

Modeling pre-clinical changes: statistical issues

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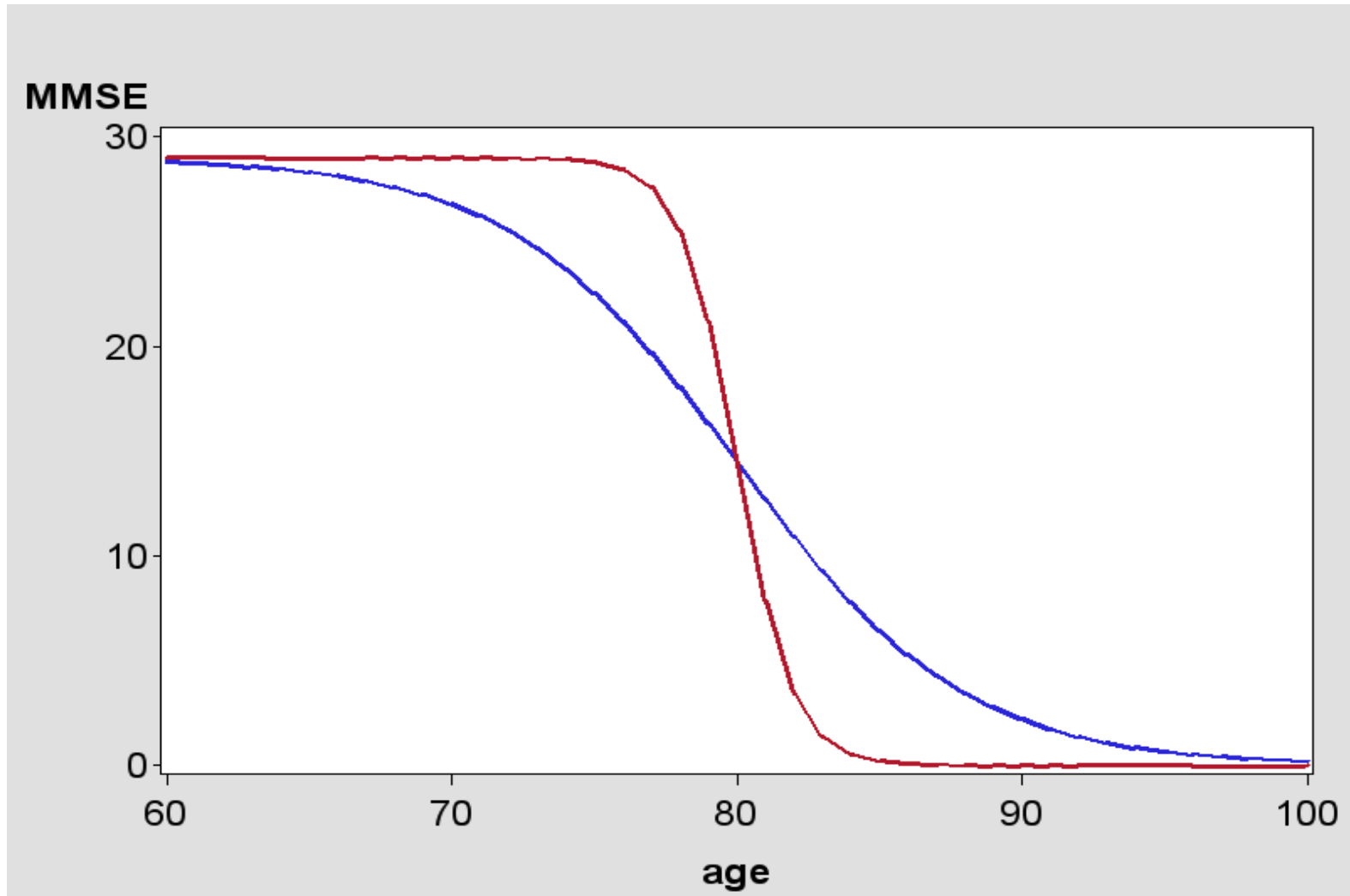
Data Core Leaders Meeting

September 24, 2011

Outline

- Change point model versus nonlinear models
- Markov models: UDS update
- Mixed dementias

Three parameter logistic model for an instrument with floor and ceiling effects



Change point model works well if

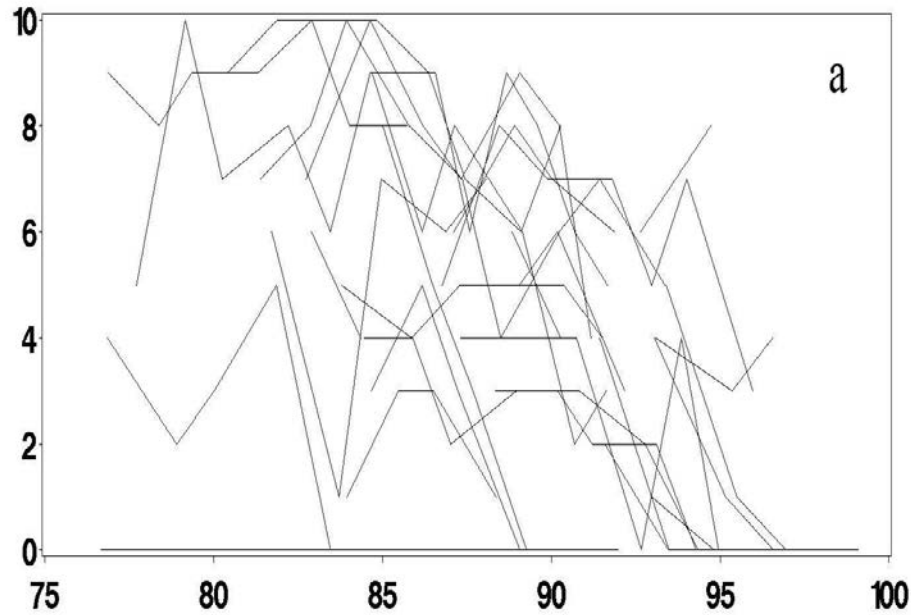
Sampling along horizontal axis is limited to the 25th % of the asymptote (avoid scores near the floor)

Linearity assumption holds:

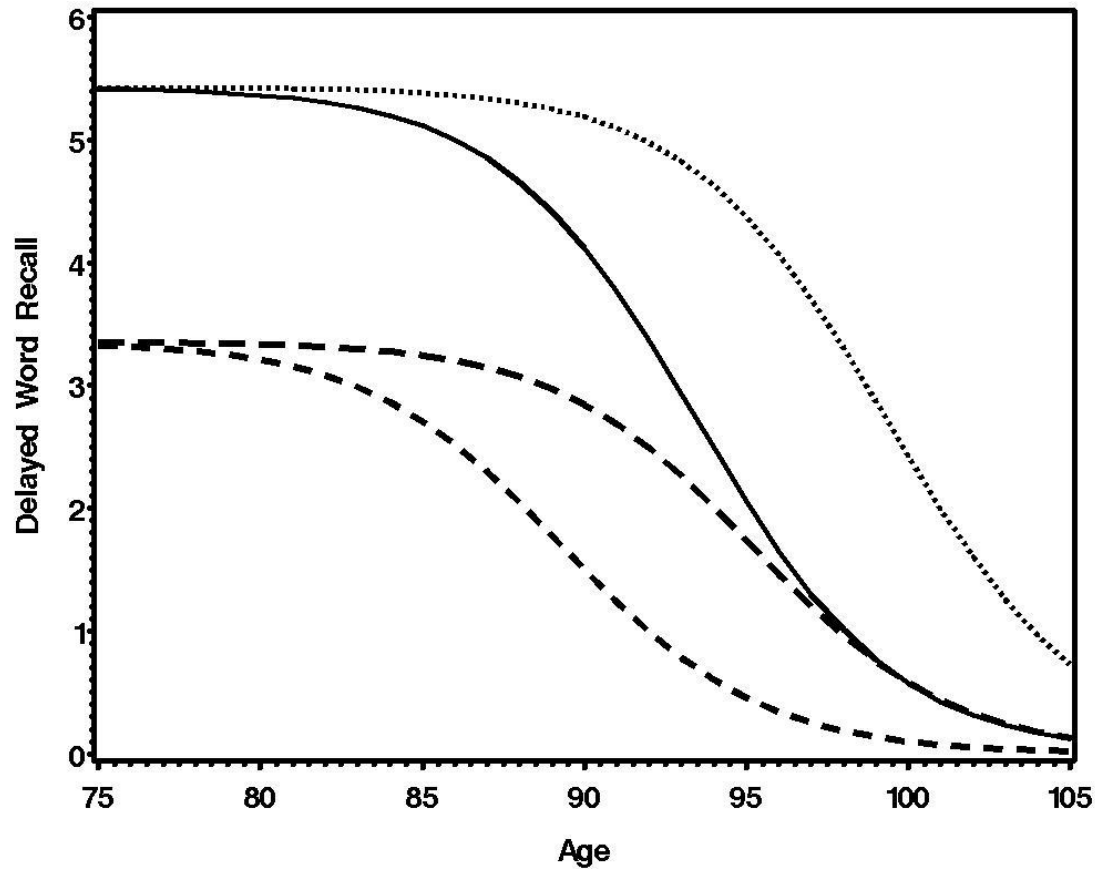
a change of a few points at the top end of the scale has same implications as a change in the middle or bottom ?

Crane et al J. Clin. Epi. 2008 ; McArdle et al 2009

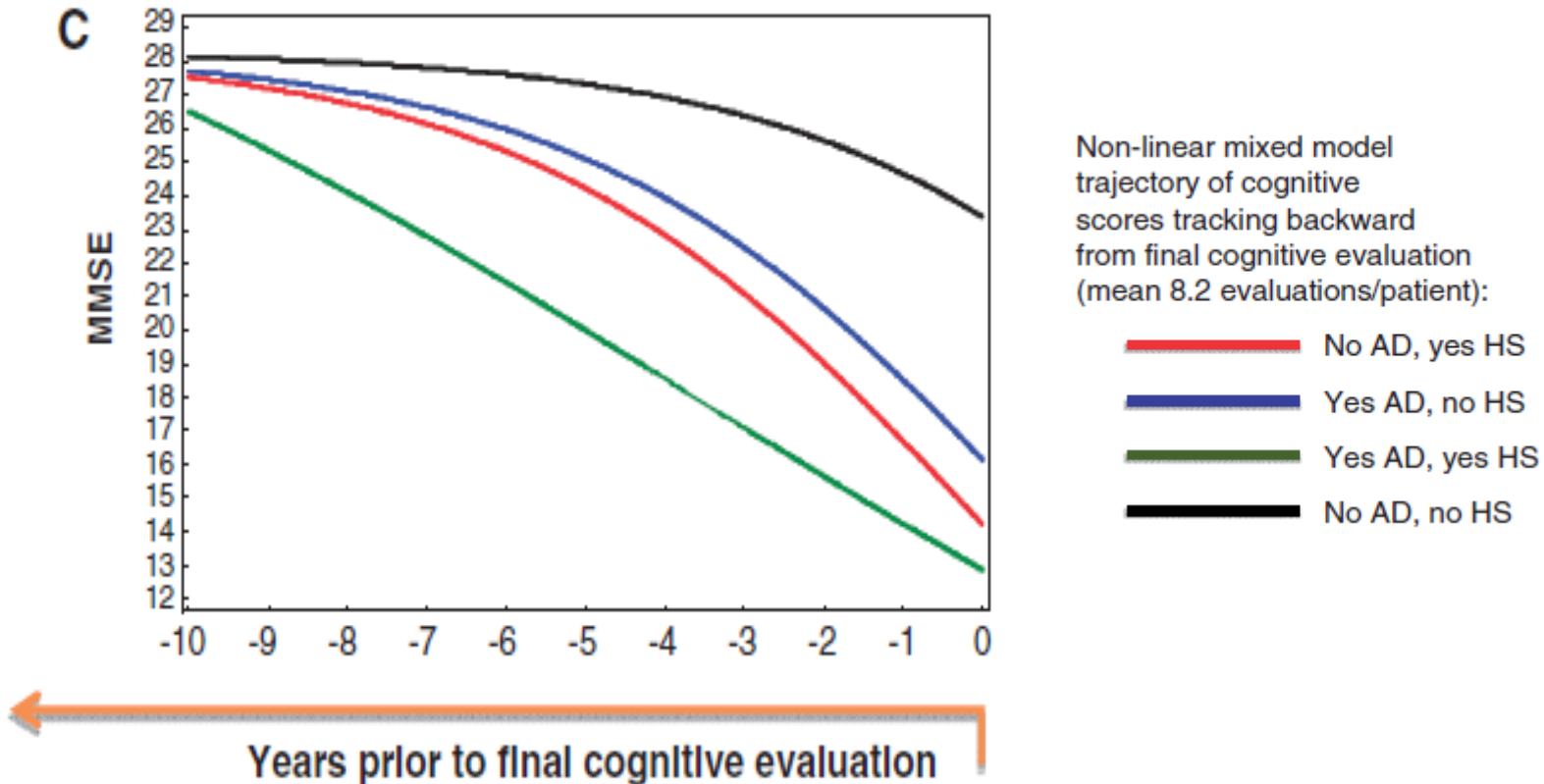
Word List Delay versus age for APOE4 negative but < 10 teeth (n = 42: Nun Study)



Nun Study : APOE 4 status by # teeth (< 10, ≥ 10)
Stein et al J Dental Res, 2010



Decline in MMSE prior to death versus autopsy result
(n = 118)
Nelson et al , BRAIN, 2011



Is MCI a transient state ?

Early MCI states:

Return to normal just as likely as advancing to dementia ?

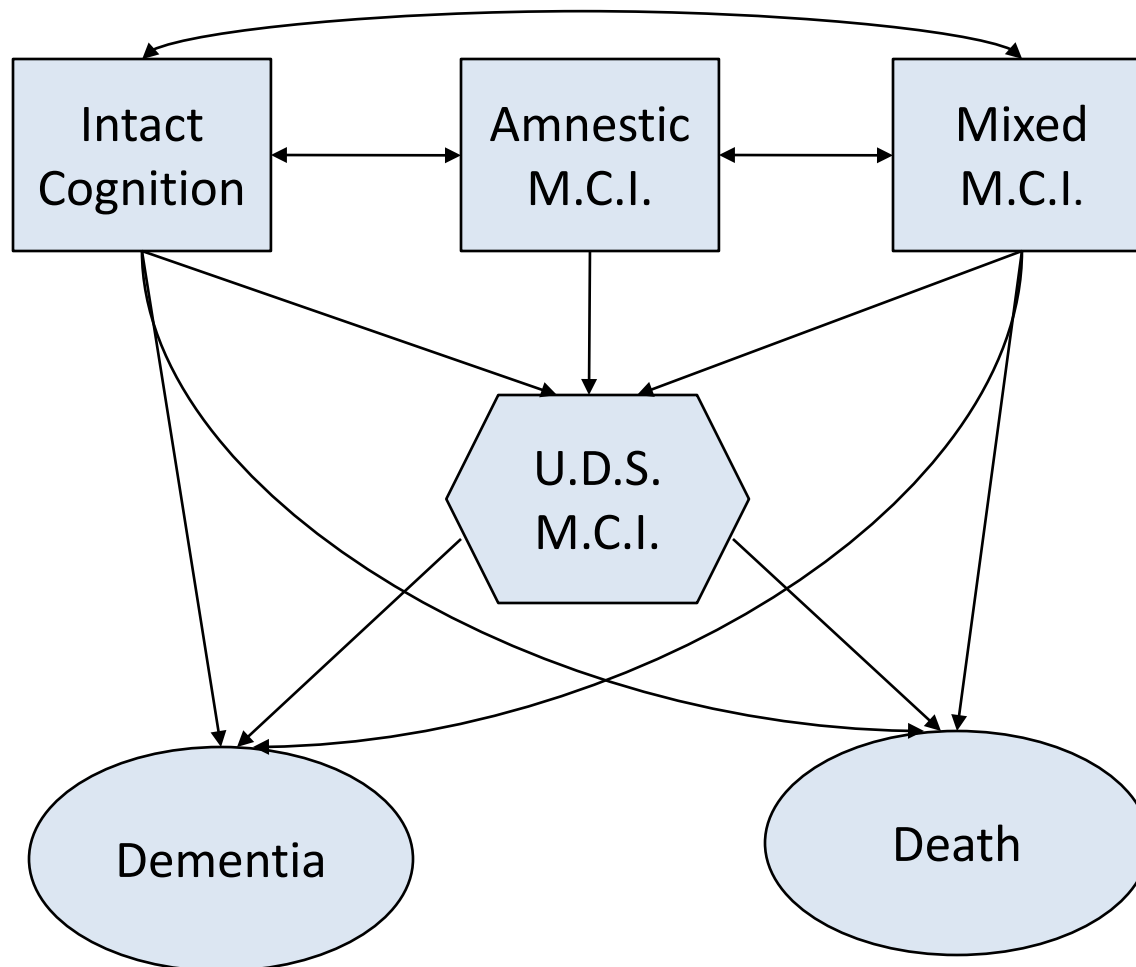
But is the return to normal permanent ?

Transient MCI states tend to vary from cohort to cohort.

Flow diagram of transitions: BRAiNS cohort

(Previous, simpler diagram:

Kryscio et al, Neurology, 2006; Salazar et al Stat Med, 2007)



One step transitions: UK-ADC BRAiNS cohort

n = 531 subjects with 5, 167 assessments

Prior State	Intact Cognition	Amnestic M.C.I.	Mixed M.C.I.	U.D.S. M.C.I.	Dementia	Death*
Intact	2,192	478	385	34	19	100
Amnestic	448	148	108	23	10	18
Mixed	341	88	453	47	27	79
UDS M.C.I.	0	0	0	101	34	16

*Died before becoming demented

Retrospective review produces a Longitudinal Record: Categorical responses

Each participant generates a “vector” of responses

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

Here y_j is the state at visit j

Examples:

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

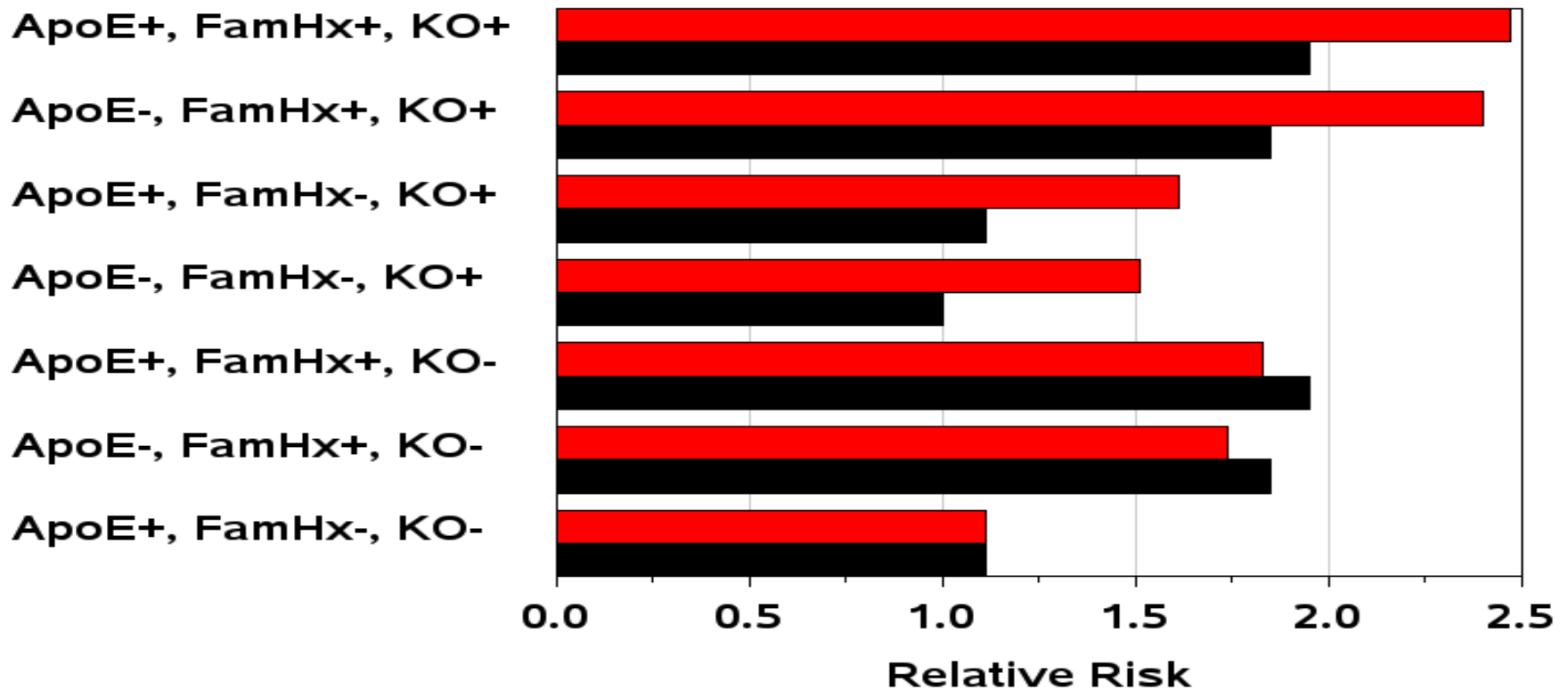
Subject 2 record (2, 1, 2, 5)

Mean length of vectors in BRAiNS is 10.3 ± 4.1

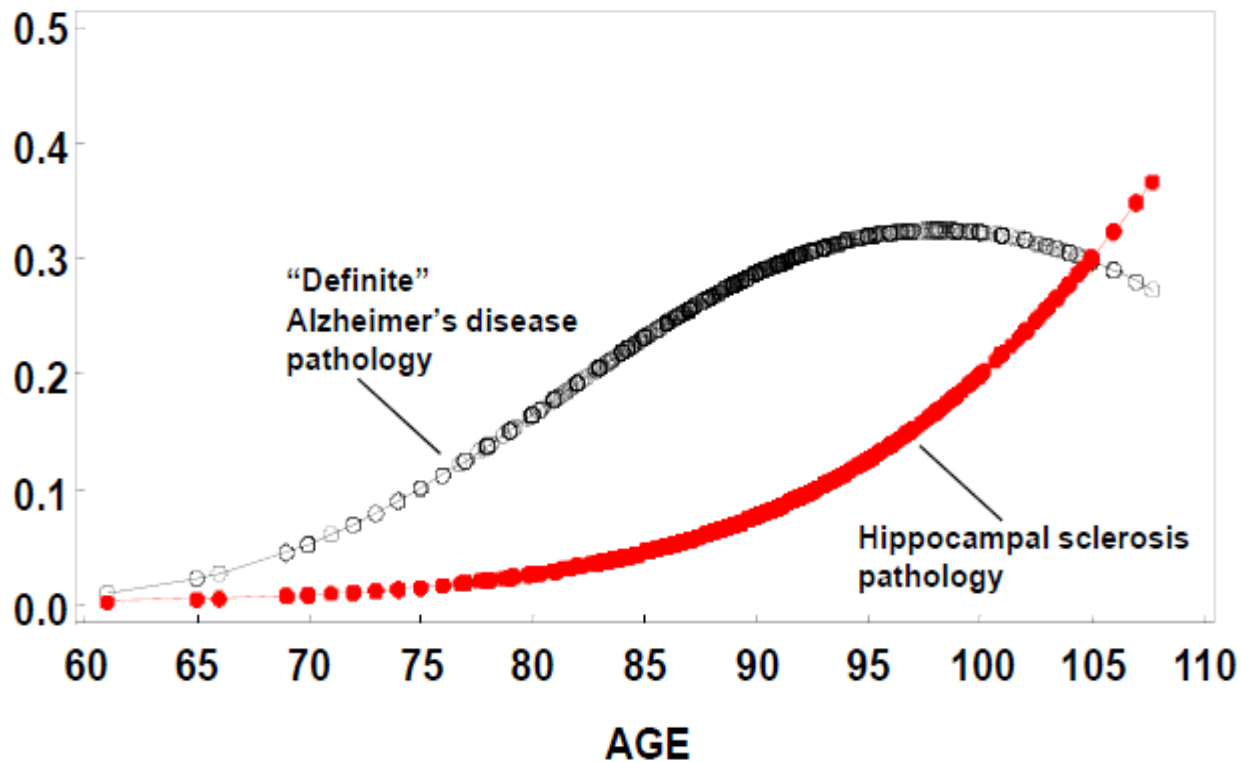
One step transitions in the Markov chain

Risk factor	Amnestic MCI	Mixed MCI	U.D.S. MCI	Dementia	Death
Age	Yes +	Yes +	Yes +	Yes +	Yes +
Male	Yes -	No	No	No	Yes -
High School Ed.	No	Yes +	No	No	No
APOE 4	No	No	Yes +	No	No
Family History	No	No	No	Yes +	No
Hypertension	No	No	No	No	Yes +
BMI	No	No	Yes +	No	No
Male: head injury	No	No	No	Yes +	No

Relative risk of an eventual Dementia:
85 year old, cognitively intact
male --- female ---



Smoothed incidence curves: dementia and hippocampal sclerosis
1,110 autopsies (three studies: BRAiNS, Nuns, Georgia Centenarians)
Nelson et al, Brain, 2011



Neuropathological diagnoses in Nun study

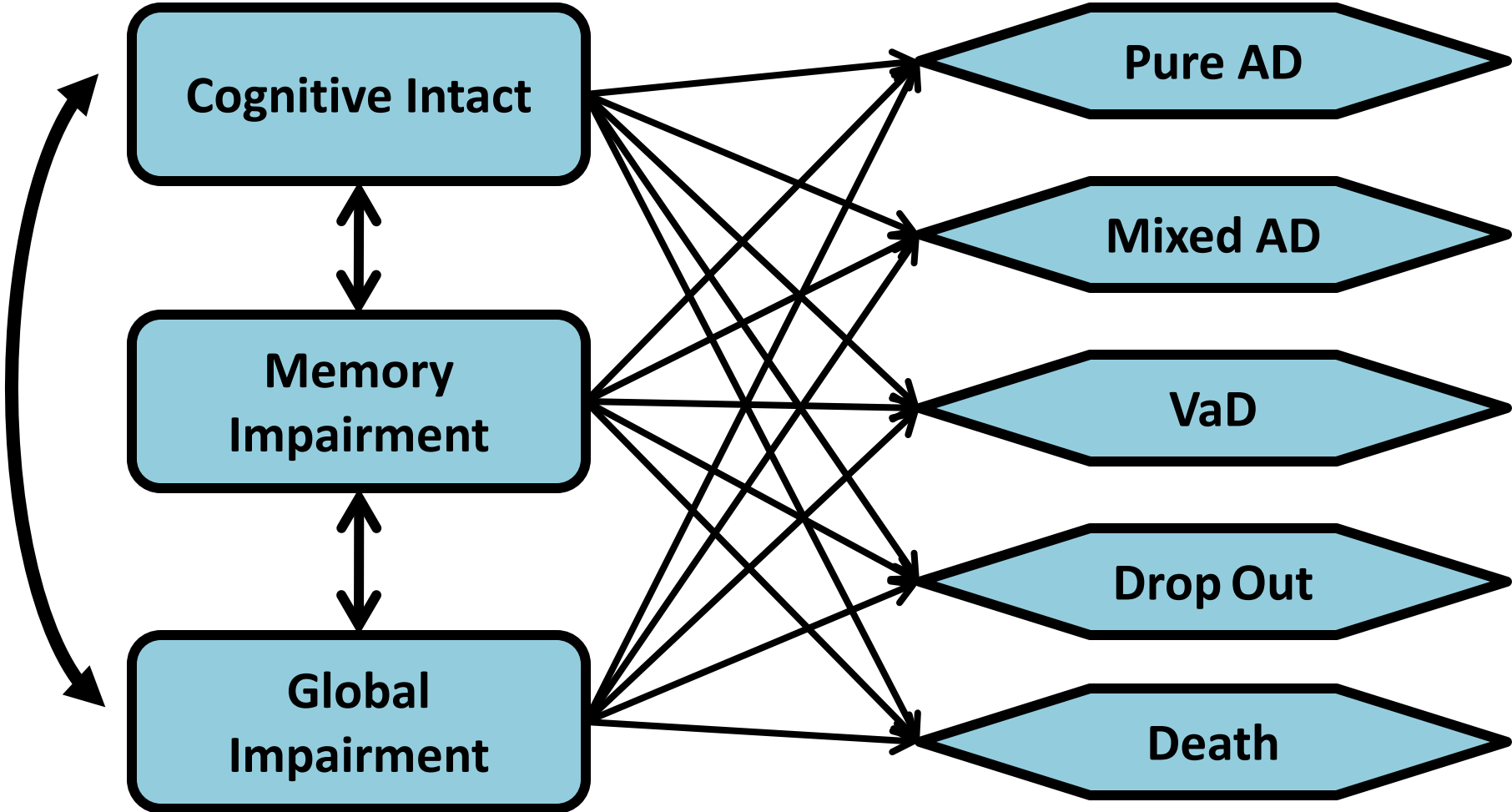
AD	129
Insufficient AD	93
Other dementia	70
Hippocampal sclerosis	28
Normal (none of above)	94

Total	414
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P values based on multinomial logistic regression model

Risk Factor	Normal vs AD	HS vs AD	OthDem vs AD	Insuf AD vs AD
Age at death	0.23	0.02	0.04	0.55
Clinical Dementia	0.0001	0.13	0.03	0.0005
Apoe4 +	<0.0001	0.03	0.0001	0.0091

Merge several mature databases which have followed individuals to autopsy



Conclusions:

We thank our speakers:

The change point model is useful in the early stages of cognitive decline; nonlinear models work best for a retrospective review of a subject's entire cognitive trajectory or late life trajectories

Early MCI states can be transient but there is no agreed upon definition of these transient states; later MCI states such as U.D.S. MCI are much less transient

There is a need to account for the role of clinico-pathological correlations especially mixed pathology when examining risks for impaired states.

Markov Model Investigators

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