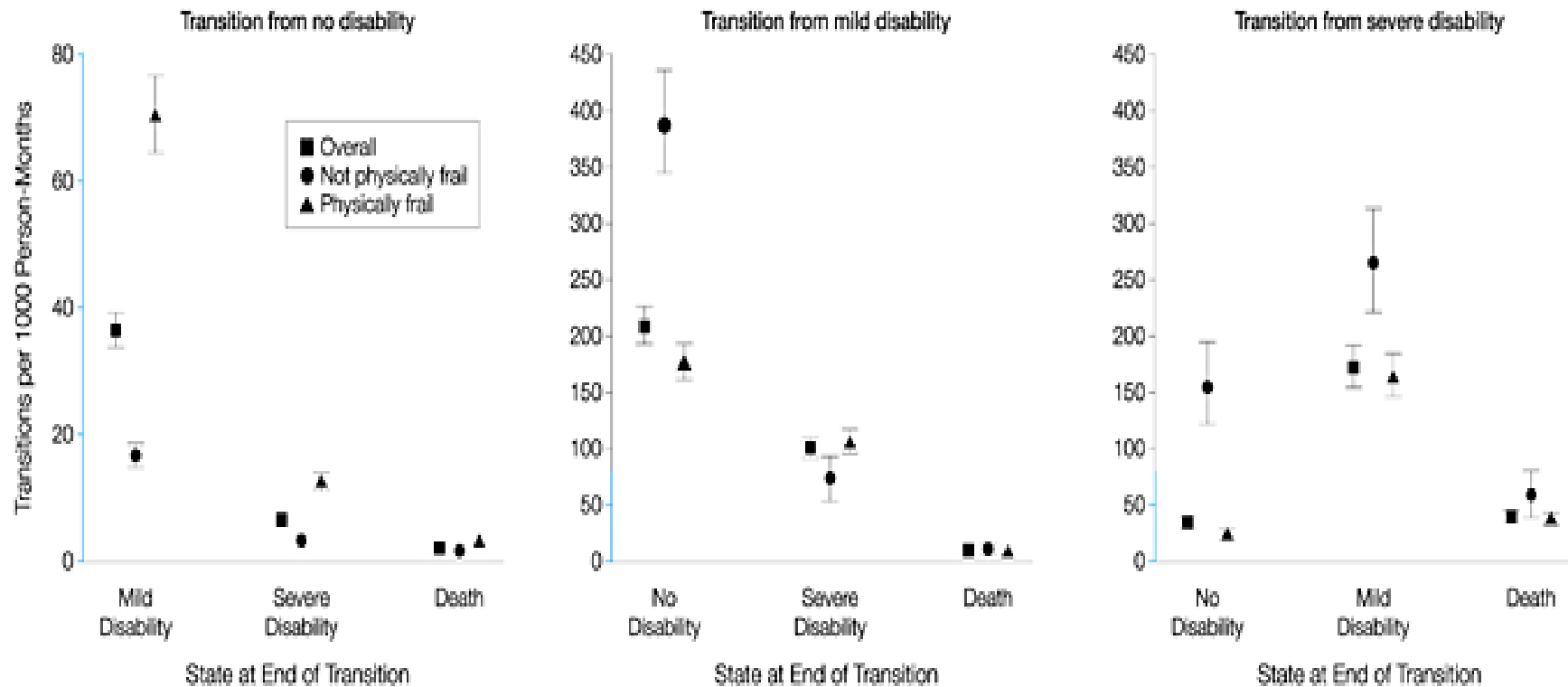
TM Gill, HG Allore, EA Gahbauer, TE Murphy

Objective: To evaluate the longitudinal effects of intervening events on transitions between states of no disability, mild disability, severe disability and death, and to determine the combined effects of intervening events and physical frailty on these transitions.



JAMA

Rates of Functional Transitions per 1000 Person-Months According to Physical Frailty



Gill, T. M. et al. JAMA 2010;304:1919-1928

JAMA

Table 2. Associations of Physical Frailty, Hospitalization, and Restricted Activity With Functional Transitions^a

Transition	Physical Frailty		Hospitalization ^b		Restricted Activity ^{b,c}	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
From no disability to						
Mild disability	4.34 (3.58-5.27)	<.001	8.90 (7.05-11.22)	<.001	2.59 (2.23-3.02)	<.001
Severe disability	3.53 (2.68-4.63)	<.001	168 (118-239)	<.001	8.03 (5.28-12.21)	<.001
Death	1.79 (1.20-2.68)	.005	23.8 (15.9-35.7)	<.001		
From mild disability to						
No disability	0.30 (0.21-0.41)	<.001	0.41 (0.30-0.54)	<.001	0.95 (0.77-1.17)	.62
Severe disability	2.15 (1.51-3.04)	<.001	7.73 (5.47-10.9)	<.001	1.45 (1.14-1.84)	.002
Death	1.26 (0.59-2.67)	.55	10.9 (6.70-17.7)	<.001		
From severe disability to						
No disability	0.13 (0.08-0.21)	<.001	1.04 (0.65-1.66)	.87	0.78 (0.46-1.32)	.35
Mild disability	0.57 (0.39-0.83)	.003	0.70 (0.51-0.95)	.02	0.93 (0.69-1.27)	.66
Death	0.87 (0.51-1.49)	.61	6.40 (4.49-9.12)	<.001		

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAs described in the "Methods" section, a single multivariable model was run that included 3 fixed covariates (sex, race/ethnicity, and years of education), 5 time-dependent covariates (age 85 years or older, living alone, number of chronic conditions, cognitive impairment, and depressive symptoms), and the transition-specific interaction terms that were statistically significant in the competing-risk Cox model. For hospitalization, significant interactions with physical frailty were observed for the transitions from no disability to mild disability and from no disability to severe disability. For restricted activity, a significant interaction with physical frailty was observed only for the transition from no disability to mild disability. Physical frailty and the time-dependent covariates were updated every 18 months during the comprehensive assessments. *P* values were adjusted for multiple comparisons assuming a false discovery rate of 5%.

^bHazard ratios refer to the risk of making the specific transitions between month *t* and month *t* + 1 based on exposure to hospitalization or restricted activity, respectively, during this 1-month interval.

^cValues for the transitions to death were not calculated because restricted activity could not be ascertained in the last month of life.

Table 3. Absolute Risk of Functional Transitions Per Month, Based on Intervening Events and Stratified by Physical Frailty^a

Transition	% (95% Confidence Interval)					
	Hospitalization ^b		Restricted Activity ^{b,c}		No Intervening Event	
	Physical Frailty Present	Physical Frailty Absent	Physical Frailty Present	Physical Frailty Absent	Physical Frailty Present	Physical Frailty Absent
No disability to						
Mild disability	12.4 (12.1-12.7)	4.9 (4.7-5.1)	6.7 (6.5-6.9)	1.5 (1.4-1.6)	2.2 (2.1-2.3)	0.61 (0.54-0.68)
Severe disability	12.0 (11.7-12.3)	3.3 (3.1-3.4)	0.88 (0.80-0.96)	0.17 (0.13-0.20)	0.07 (0.04-0.09)	0.02 (0.00-0.03)
Death	5.1 (4.9-5.3)	3.9 (3.7-4.0)			0.06 (0.04-0.09)	0.04 (0.03-0.06)
Mild disability to						
No disability	14.6 (13.8-15.3)	27.6 (26.6-28.6)	29.6 (28.6-30.6)	43.8 (42.7-44.9)	30.0 (29.0-31.0)	44.1 (43.0-45.2)
Severe disability	18.1 (17.2-18.9)	11.3 (10.6-11.9)	4.6 (4.2-5.1)	2.6 (2.2-2.9)	3.3 (2.9-3.7)	1.8 (1.5-2.1)
Death	6.1 (5.6-6.7)	4.5 (4.1-5.0)			0.12 (0.04-0.19)	0.08 (0.02-0.15)
Severe disability to						
No disability	8.4 (7.8-9.0)	24.2 (23.3-25.1)	7.4 (6.8-7.9)	22.6 (21.7-23.5)	9.7 (9.0-10.3)	27.1 (26.1-28.1)
Mild disability	14.5 (13.7-15.2)	17.5 (16.6-18.3)	19.8 (18.9-20.6)	23.9 (23.0-24.9)	21.2 (20.3-22.1)	26.1 (25.2-27.1)
Death	14.0 (13.2-14.7)	12.8 (12.0-13.5)			0.61 (0.44-0.77)	0.55 (0.39-0.72)

^aAs described in the "Methods" section, the absolute risks were calculated using coefficients obtained from a set of pooled logistic regression models (one for each transition) that included the 3 independent variables, 8 covariates, and the transition-specific interaction terms that were statistically significant in the competing-risk Cox model. For hospitalization, significant interactions with physical frailty were observed for the transitions from no disability to mild disability and from no disability to severe disability. For restricted activity, a significant interaction with physical frailty was observed only for the transition from no disability to mild disability. Physical frailty and the time-dependent covariates were updated every 18 months during the comprehensive assessments.

^bValues refer to the absolute risk of making the specific transitions between month t and month $t + 1$ based on exposure to hospitalization or restricted activity, respectively, during this 1-month interval.

^cValues for the transitions to death were not calculated because restricted activity could not be ascertained in the last month of life.

Trajectories of Functional Disability Team



HG
Allore



TM
Gill



L Han



H Lin

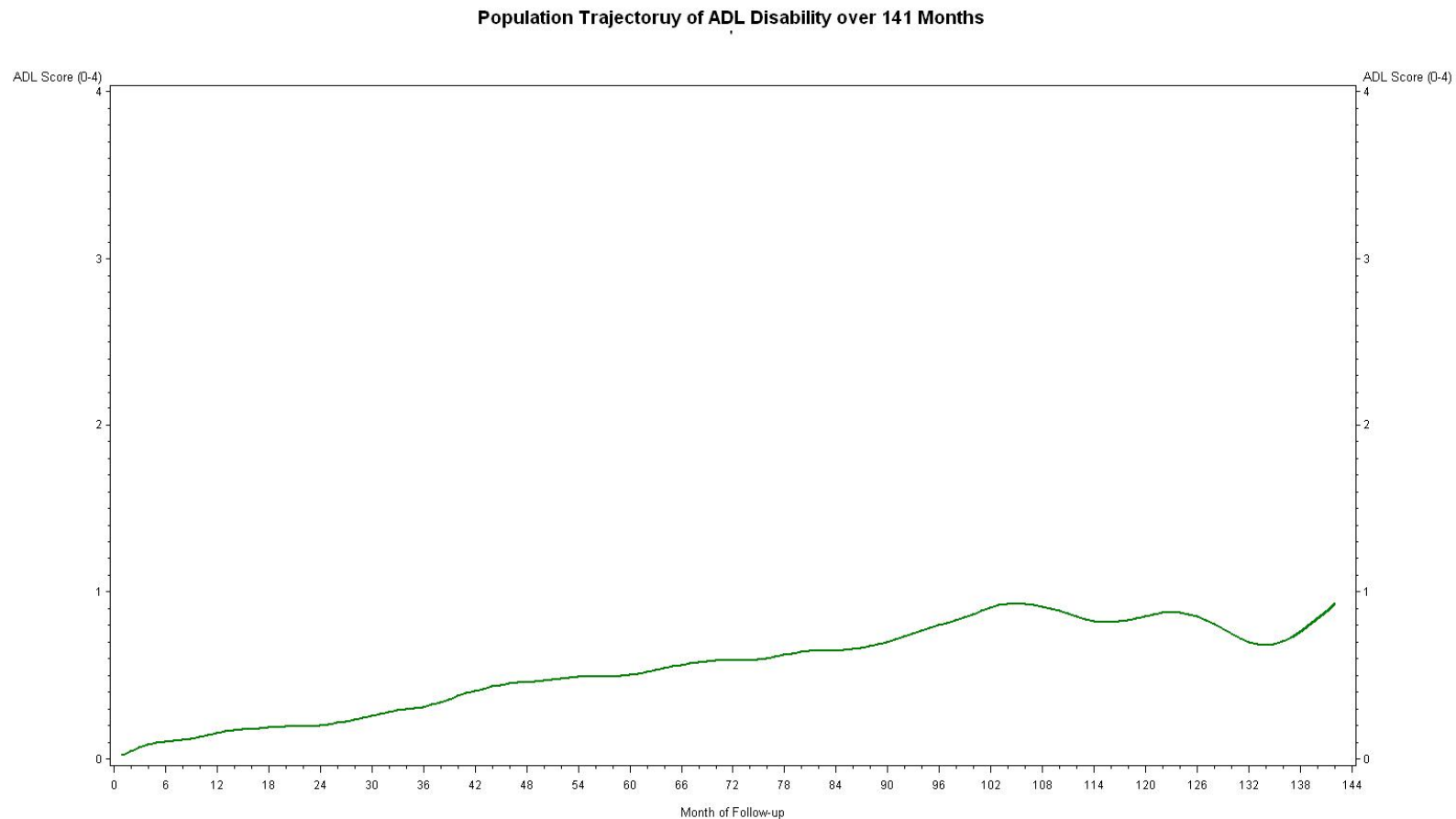


TE
Murphy

Yale University

Longitudinal Trajectories

- Most forms of regression modeling yield a single trajectory in which risk factors represent increases or decreases in slope estimates.



Assumptions

- Subsets of the sample are relatively homogeneous and share this trajectory
- Covariates can describe shifts from the common trajectory
- Missing values resulting from decedents are missing at random, so they would share the same trajectory

Latent Class Trajectories

- Identify distinct trajectories of disability
- Allows for simultaneously estimations of class membership probabilities (a probability for each trajectory)
- More flexible when cohort is heterogeneous
- Covariates refine trajectory estimates (growth model) AND provide estimates of class membership
- The number of disabled ADLs per month was modeled as a zero-inflated Poisson distribution.

Trajectories of Disability in the Last Year of Life

TM Gill, EA Gahbauer, L Han, HG. Allore



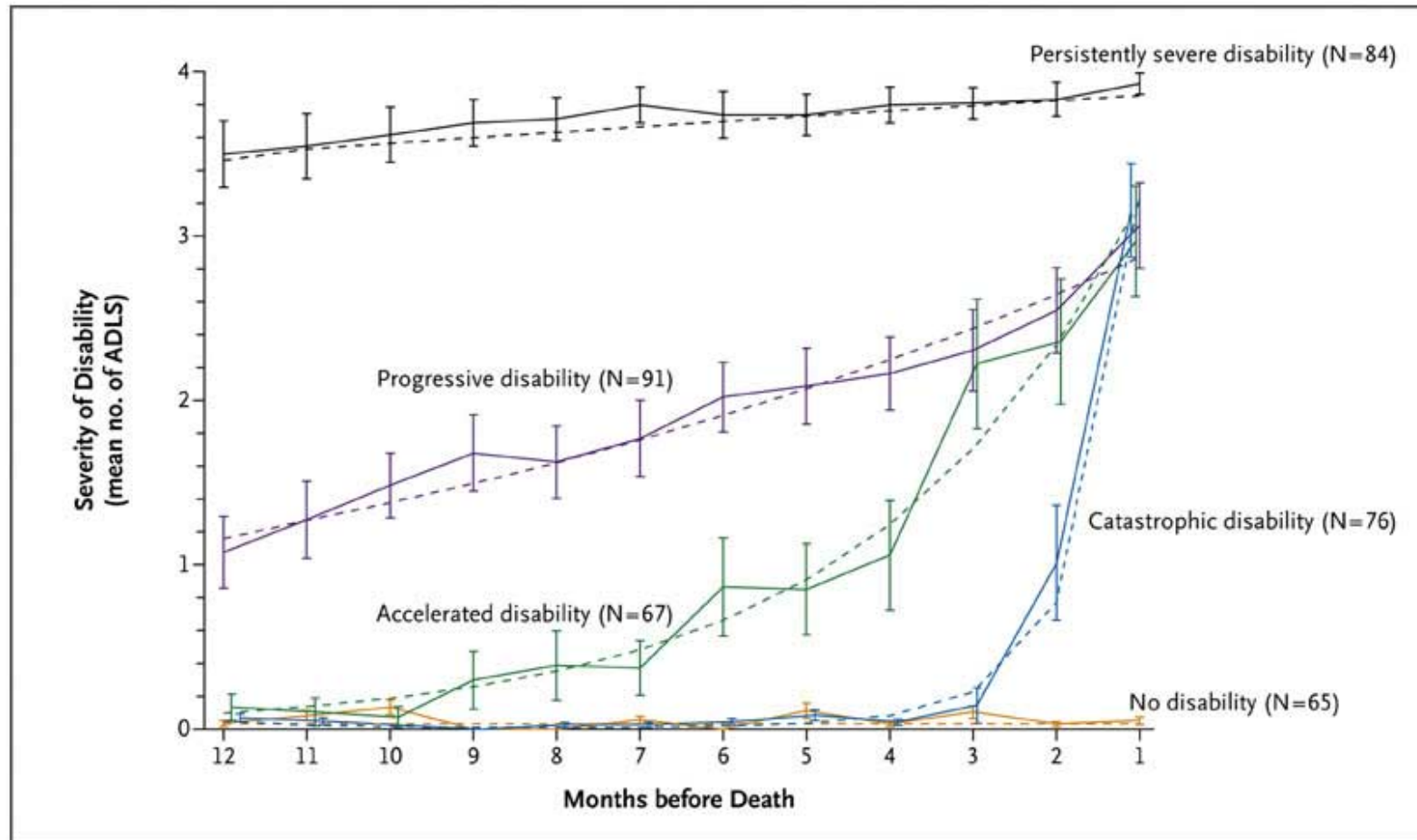
N Engl J Med
2010; 362(13):1173-1180



Statistical Methods

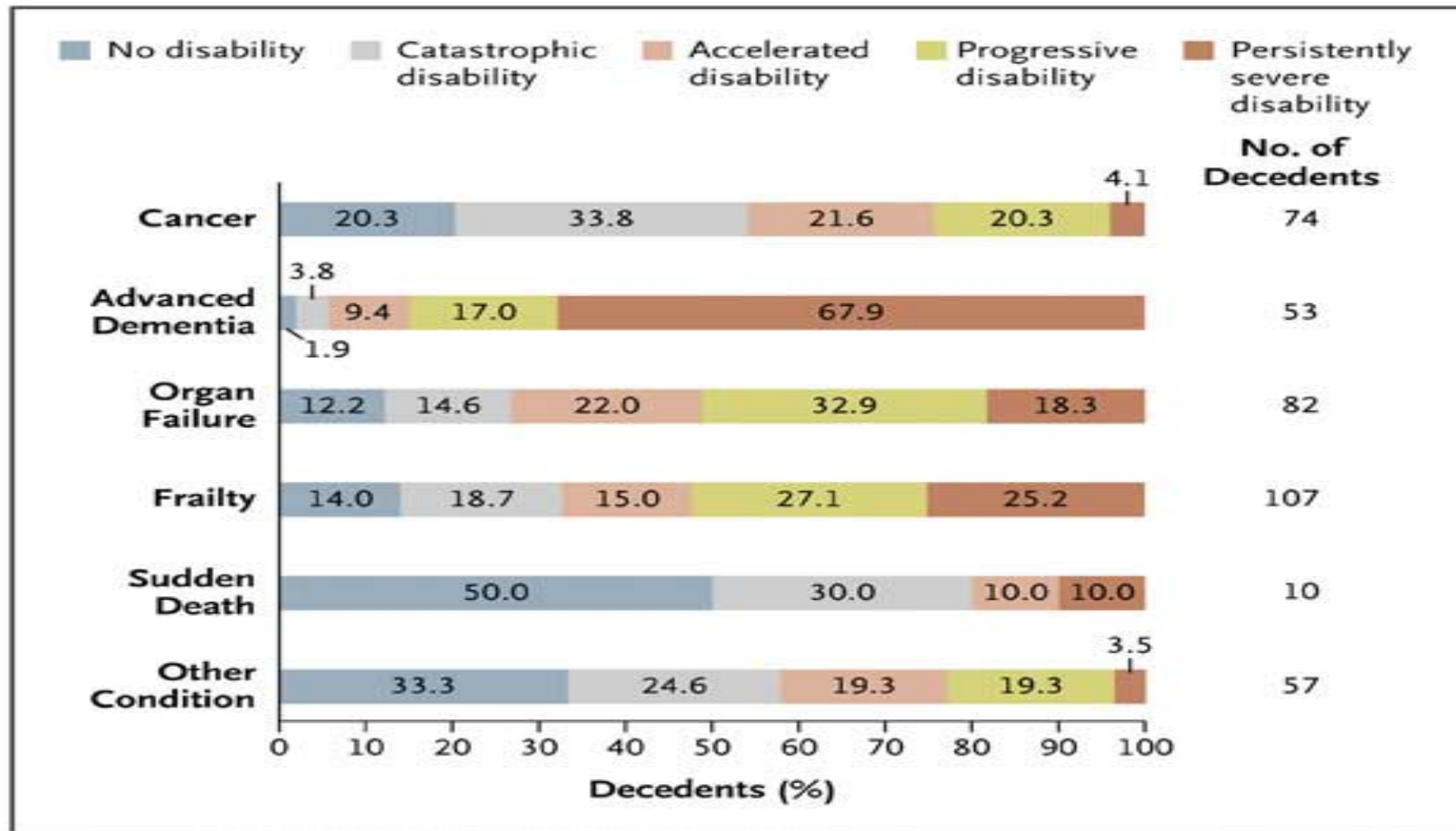
- To identify clinically distinct trajectories of disability, we used latent class analysis.
- We simultaneously estimate probabilities for multiple trajectories rather than a single mean within the population.
- We fit a semiparametric (discrete) mixture model to longitudinal data using a maximum likelihood method. The number of disabled ADLs per month in the last year of life was modeled as a zero-inflated Poisson distribution.

Trajectories of Disability in the Last Year of Life among 383 Decedents



Gill TM et al. N Engl J Med 2010;362:1173-1180

Distribution of Disability Trajectories in the Last Year of Life, According to Condition Leading to Death among the 383 Decedents



Characterizing Successful Aging – Growth Mixture Models



A Dynamic Trajectory Class Model For Intensive Longitudinal Categorical Outcome Stat Med. 2014



Disentangling Population Heterogeneity— A *Growth Mixture Model (GMM) Approach*

- A family of models that integrates a growth curve model of longitudinal responses and multinomial model of membership probability to distinct growth-curves.
- Predictors of growth curves and of probability of trajectory group membership can be examined simultaneously.
- Can be extended to jointly modeling more than one outcomes (*e.g., death, cognitive function etc*).

Latent Class Trajectories

- Identify distinct trajectories of disability
- Allows for simultaneously estimations of class membership probabilities (a probability for each trajectory)
- More flexible when cohort is heterogeneous
- Covariates refine trajectory estimates (growth model) AND provide estimates of class membership

Implication of the Trajectory Switching Model

- The response (ADL) is measured more frequently than the covariates.
- A trajectory switching model distinguishes changes between trajectories from fluctuations within a trajectory.
- Within-subject longitudinal responses are correlated both within and across different intervals.
- Although the covariates are used directly in modeling the class prevalence probability in interval m , the longitudinal ADL, death, and the random effects all affect class membership probability.

Notation

- $Y_{ij(m)k}$ denotes the indicator for the ADL response in k th category for subject i at time point j (nested within interval m);
 - $\mu_{ij(m)kl}$ denotes the corresponding mean if the subject is in class l in interval m .
- C_{iml} denotes the indicator of class l for subject i interval m
- X_{im} is a vector of covariates for subject i in interval m .

Model Assumptions and Likelihood Estimation

- Irregularly spaced longitudinal data are allowed;
- Given the latent classes, the longitudinal ADL response and the death are conditionally independent;
- Likelihood for the observed data:

$$\prod_{i=1}^N \int \prod_{m=1} \underbrace{\sum_{l=1} \pi_{iml} \prod_{j(m)=1}^{J_{im}} \left(\prod_{k=1}^K \mu_{ij(m)kl}^{Y_{ij(m)k}} \right)}_{\text{likelihood for individual } i \text{ in } m\text{th interval given } b_i} \text{df}(b_i)$$

- Code written in SAS Proc NLMIXED and R are used to estimate all the model parameters.

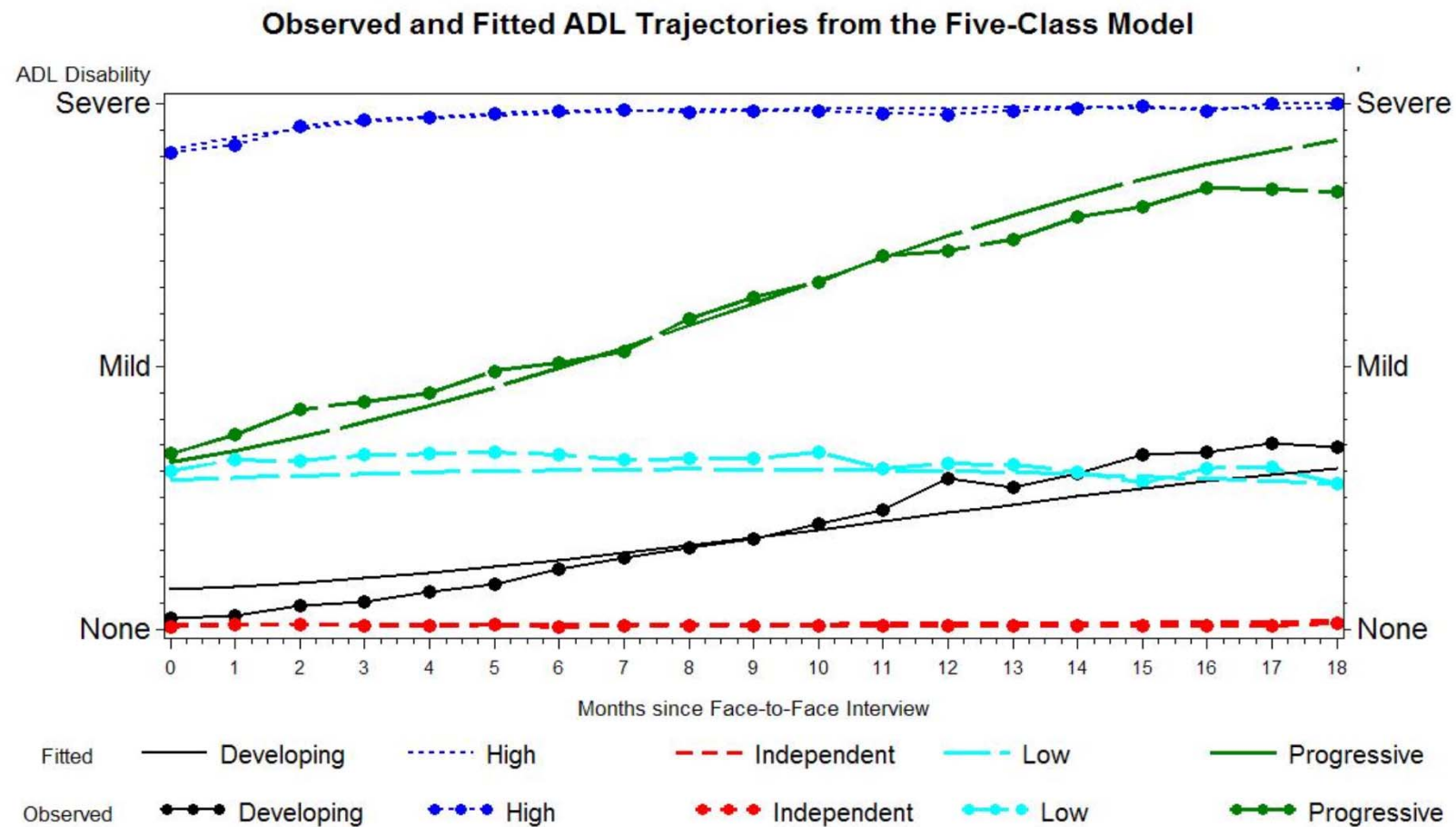
Assign Class Membership

- The subject i is assigned a class membership in interval m according to $\max(\tilde{c}_{iml})$ where \tilde{c}_{iml} is:

$$\begin{aligned}\tilde{c}_{iml} &= P(C_{iml} = 1 \mid \underline{Y}_{im}) \\ &= \frac{\pi_{iml} f(\underline{Y}_{im} \mid C_{iml} = 1)}{\sum_l \pi_{iml} f(\underline{Y}_{im} \mid C_{iml} = 1)}\end{aligned}$$

- Because the class membership assignment is based on the data within a m th interval only, the class membership can switch from one interval to another within a same person.

ADL Trajectories Of A Joint Multinomial GMM With Mortality



A Joint Multinomial GMM — Prevalence Of Trajectory Class And Mortality

Class	(Prev %)	Mortality	
		Data	Est
Independent	66.83	1.30	1.0
Developing	11.76	3.17	2.9
Low	6.12	0.41	0.8
Progressive	11.39	60.7	57.0
High	5.90	44.3	43.0

Class	% Prevalence % in interval m						
	1	2	3	4	5	6	7
Independent	81.1	74.9	66.1	61.5	54.7	52.0	46.7
Developing	12.3	11.6	11.2	12.8	13.2	11.1	9.4
Low	2.3	4.8	6.9	6.8	9.0	7.3	8.4
Progressive	4.2	6.6	12.2	11.0	14.9	16.9	21.8
High	0.13	2.1	3.6	7.9	8.2	12.7	13.7

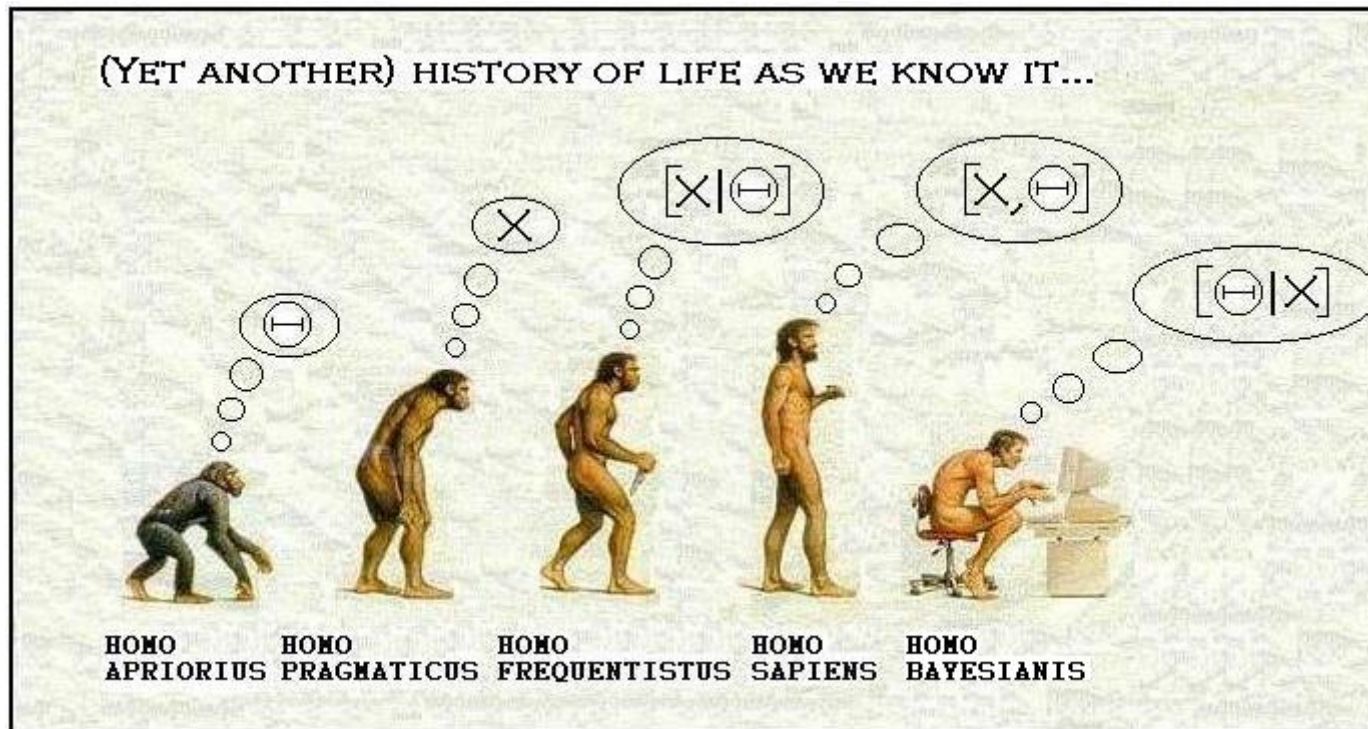
Class Switching Probabilities

	Indep	Worsen	Low	Progressive	High	Death
Indep	.79	.10	.02	.06	.005	.013
Worsen	.16	.23	.21	.32	.05	.03
Low	.11	.13	.37	.33	.06	.004
Progress	.003	.003	.02	.14	.84	.61
High	0	.005	.01	.08	.46	.44

Summary

- We found 5 distinct ADL trajectories
- Mortality differed across the 5 trajectories
- Over time fewer persons were independent and more person-intervals were mild or severely disabled
- Switching probabilities revealed greater probability of staying the same or worsening than recovery
- Factors associated with class membership differed across trajectories

Bayesian Approaches



Murphy T, Allore HG, Han L, Xu X, Peduzzi PN, Gill TM, Lin H. A Longitudinal, Observational Study with Many Repeated Measures Demonstrated Improved Precision of Individual Survival Curves Using Bayesian Joint Modeling of Disability and Survival, *Exp Aging Res.* 2015; 41(3):221-239

Bayesian Model of Ordinal Disability

- Disability modeled with a cumulative logit

$Logit(Q_{itj}) = - (a_j + \mu_{it})$ where

$$\mu_{it} = \alpha_0 + \alpha_1 x_{1it} + \dots + \alpha_k x_{kit} + \alpha_{k+1} \log(t) + \mathbf{b}_{0i}$$

$x_{1it} \dots x_{kit}$ can be time-dependent covariates

\mathbf{b}_{0i} are independently distributed normal
random intercepts with standard normal priors
mean zero and a variance parameter with
vaguely dispersed gamma hyperparameters

Bayesian Model for Death

- The combination of a binomial distribution and the complementary log-log link is a discrete analog of the continuous proportional hazards model.
- Given survival time T_i in discrete units with the time-dependent vector of covariates \mathbf{X}_{it} , the discrete time hazard rate is $P_{it} = \Pr[T_i = t \mid T_i \geq t, \mathbf{X}_{it}]$

$$\log[-\log(1 - P_{it})] = \tau_t + \beta_1 x_{1it} + \dots + \beta_k x_{kit} + \sigma_{0i}$$

τ_t and σ_{0i} are independently distributed **random effects** for month- and person-specific intercepts, each with normal priors with mean zero

Joint Models with Shared Random Effects

- Estimates disability and survival sub-models with a **shared random intercept** \mathbf{b}_{0i} which is multiplied by the **random effect** r_0 in the survival sub-model

- *Disability Sub-model;*

$\text{Logit}(Q_{itj}) = -(a_j + \mu_{it})$ where

$$\mu_{it} = \alpha_0 + \alpha_1 x_{1it} + \dots + \alpha_k x_{kit} + \alpha_{k+1} \log(t) + \mathbf{b}_{0i} ,$$

- *Survival Sub-model;*

$$\log[-\log(1 - P_{it})] = \tau_t + \beta_1 x_{1it} + \dots + \beta_k x_{kit} + r_0 \mathbf{b}_{0i} ,$$

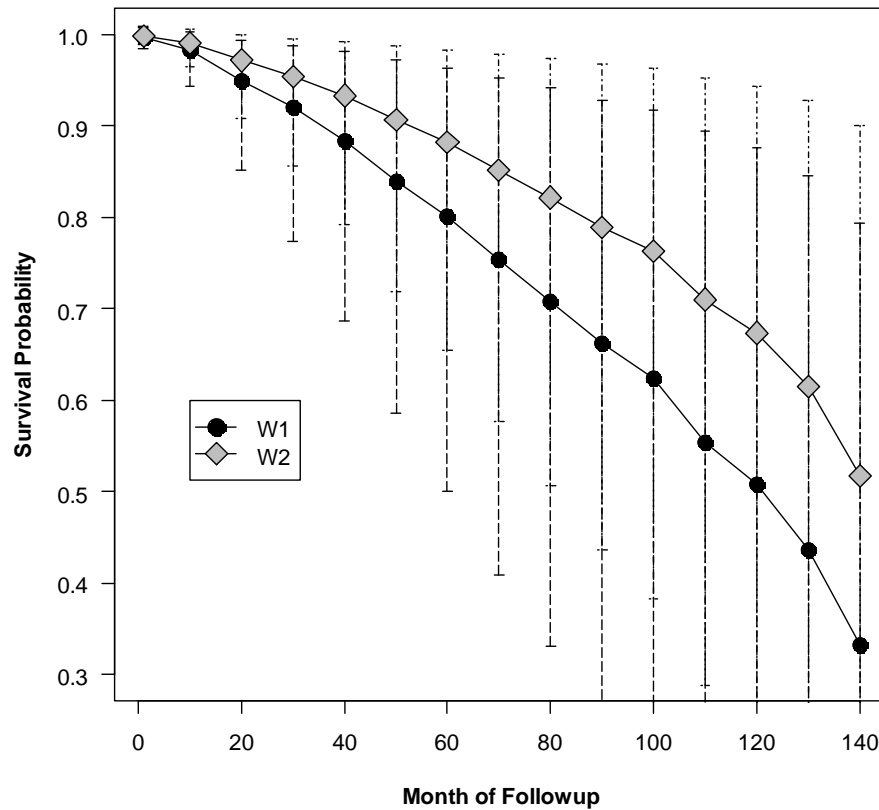
Joint Shared Random Effects

- b_{0i} is the “**shared**” person-specific random effect that transmits information between the sub-models whereas r_0 “scales” the person-specific intercept in the survival sub-model
- sign of r_0 reveals the direction of the correlation between the two outcomes
- point estimate and credible interval for r_0 0.34 (0.29 , 0.38), show that worsening ADL disability is positively correlated with risk of death

Results

Model Terms	Model Type and Outcome				
	Separate Longitudinal Model of Ordinal ADL	Jointly Estimated Longitudinal Sub-model of Ordinal ADL		Separate Survival Model of Time to Death in Months	Jointly Estimated Survival Sub-model of Time to Death in Months
	Odds Ratio (95% Credible Interval)	Odds Ratio (95% Credible Interval)		Hazard Ratio (95% Credible Interval)	Hazard Ratio (95% Credible Interval)
Slow Gait (time varying)	4.66 (4.26 , 5.05)	4.66 (4.22 , 5.10)		2.39 (1.86 , 3.06)	1.40 (1.12 , 1.79)
Female Sex	1.39 (1.17 , 1.65)	1.38 (1.17 , 1.62)		0.58 (0.44 , 0.75)	0.65 (0.53 , 0.80)
Mean (SD) of Person-Specific Random Intercepts	-0.02 (1.86)	-0.02 (1.88)		0.00 (0.55)	-0.01 (0.64)
DIC (lower is better)	49770	49718		5067	5004

Survival Model



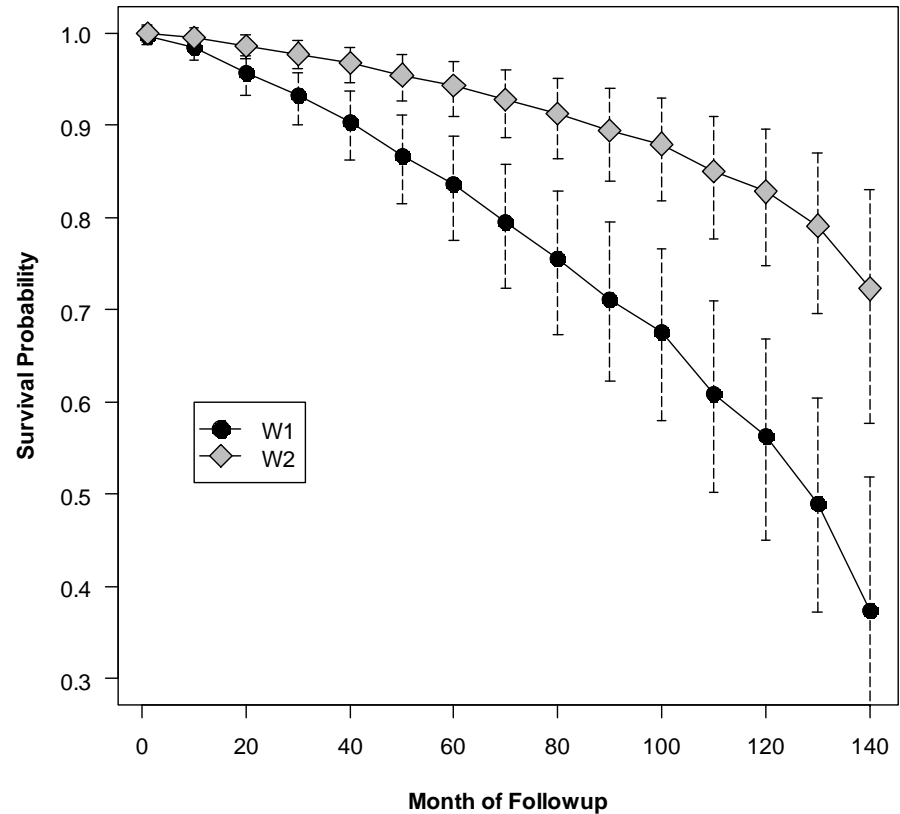
Unique Person-Specific Random Intercepts ($W1 = 0.7$, $W2 = -0.45$) But No Shared Random Effect

W1's Ordinal Disability from 91 months: 000000000010000000000000001000000000End

W2's Ordinal Disability from 91 months: 000000211012222222222222222222222211222End

(0 = No disability, 1 = Mild disability, 2 = Severe disability)

Joint Survival Sub-Model



Unique Person-Specific Random Intercepts ($W1 = 1.15$, $W2=0.86$) & Shared Random Effects

Ongoing Work

- Joint models are being created in a pairwise manner using non-linear mixed effects models for self-rated health, function and mortality.
- Individualized Absolute Risk Calculator for Persons with Multiple Chronic Conditions
- Among persons with dementia estimate the interrelationship between complicated self-care conditions, healthcare utilization, functional disability and having an informal caregiver who provides support for medical self-care tasks.
- Estimate patterns of medication use overall and according to the major types of dementia diagnosis and healthy controls (polypharmacy, Beers criteria, anticholinergics).

Questions?

