The early detection of cognitive impairment: Two approaches to assess longitudinal trajectories

Hiroko H. Dodge, PhD
Data Core Leader
NACC Scientific Review Committee
Assistant Professor
Department of Neurology
Oregon Health and Science University
Portland, OR

Adjunct Assistant Professor
Department of Epidemiology
University of Pittsburgh
Pittsburgh, PA

Today's Presentation

Briefly introduce **two** methods suited for the analysis of **longitudinal trajectories**.

1) Change point model
2) Latent (Cluster) Trajectory model

Why Trajectories?

Early detection of dementia is becoming more important for treatment and long-term planning.

Therefore, it is critical to detect ***early signals*** indicating the transition from normal cognitive aging to MCI and early dementia.

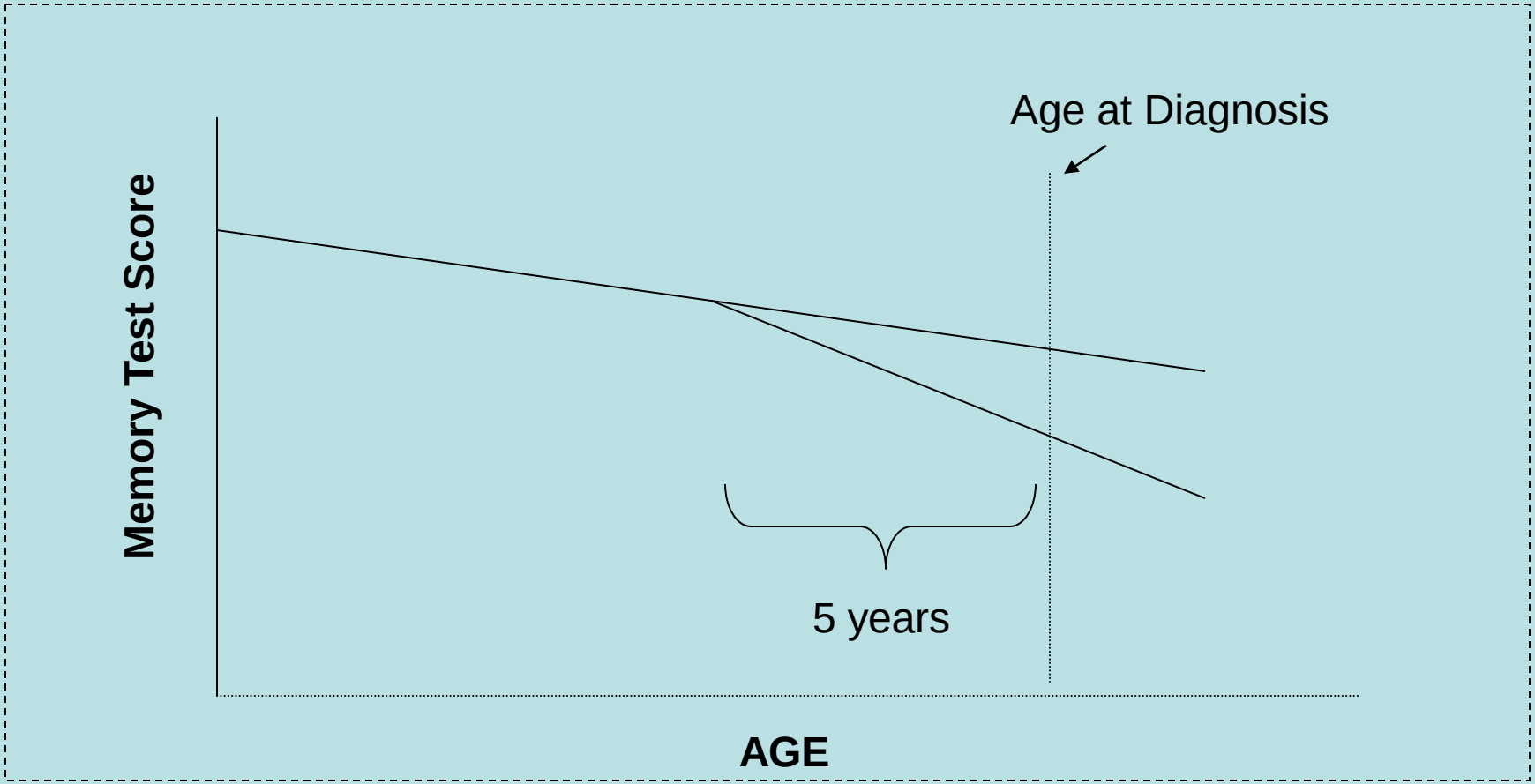
Studying the trajectories of biomarkers and cognitive and functional measurements could help identify these “early signals”.

1) Change point analysis

Hall CB, Lipton RB, Sliwinski M, Stewart WF. A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease. *Statistics in Medicine* 2000;19(11-12):1555-66.

This study found that approximately 5 years before the diagnosis of dementia, memory function (as measured by Buschke Selective Reminding test) started accelerating in decline. (Sample: Bronx Aging Study)

When does acceleration (change point in slope) starts?



Outcome$_{it}$ (memory test score)= intercept+ (age$_{it}$− 75)+ (age$_{it}$-(agedx$_i$−τ))

(age$_{it}$-(agedx$_i$−τ))=max (0, age$_{it}$-(agedx$_i$−τ))

Research questions

What variables are sensitive to transition from normal cognition to MCI ?

For example…..

***When* do ventricular volumes change; Or neuropscyhological test scores; Or motor function (gait speed) change?**

Application of Change Point Analysis (Examples)

1)Ventricular volume

2)Neuropsychological tests

3)Gait speed

4)Hand tapping speed

DATA: The **Oregon Brain Aging Study (aka OBAS) -** a longitudinal community-based cohort of healthy elderly.

At entry, all subjects were cognitively intact with **CDR=0** and a **MMSE score>=24**.

Application of Change Point Analysis

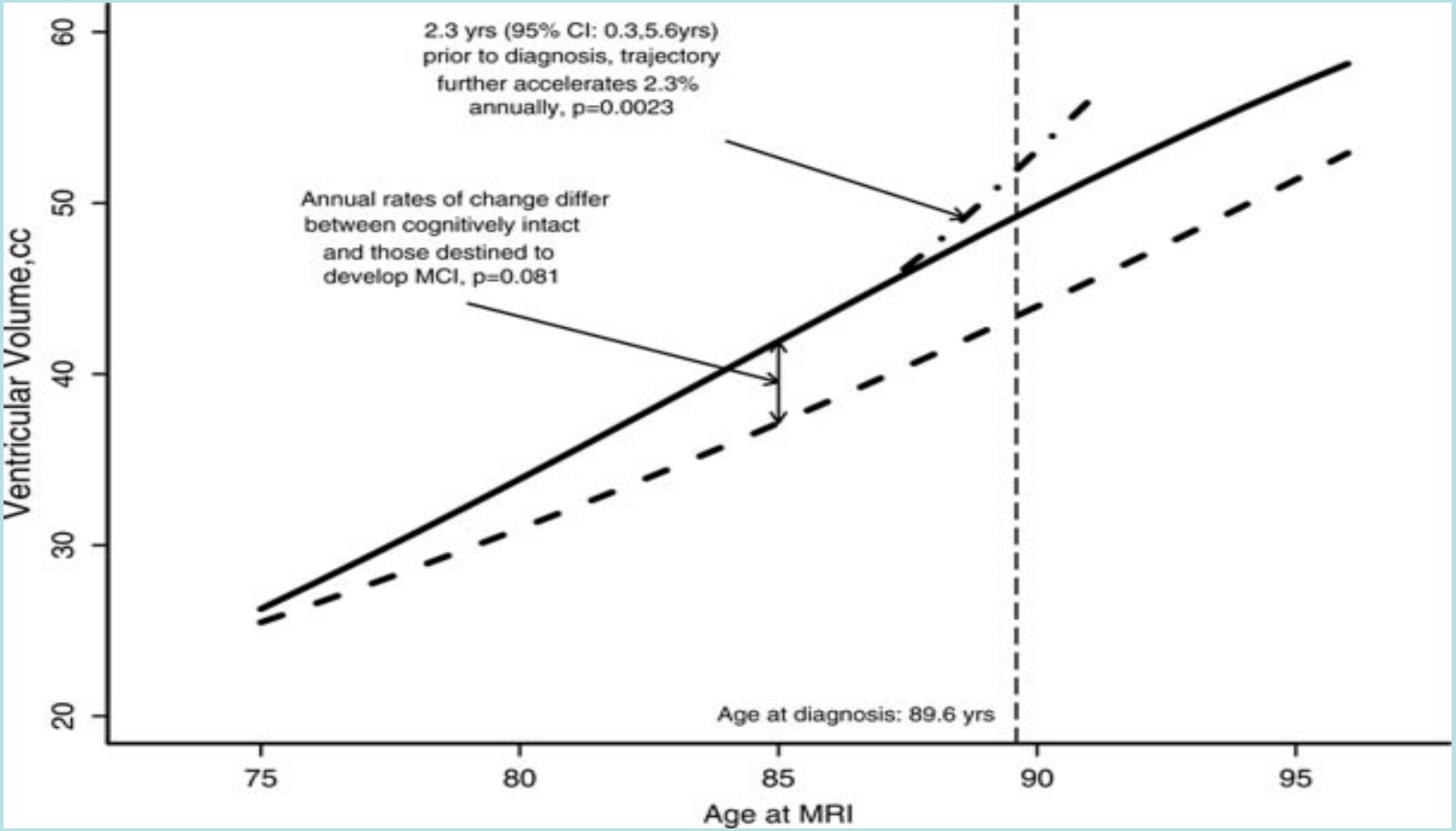
Step 1: Mixed effects model

Assess if overall trajectories were different between normal cognition vs. those who developed MCI

Step 2: Among those who developed MCI, determine whether there was a change point, and if so, when the change point occurred in relation to the development of MCI.

When the acceleration starts in relation to the development of MCI ?

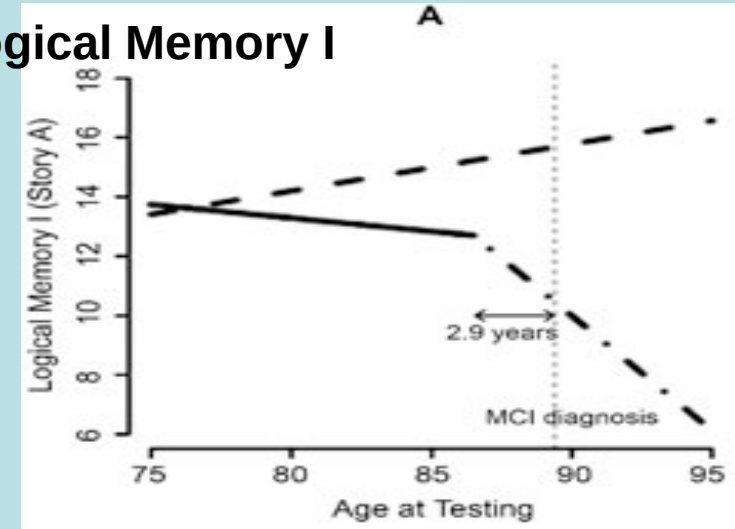
Ventricular volume



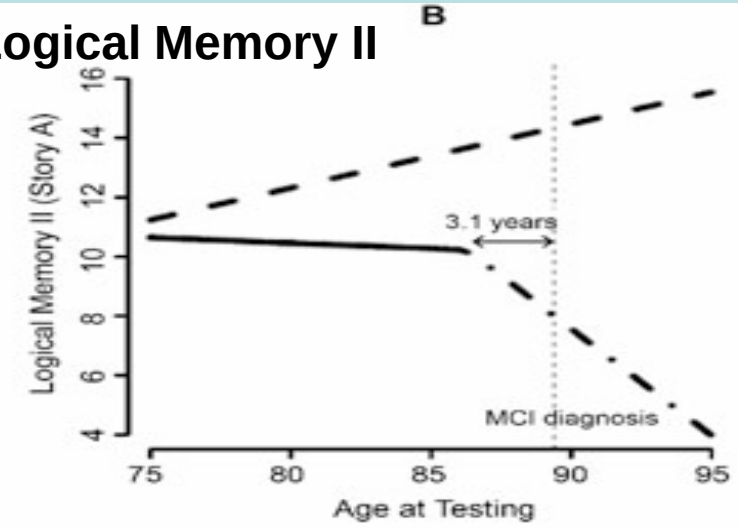
Carlson, et al., *Neurology* 2008;70:828–833

When the acceleration starts? Neuropsychological tests

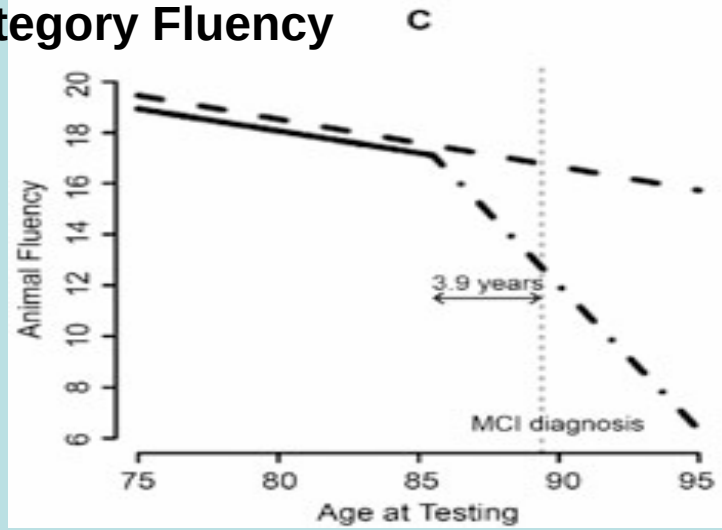
Logical Memory I



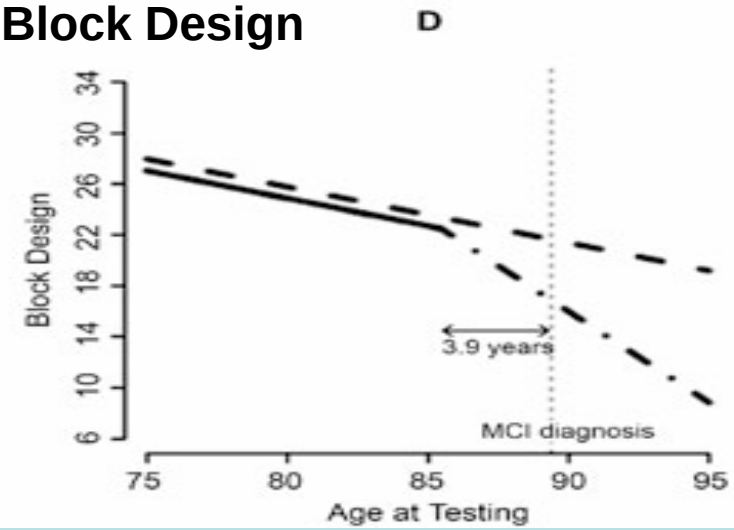
Logical Memory II



Category Fluency



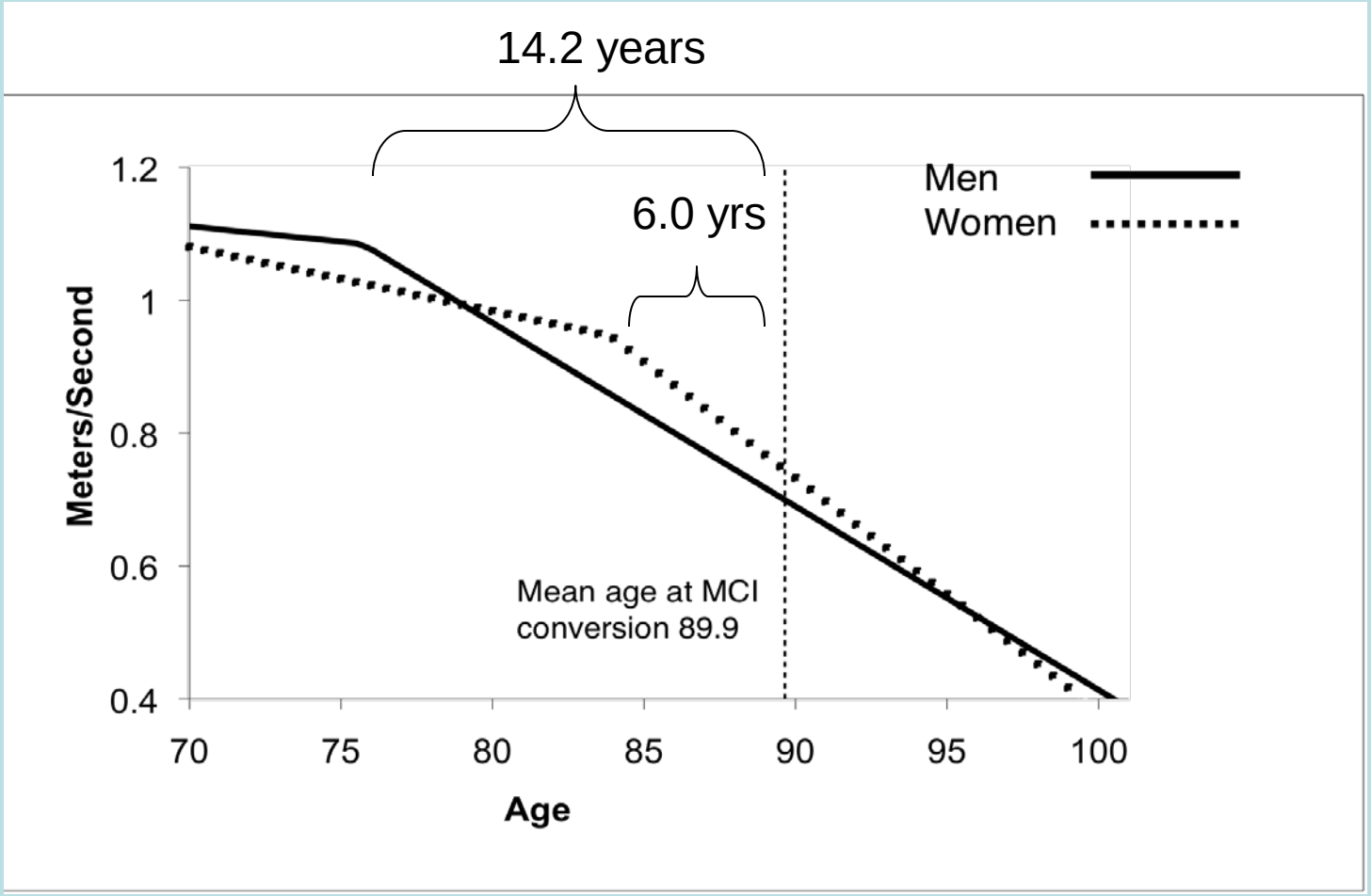
Block Design



Howieson, et al., *Journal of the International Neuropsychological Society,* 2008:14;192–198.

When the acceleration starts in relation to MCI ?

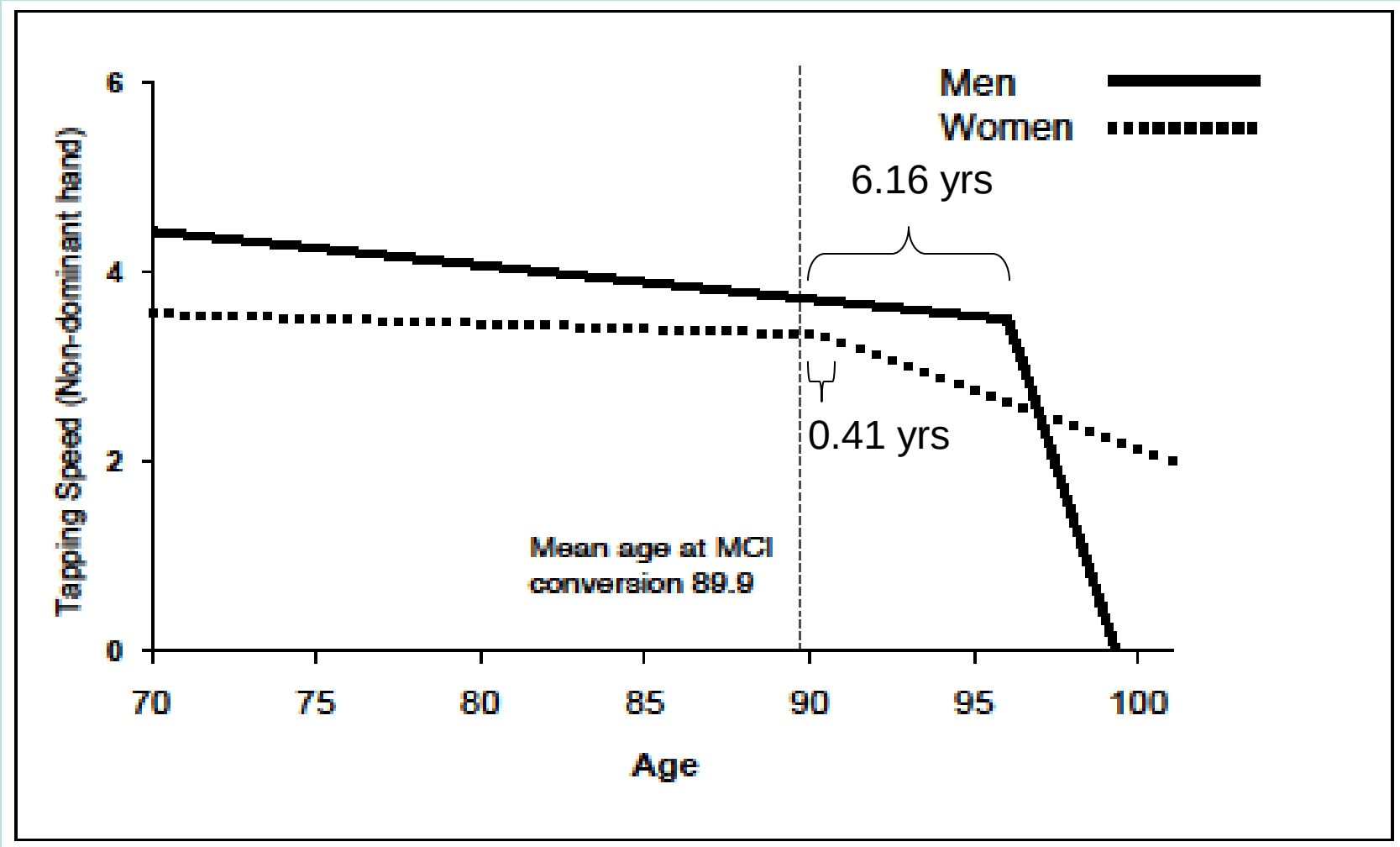
Gait Speed



Buracchio, et al., presented at the 2009 AAN Annual Meeting in Seattle

When the acceleration starts in relation to the development of MCI ?

Tapping Speed (Non-Dominant Hand)



Conclusion

- Change points were recognized several years prior to the development of MCI in several domains (brain volume, cognition, motor function).
- These change points may be useful markers for guiding the timing of assessments used in clinical trials and other prodromal dementia research designs.

Limitations of Change Point Analysis

- The amount of acceleration is “on average”. It is hard to generalize the result to individuals in clinical practice (e.g., decline in walking speed by 0.023 meter/second/year--predicts MCI a decade later?).

- Ecological fallacy: Using group data, we found the order of accelerations (gait speed->ventricular volume–>neuropsychological tests->hand tapping speed). But individuals might not necessarily follow this order.

Further steps are required to translate the findings into clinical practice for early detection of MCI/Dementia

2) Latent Trajectory Analysis

- **Latent Trajectory Analysis**

  Jones, B. L., Nagin, D. S., and Roeder, K. “A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories,” *Sociological Methods & Research*, 2001;29: 374-393.

- Implemented in **PROC TRAJ** procedure in SAS (Jones BL, et al., 2001)

  http://www.andrew.cmu.edu/user/bjones

PROC TRAJ Outline

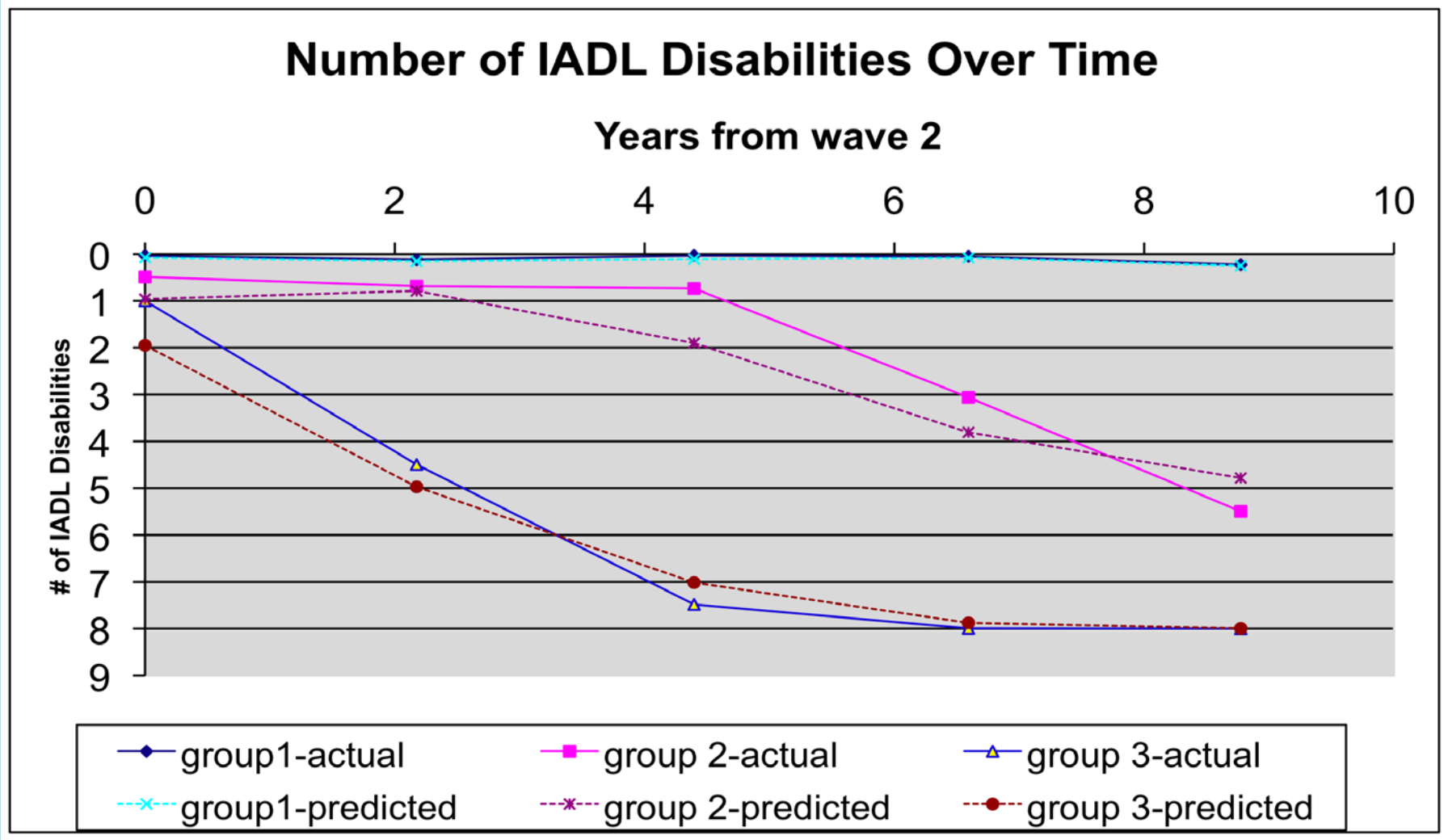
A latent class analysis which identifies homogeneous trajectory patterns and associated factors for each pattern. (Nagin, 1999).

Given that there are K latent trajectory groups, the conditional distribution of the observable outcome for subject *i* (y_i), given risk factors z_i, is written as follows:

$$f(y_i|z_i) = \sum_{k=1}^{K} \Pr(C_i = k|Z_i = z_i) \Pr(Y_i = y_i|C_i = k)$$

where C_i is latent group identification for subject *i*.

Application of Latent Trajectory Analysis to an Epidemiological Study



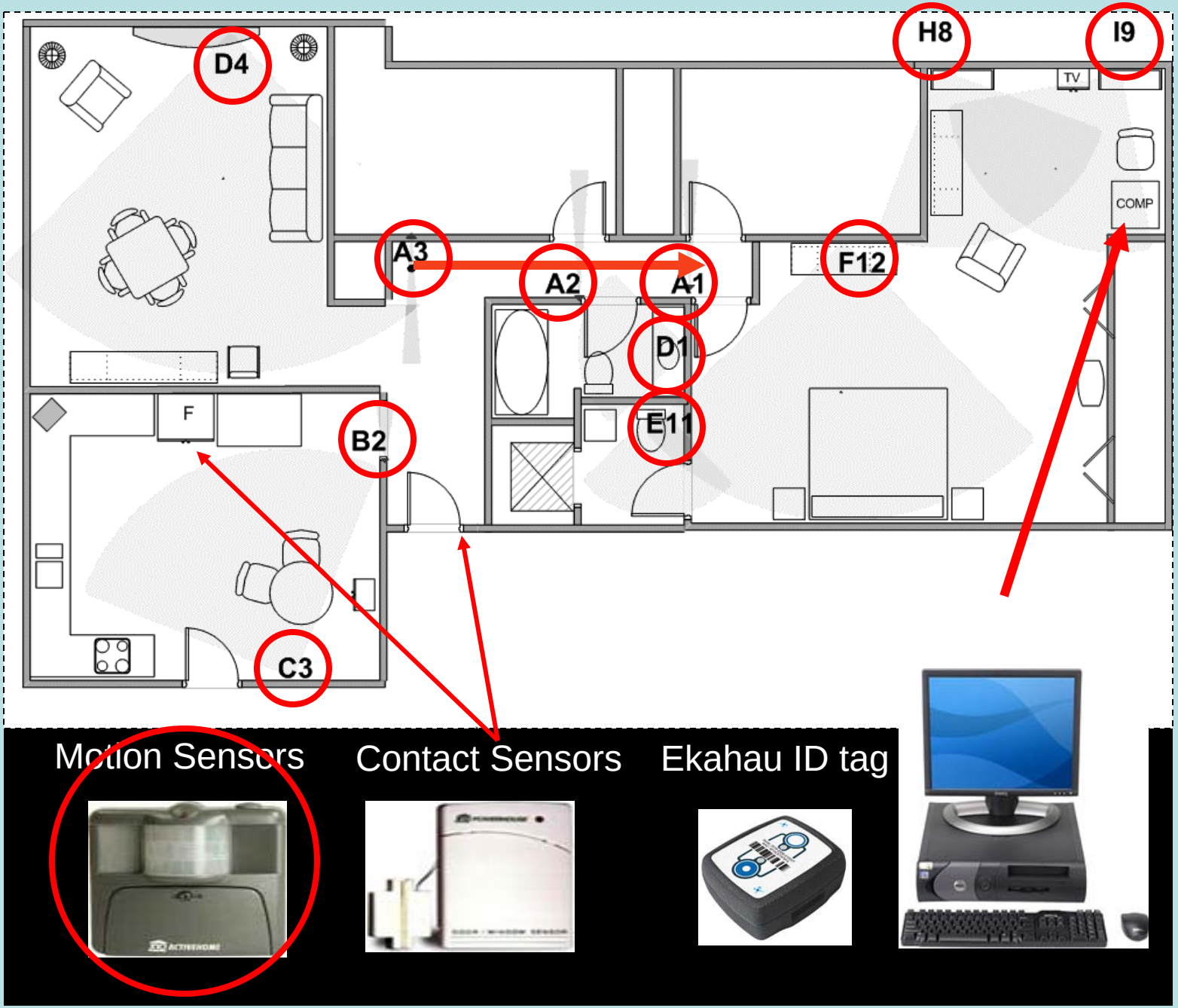
Dodge et al., *The Journal of Gerontology: Medical Sciences*, 2007;61(12):1330-1337

Application of Latent Trajectory Analysis

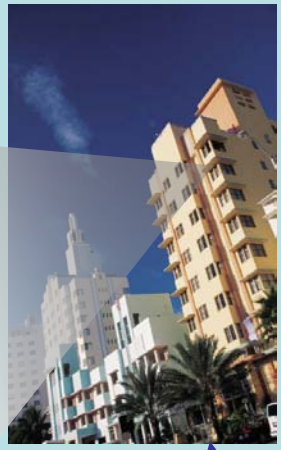
ORCATECH (Oregon Center for Aging and Technology):

BRP Study - Intelligent Systems to Assess Aging Change (aka ISAAC study).

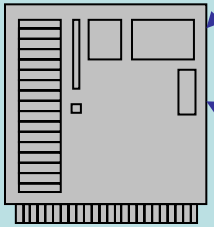
Following approximately 230 Portland area elders (mean age, 84) with **in-home monitoring technologies**


D4
H8
I9
TV
COMP
A3
A2
A1
F12
D1
E11
F
B2
C3
Motion Sensors
Contact Sensors
Ekahau ID tag

Community-wide home-based assessment: "The ORCATECH Living Laboratory"



Secure Internet

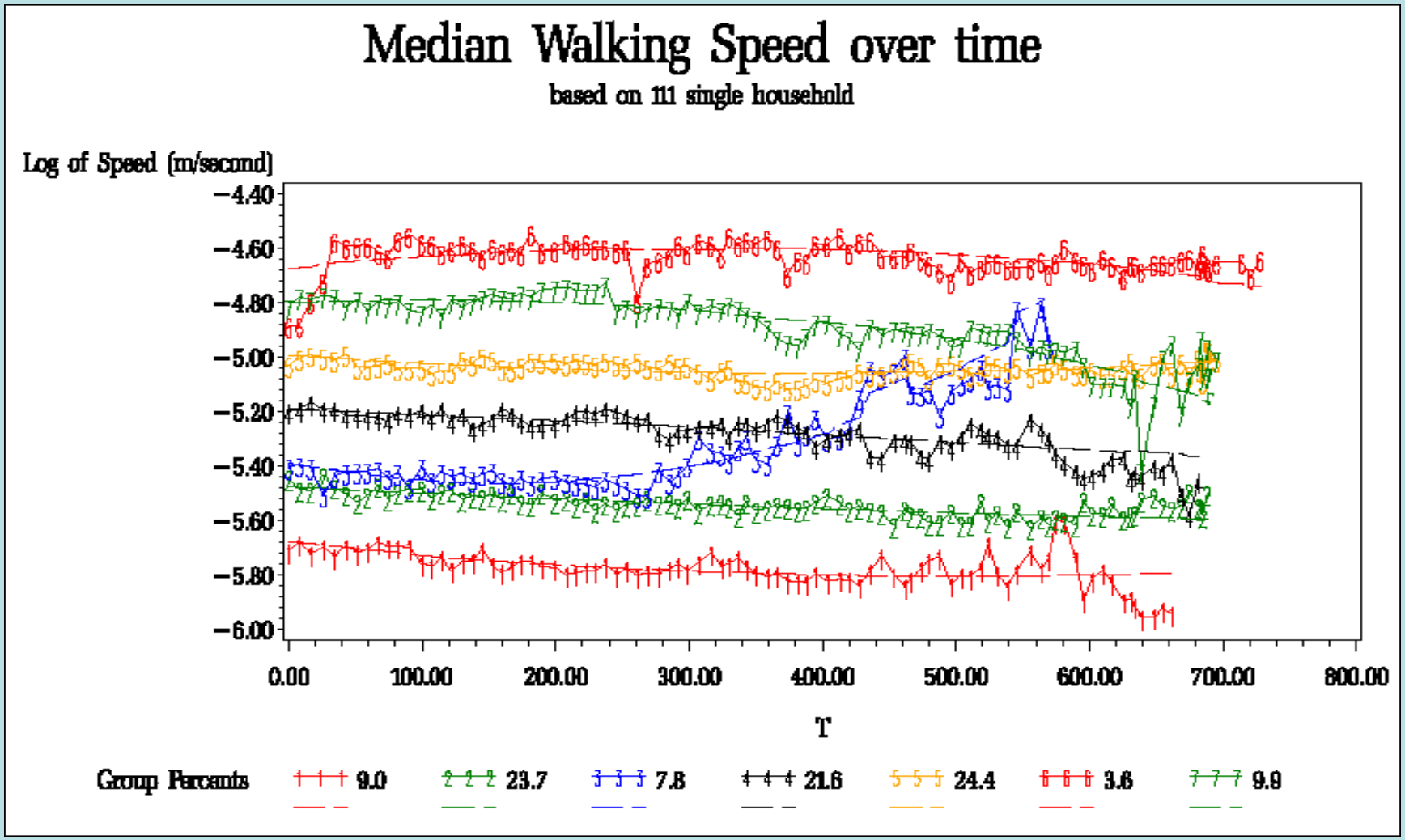


ORCATECH
SUCCESSFUL AGING WITH TECHNOLOGY

Intelligent Systems to Assess Aging Change (aka ISAAC study)

Goal: to determine whether the unobtrusive monitoring data from activity and computer sensors can be used to **effectively predict when an elder starts to develop cognitive decline.**

Application of Trajectory Analysis to walking speed measured unobtrusively at home



Data Source: Intelligent Systems to Assess Aging Change (ISAAC)
The Oregon Center for Aging and Technology (ORCATECH)

Summary

- ***Analytical methods*** aimed to ***efficiently examine trajectories*** of various predictive variables for the development of MCI

✓ Change point model (Hall CB, et al., 2000)

✓ Latent Trajectory model (Jones BL, et al., 2001)

- ***Allow us to clarify what changes are occurring during a (long) pre-symptomatic period of dementia***
- ***Further methodological developments are required to translate these findings into clinical practice for the early detection of MCI/dementia onset.***

Thank you!