Risk factors for MCI & Dementia: new statistical tools

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Outline

- Contrasting two cohorts: BRAINS and Nuns
- Analysis of retrospective data: the Nun Study

  Markov chain defines transitions between assessments
  One step transition probabilities
  Adjusting for baseline

- Analysis of prospective data:

  Censored versus competing events
  Kaplan-Meier curves and Cox models
  Cumulative incidence curves

Descriptive statistics

Factor	BRAiNS	Nuns
n	553	424
Age at entry	73.5 ± 7.6	83.1 ± 5.1
No. visits	8.0 ± 4.0	7.2 ± 2.8
Female	64.2 %	100 %
Positive family hx	37.5 %	-
APOE 4 allele	30.2 %	19.3 %
Years of Education:		
≤12	11.9 %	9.7 %
13-15	21.0 %	0.0 %
16	31.6 %	41.5 %
> 16	35.4 %	48.6 %

Recognizing impairments retrospectively

At each annual assessment each participant is categorized into one of five states:

1. Cognitively intact
2. "Mild Cognitive Impairment"
3. Global Impairment
4. Demented
5. Dead

Retrospective review produces a Longitudinal Record: Categorical responses

Each participant generates a "vector" of responses

$$(y_1, y_2, \ldots, y_n)$$

Here y_j is the state at visit j

Examples:

Subject 1 record (1, 1, 2, 3, 1, 4)

Subject 2 record (2, 1, 2, 5)

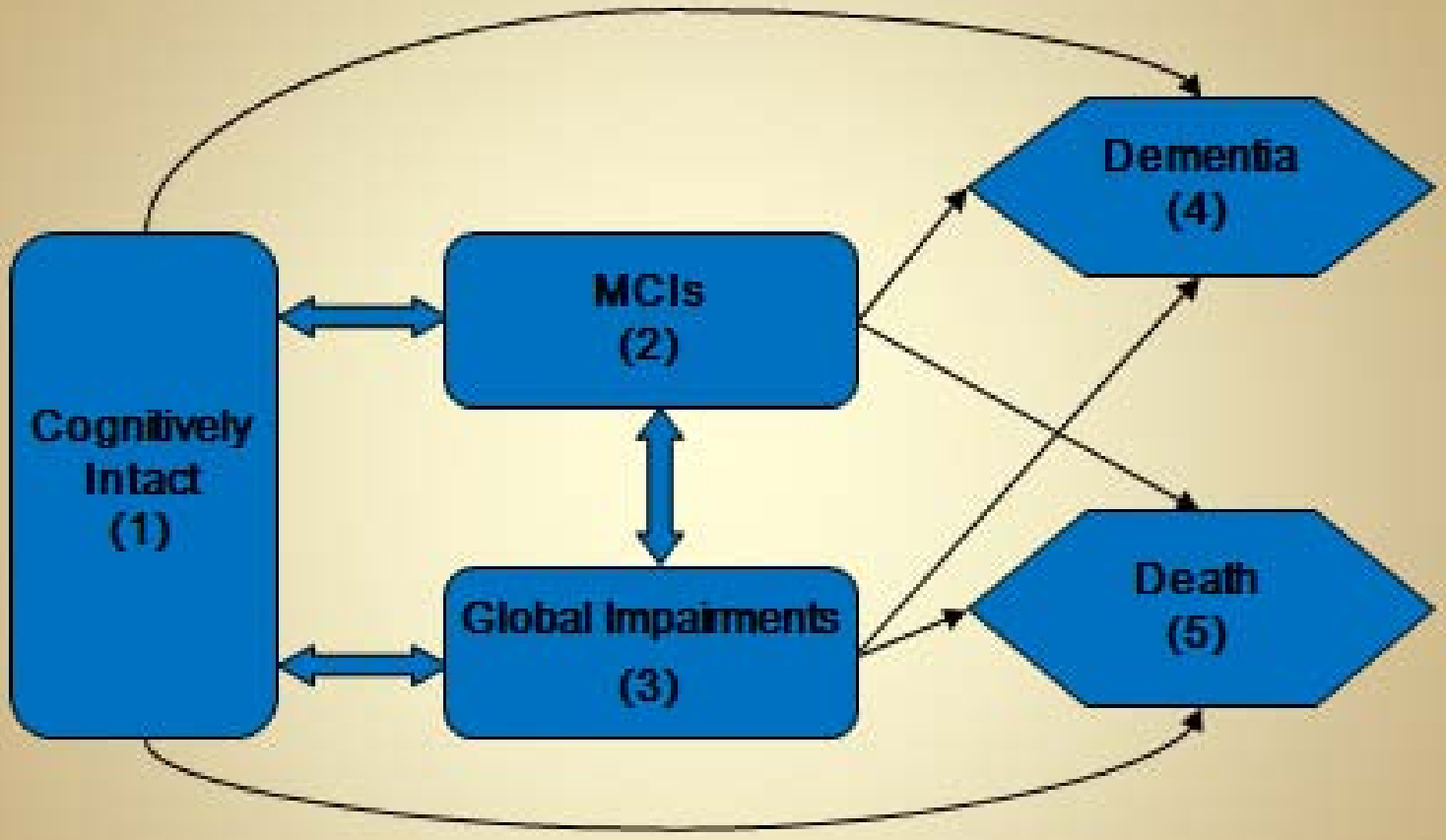
Challenge: analyze categorical vectors of varying lengths

Solution: (proposed by our Core)
use a Markov chain with a shared random effect

Markov: next cognitive assessment depends on current assessment and is independent of prior assessments

Subj. 1: (1, 1, 2, 3, 1, 4) provides 5 data points
Subj. 2: (2, 1, 2, 5) provides 3 data points
one step transitions $2 \rightarrow 1$, $1 \rightarrow 2$, and $2 \rightarrow 5$

Shared random effect: a latent (unobservable variable) used to correlate the transitions for a given subject


Cognitively Intact (1)
MCIs (2)
Global Impairments (3)
Dementia (4)
Death (5)

Markov chain (ignores risk factors)
Nun Study (n = 424)

Prior Assessment	Current Assessment: Cognitively Intact	MCIs	Global Impairment	Dementia	Death
Intact	537 (65.8)	183 (22.4)	53 (6.5)	5 (0.6)	38 (4.7)
MCIs	163 (15.0)	644 (59.2)	123 (11.3)	81 (7.4)	77 (7.1)
Glob. Imp.	15 (4.1)	36 (9.9)	163 (44.9)	68 (18.7)	81(22.3)

Regression analysis

Consider a one step transition and let

$P_{sk}(\theta \mid \mathbf{Z}_i)$ = P [i^{th} subject next visits state k given state s]

Assume: **Polytomous logistic regression model**

$$\text{Log}\,[P_{sk}(\theta \mid \mathbf{z}_i) \,/\, P_{ak}(\theta \mid \mathbf{z}_i)] = \alpha_{sk} + \boldsymbol{\beta}_{sk}\,\mathbf{Z}_i + \gamma$$

Here

- a = baseline state ,
- $\mathbf{Z}_i$ = vector of fixed effects (risk factors) for i^{th} person
- $\boldsymbol{\theta}$ = vector of unknown parameters (α, $\boldsymbol{\beta}$)
- γ = unobservable shared random effect

Definition: Likelihood function for the unknown vector $\boldsymbol{\theta}$ **is the product of** $P_{sk}(\theta \mid \mathbf{Z}_i)$ **over** all transitions and subjects with the shared random effect integrated out

To evaluate the likelihood must solve a numerical integral

Results of the regression analysis
Significant risk factors for a single transition

Factor	BRAiNS	Nun Study
Age	All four states	All four states
APOE 4	Amnestic MCI Dementia	All four states
Education: ≤ 12 yrs.	Amnestic MCI non Amnestic MCI	MCI Global Impairment Dementia
	Salazar et al Stat. Med, 2007	Tyas et al Am J Epi, 2007

Event rates in BRAiNS versus Nuns

Cohort	n	Baseline Dementias	Follow-up Dementias	Deaths*	Percent Events
BRAiNS	553	0	55	144	36.0%
Nuns	501	77	153	184	82.6%

*died before dementia

Conclude: do ADCs introduce a selection bias in their recruiting protocols ?

Adjusting for baseline

In a recent simulation study we showed
(Yu et al, Comp Stat Data Analysis, 2009)

If some subjects are demented at baseline (so called left truncated events),
then ignoring baseline attentuates the effects of the risk factors

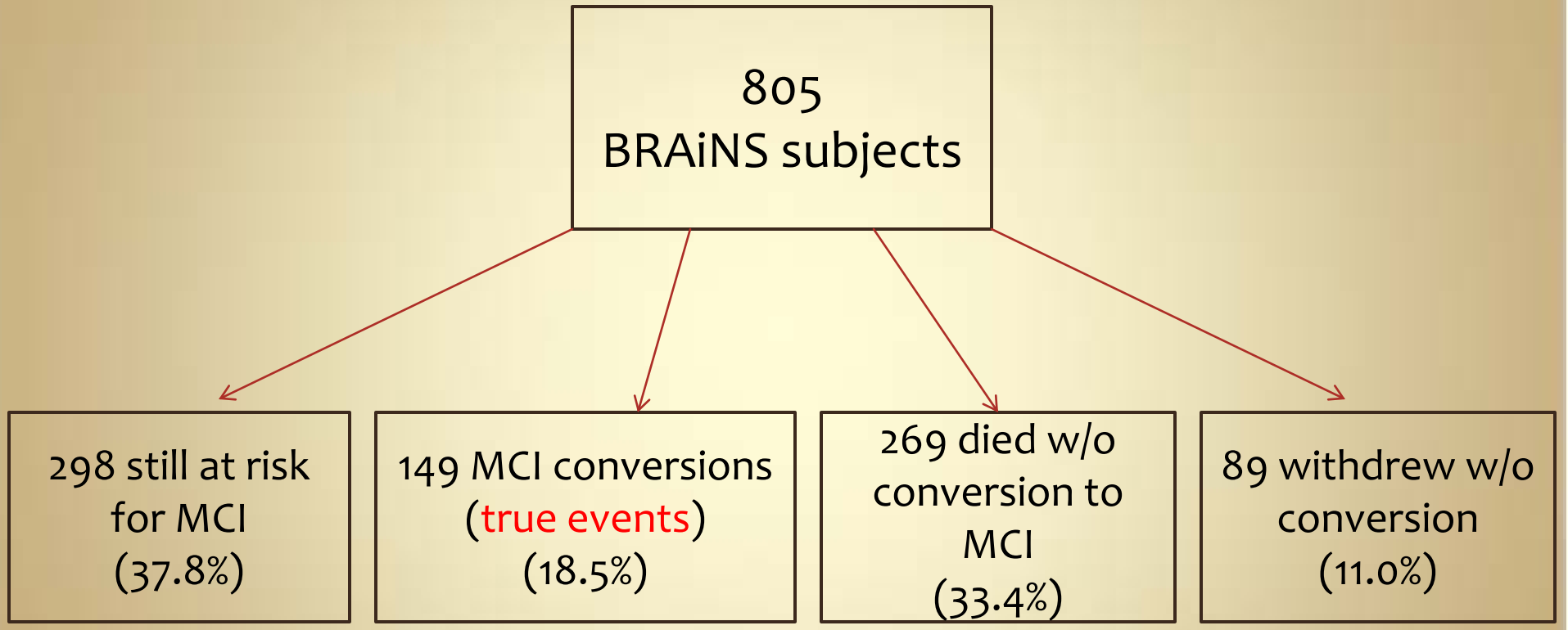
Dependent variable = time to MCI

Problems of interest:

1. Identify an appropriate statistical method for determining the probability of conversion to MCI after t years of follow-up

2. Adjust 1 for risk factors: education, family history of dementia, APOE 4 status, gender

Events and non events



Competing Risks

Gooley, Leisenring, Crowley,& Storer (2002)

Definition: a competing risk is an event whose occurrence either

precludes the occurrence of another event under examination or

fundamentally alters the probability of occurrence of this other event

Clearly: death before conversion to MCI is a competing risk and not a right censored event

withdrawals could be competing events if they are informative

Adjustment for competing risks

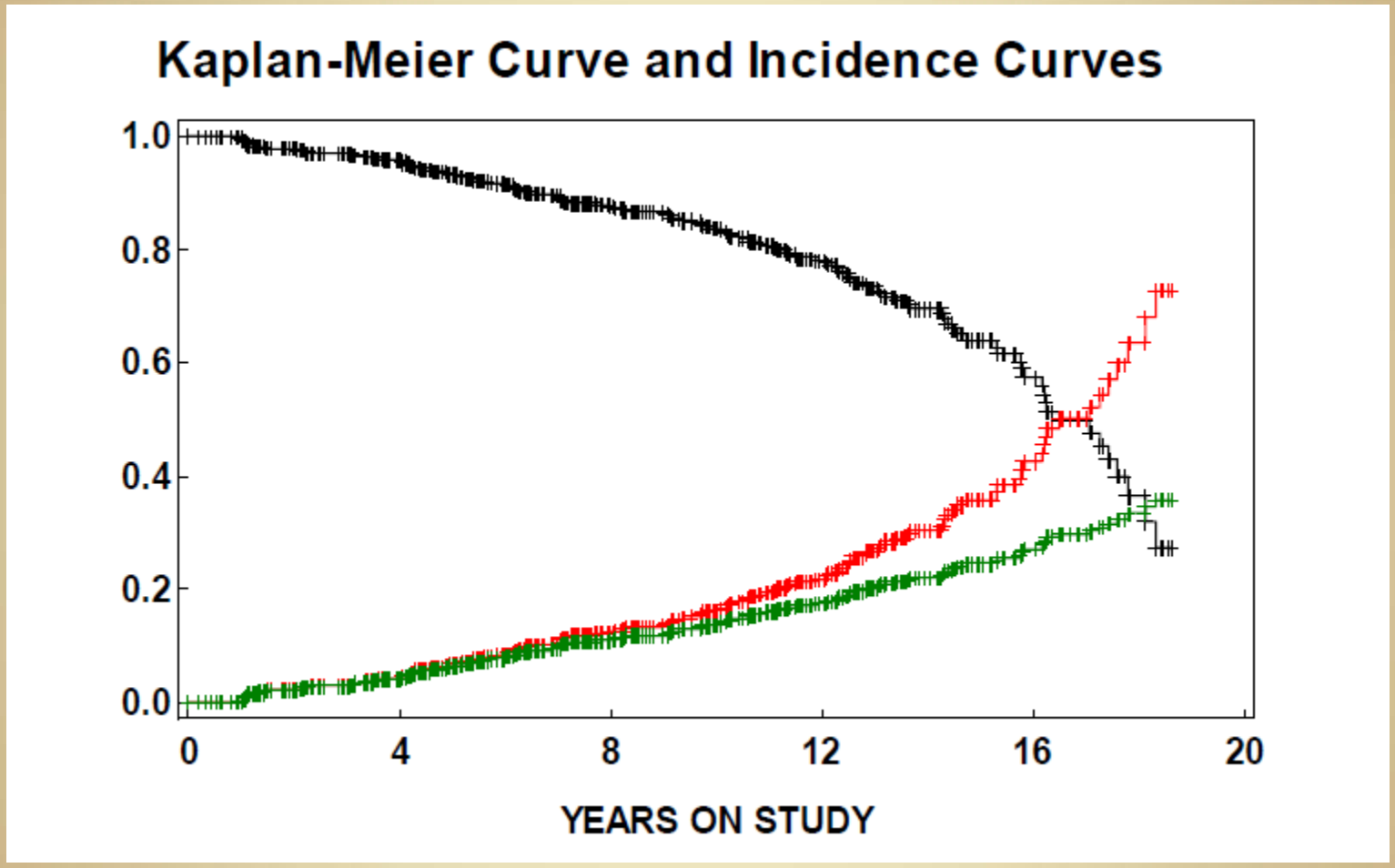
Simplest cure: use **Incidence curves** instead

Two facts:

1. If there are no competing events:
   Incidence = 1 – Kaplan Meier

2. If there are competing events
   a. calculate Kaplan-Meier for combined risks

   b. calculate Incidence for a specific cause by adjusting the hazard of an event age a for the risk of that event occurring at that age


Kaplan-Meier Curve and Incidence Curves
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
YEARS ON STUDY

Cox model, marginalized Cox model, Gompertz models event: conversion to MCI; competing risk = death

Factor	Cox model HR (P value)	marginal Cox HR (P value)	Gompertz * HR (P value)
Age entry	1.045 (0.0009)	1.089 (0.0001)	1.087 (0.005)
Apoe 4	1.44 (0.045)	1.20 (0.09)	1.20 (0.21)
Family Hx	1.09 (0.66)	0.91 (0.39)	1.92 (0.015)
Female	0.83 (0.31)	0.70 (0.0003)	0.49 (0.025)

Jeong & Fine, 2007

Conclusions:

1. Analyze cohort data retrospectively means examining transitions into and out of impaired states before absorption into dementia and/or death

   Need new statistical tools for analyzing longitudinal data with categorical responses: Markov model with shared random effect

   Extend this to delineate risk factors for different forms of dementia

2. Analyze prospective data: examine age at which clinical MCI first occurs

   Standard tools: Kaplan-Meier curves and Cox models may not be applicable in the presence of a competing event such as death.