Imaging Biomarkers in Predicting MCI and Dementia

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Mayo Clinic College of Medicine

Rochester, MN

Mild Cognitive Impairment Symposium

Miami

January 18, 2014

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Disclosures

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- Roche: Consultant
- Merck: Consultant

- Funding
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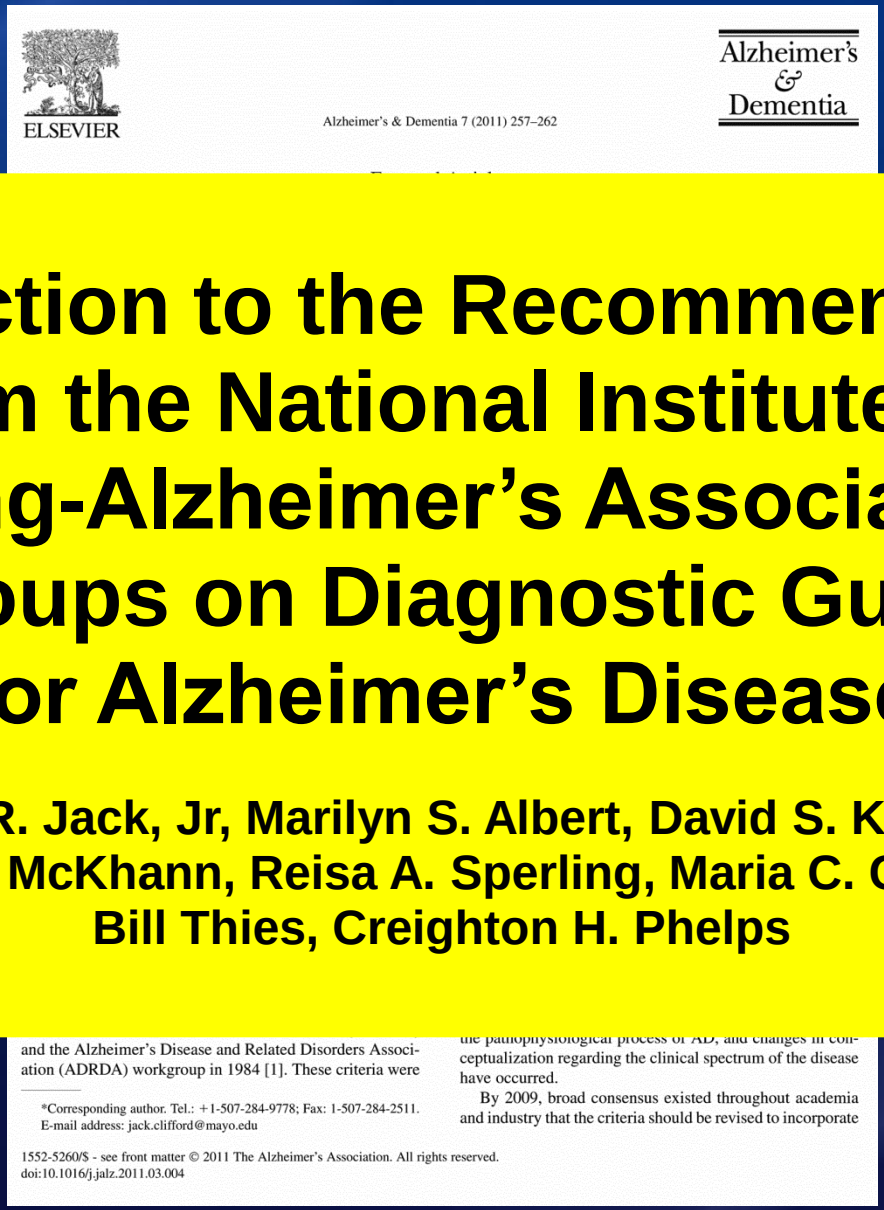
  - P50 AG016574
  - U01 AG011378


ELSEVIER

Alzheimer's & Dementia 7 (2011) 257–262

Alzheimer's & Dementia

Introduction to the Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease

Clifford R. Jack, Jr, Marilyn S. Albert, David S. Knopman, Guy M. McKhann, Reisa A. Sperling, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984 [1]. These criteria were

the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease have occurred.

By 2009, broad consensus existed throughout academia and industry that the criteria should be revised to incorporate

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doi:10.1016/j.jalz.2011.03.004

Alz and Dementia, 2011

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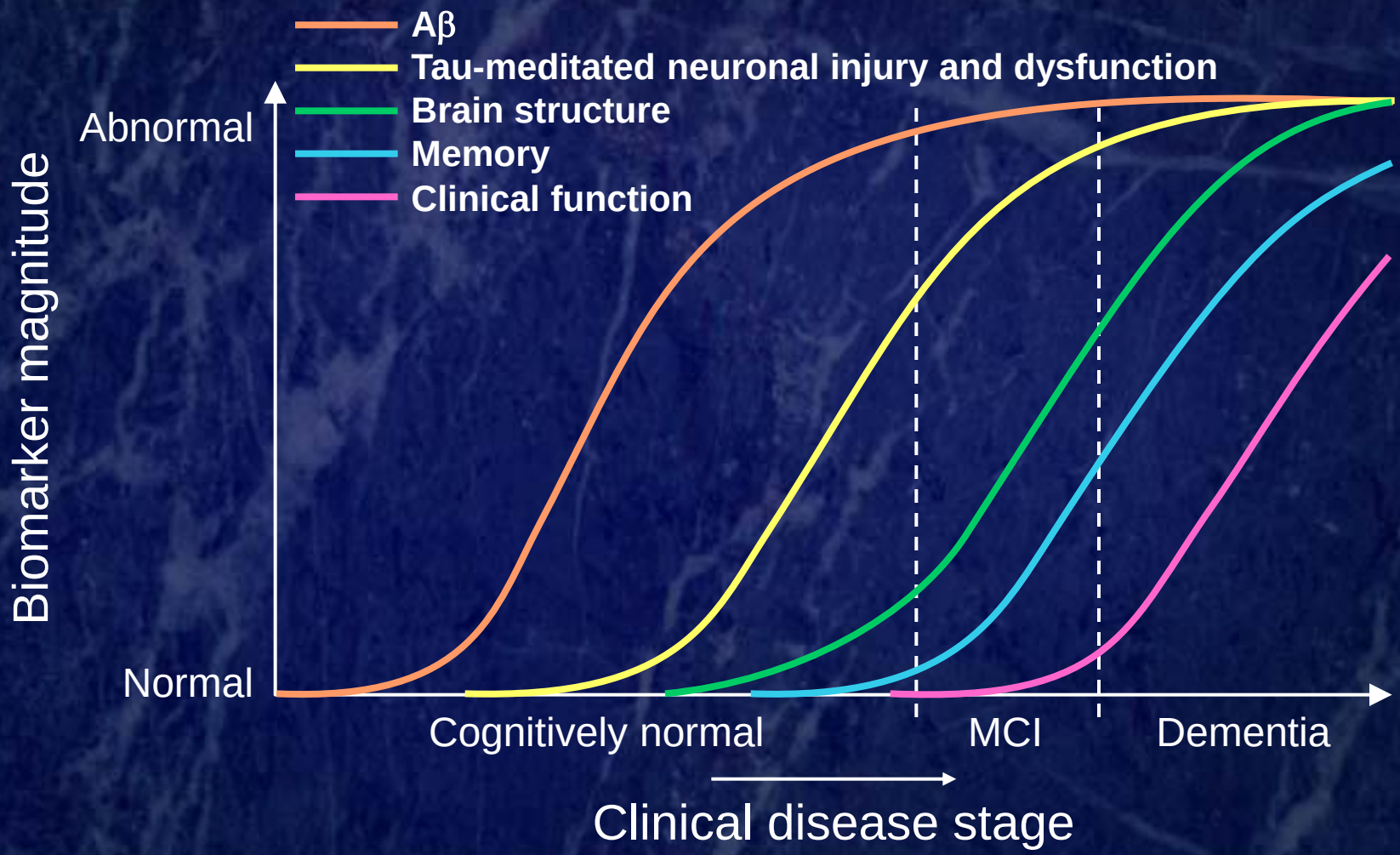
Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade



Jack et al: Lancet Neurol 2010

Criteria Approach

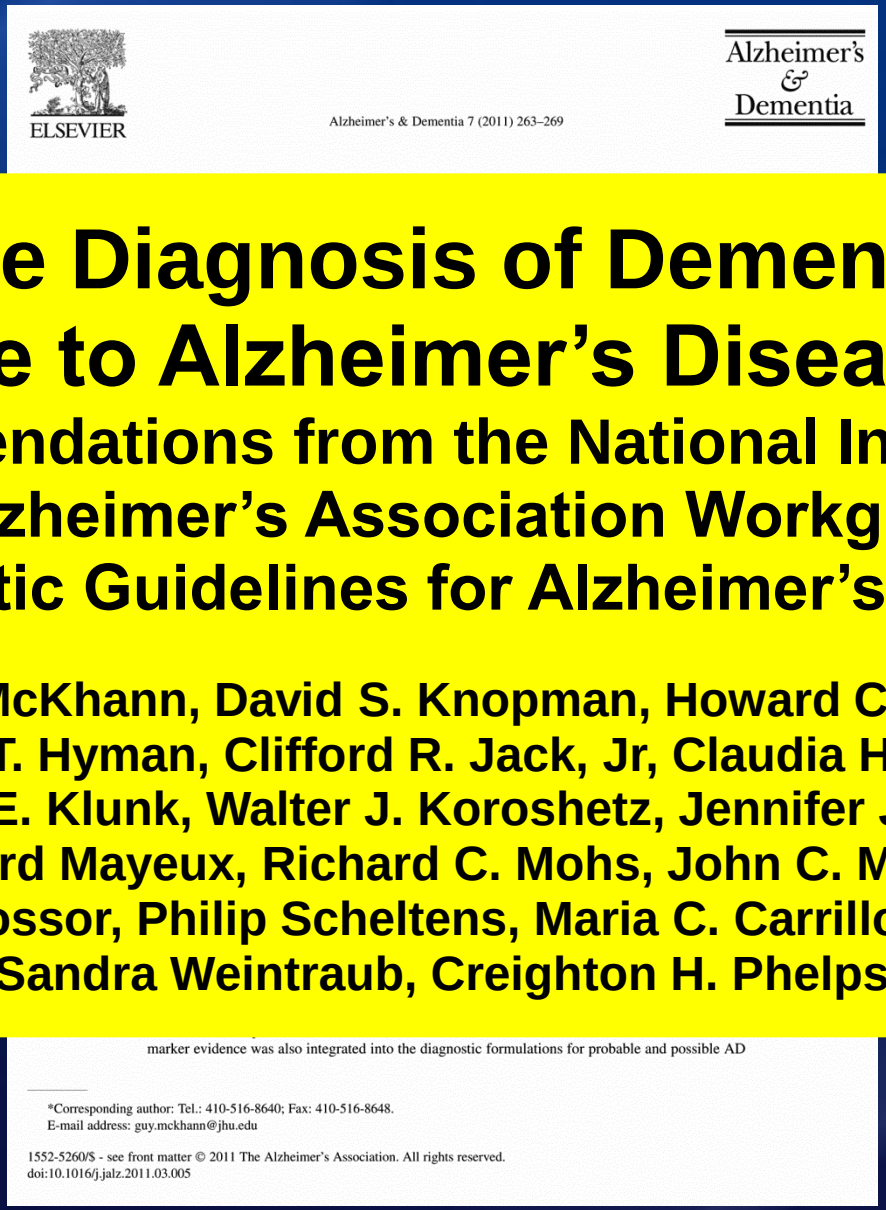
- Clinical criteria
- Biomarkers
- Molecular neuropathology
  - CSF AB42
  - Amyloid imaging
- Measures of neuronal injury
  - Structural, e.g., MRI
  - Functional, e.g., FDG PET
  - CSF tau

Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD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Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

The Diagnosis of Dementia Due to Alzheimer's Disease:

Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease

Guy M. McKhann, David S. Knopman, Howard Chertkow, Bradley T. Hyman, Clifford R. Jack, Jr, Claudia H. Kawas, William E. Klunk, Walter J. Koroshetz, Jennifer J. Manly, Richard Mayeux, Richard C. Mohs, John C. Morris, Martin N. Rossor, Philip Scheltens, Maria C. Carrillo, Bill Theis, Sandra Weintraub, Creighton H. Phelps

marker evidence was also integrated into the diagnostic formulations for probable and possible AD

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doi:10.1016/j.jalz.2011.03.005

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Alz and Dementia, 2011

Dementia Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
Probable AD dementia	Uninformative/ available	Conflicting/ indeterminant or unavailable	
Probable AD with evidence of path AD	Intermediate Highest	? Positive	Positive Positive
Possible AD dementia atypical with path	High consider secondary	Positive	Positive
Dementia unlikely AD	Lowest	Negative	Negative

McKhann et al: 2011

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Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD

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Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The Diagnosis of Mild Cognitive Impairment Due to Alzheimer's Disease:

Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

The National Institute on Aging and the Alzheimer's Association convened a working group to revise the diagnostic

to the working group are outlined in the Introduction to the revised criteria for AD that accompanies this article [1]. The present article summarizes the recommendations of the working group.

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doi:10.1016/j.jalz.2011.03.008

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Alz and Dementia, 2011

MCI Due to AD

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI	Uninformative	Conflicting/ indeterminant or unavailable	
MCI due to AD – intermediate likelihood	Intermediate Intermediate	Positive Untested	Untested Positive
MCI due to AD – high likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al: 2011

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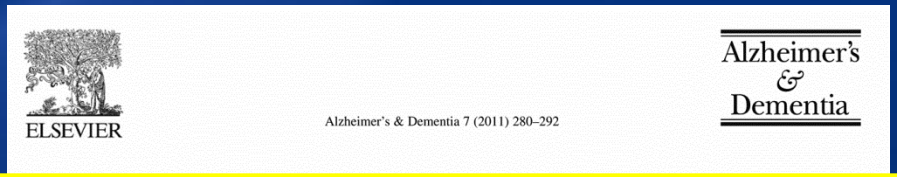
Alzheimer's Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD



Toward Defining the Preclinical Stages of Alzheimer's Disease:

Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease

Reisa A. Sperling, Paul S. Aisen, Laurel A. Beckett, David A. Bennett, Suzanne Craft, Anne M. Fagan, Takeshi Iwatsubo, Clifford R. Jack, Jr, Jeffrey Kaye, Thomas J. Montine, Denise C. Park, Eric M. Reiman, Christopher C. Rowe, Eric Siemers, Yaakov Stern, Kristine Yaffe, Maria C. Carrillo, Bill Thies, Marcelle Morrison-Bogorad, Molly V. Wagster, Creighton H. Phelps

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doi:10.1016/j.jalz.2011.03.003

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Alz and Dementia, 2011

Preclinical AD

Diagnostic category	Aβ (PET or CSF)	Neuronal injury	Clinical
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive
Stage 0	Negative	Negative	Negative

Sperling et al: 2011

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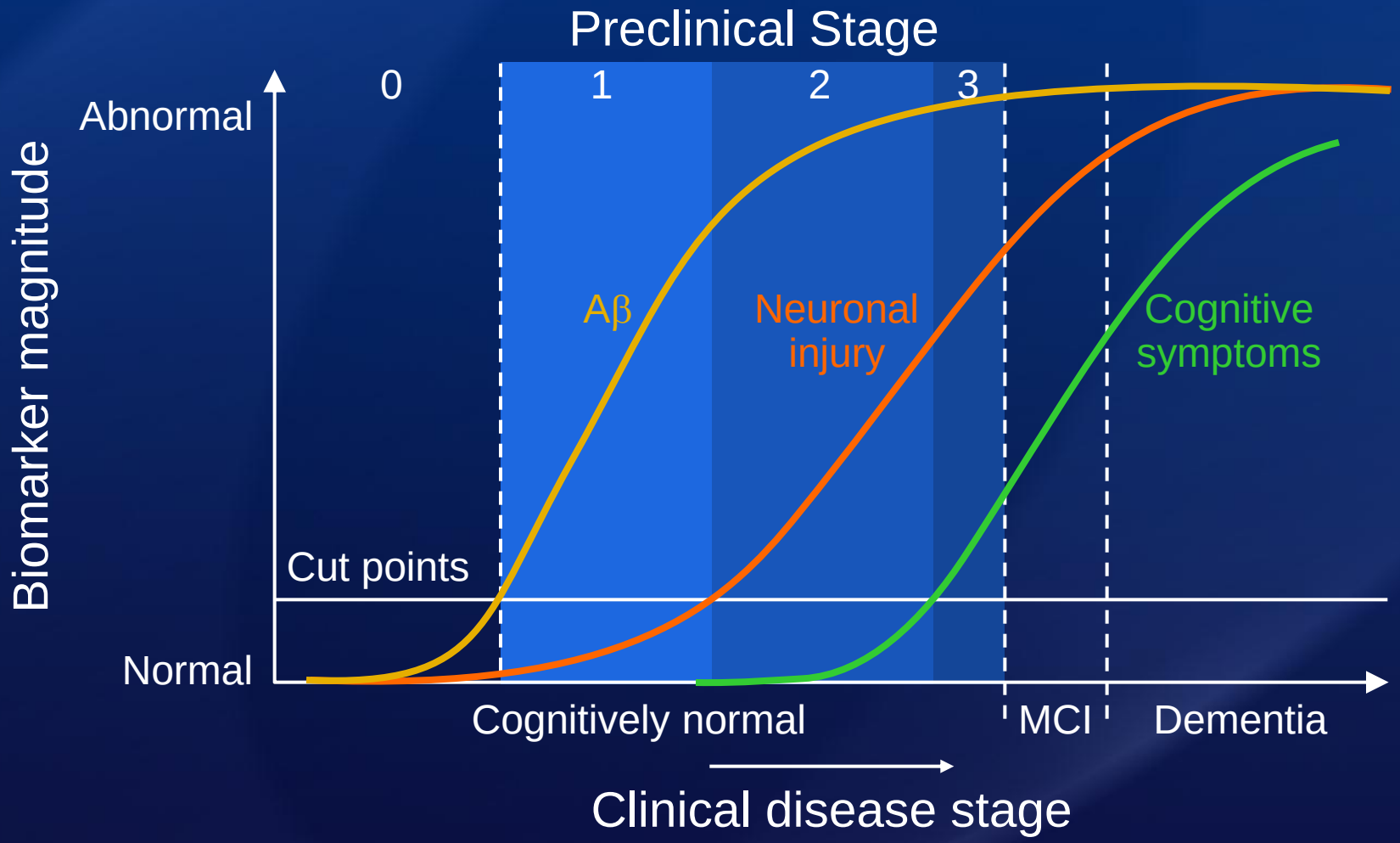
NIA-AA Preclinical AD Staging in Relation to Our Hypothetical Model of Biomarkers



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Do the Criteria Work?

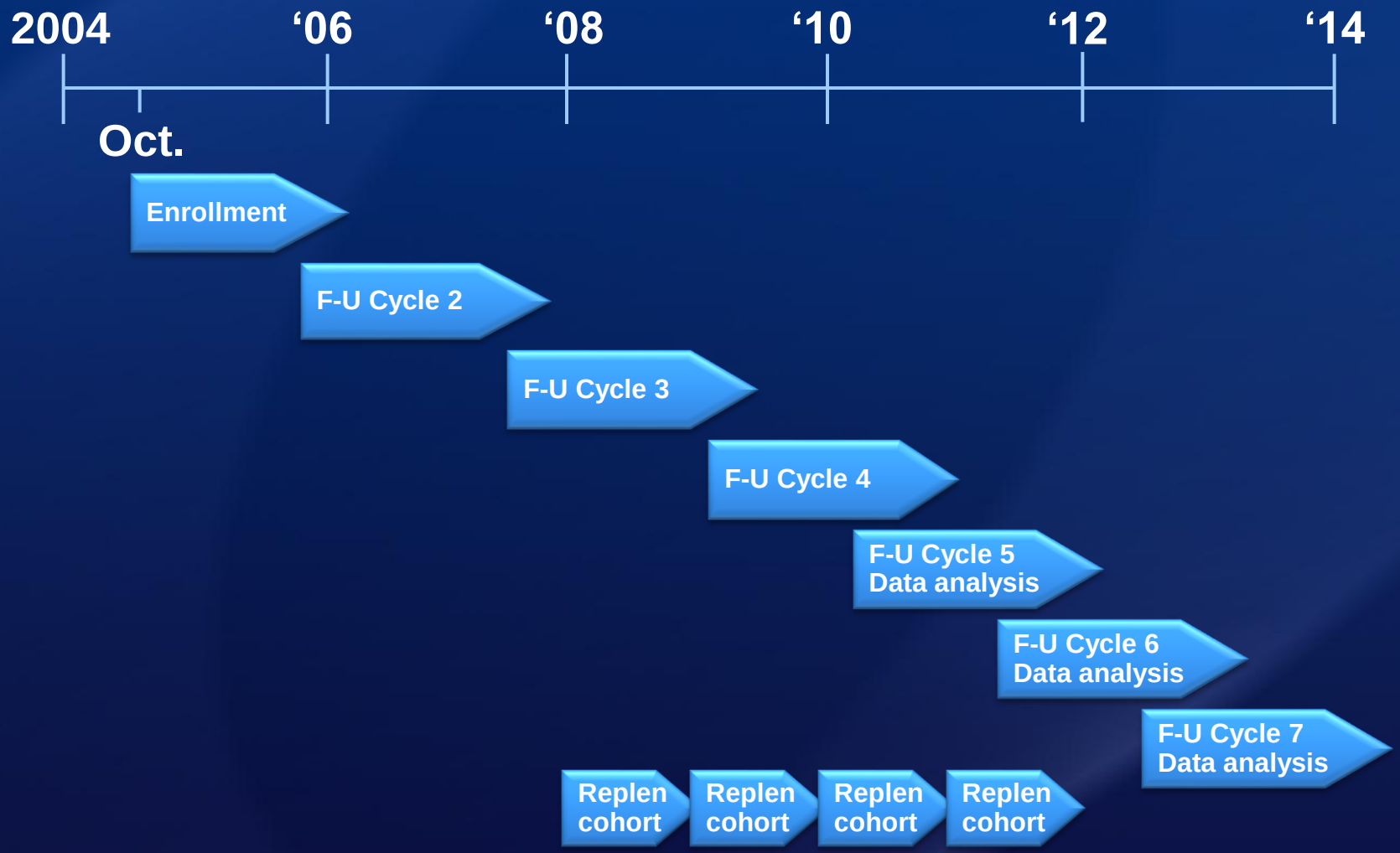
Mayo Clinic Study of Aging (MCSA)

Mayo Olmsted County Study of Aging (U01 AG006786)

Mayo Clinic Study of Aging

Population-based study of 3000-4000 nondemented persons age 50-89 years in Olmsted County, MN

Mayo Clinic Study of Aging



F-U = follow-up

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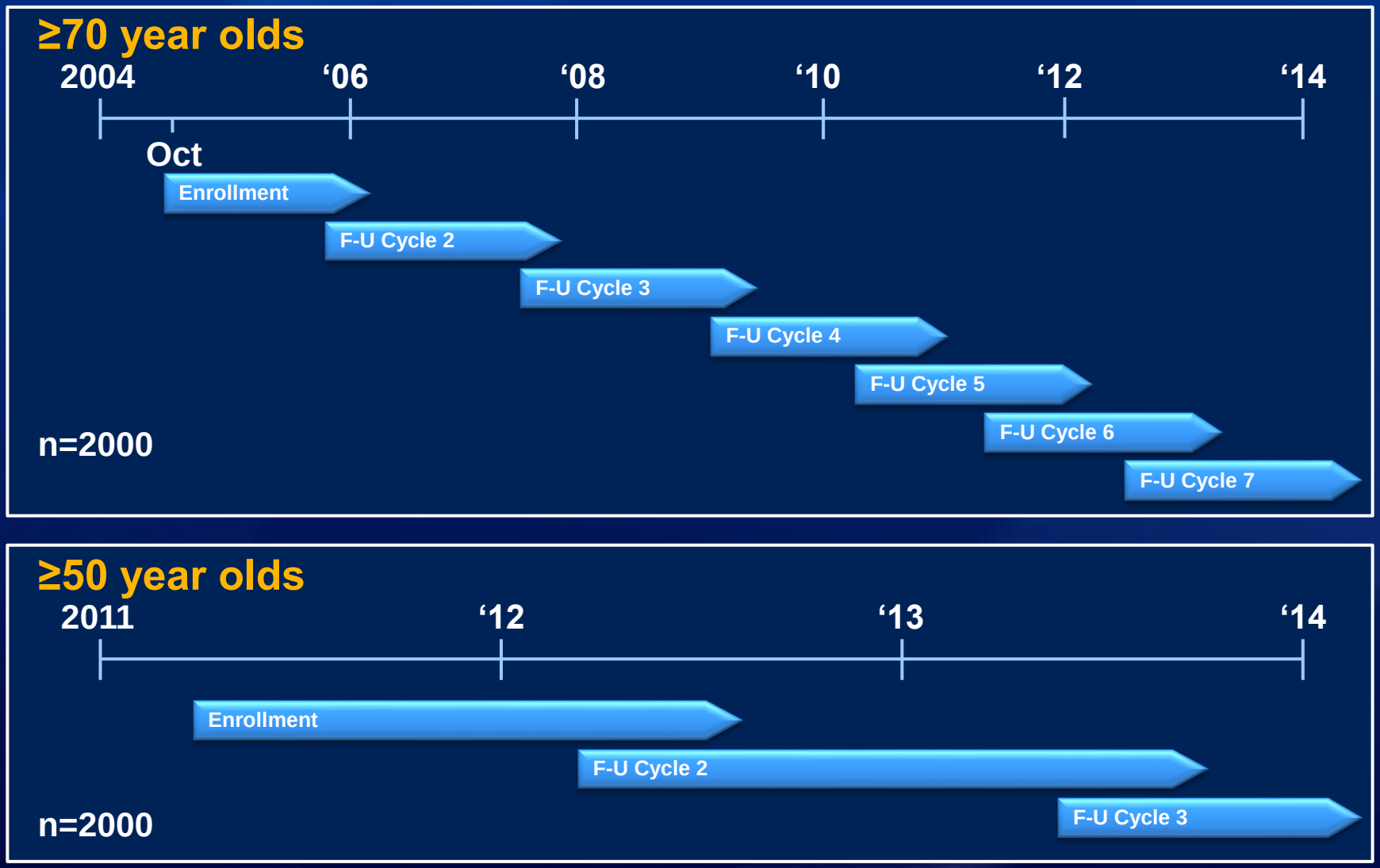
Mayo Clinic Study of Aging



F-U = follow-up

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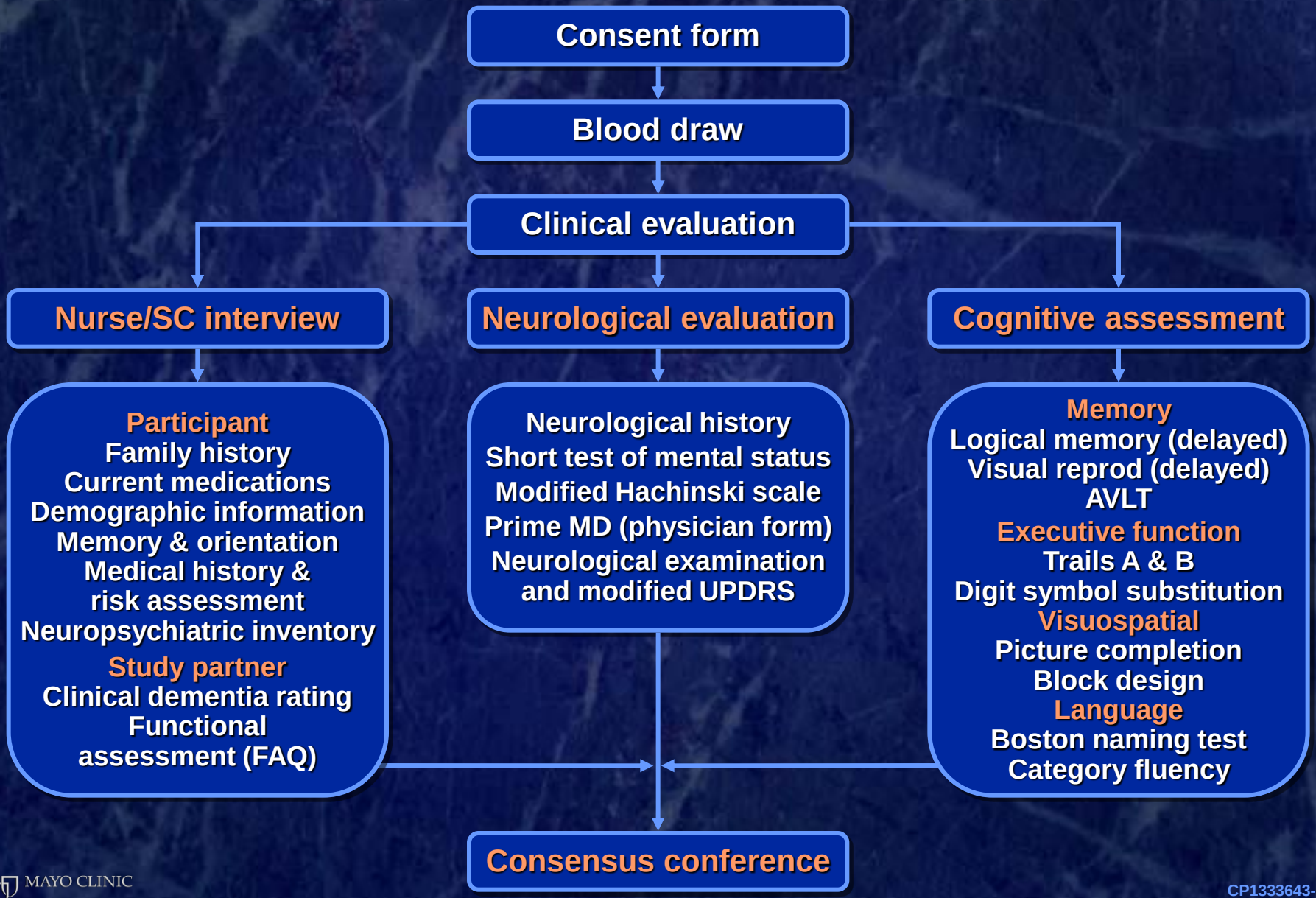
Evaluation


Consent form
Blood draw
Clinical evaluation
Nurse/SC interview
Neurological evaluation
Cognitive assessment
Participant
Family history
Current medications
Demographic information
Memory & orientation
Medical history &
risk assessment
Neuropsychiatric inventory
Study partner
Clinical dementia rating
Functional
assessment (FAQ)
Neurological history
Short test of mental status
Modified Hachinski scale
Prime MD (physician form)
Neurological examination
and modified UPDRS
Memory
Logical memory (delayed)
Visual reprod (delayed)
AVLT
Executive function
Trails A & B
Digit symbol substitution
Visuospatial
Picture completion
Block design
Language
Boston naming test
Category fluency
Consensus conference

Resources Acquired

- 4000 non-demented subjects
  - 3000 cognitively normal
  - 800 MCI
- 2500 quantitative MRI scans
- ~ 4000 DNA samples
- ~ 4000 frozen plasma/serum samples plus annual samples
- Clinical and performance measures

Extension of MCSA

- Add new subjects older cohort
- Add 1000+ subjects younger cohort
- Continue annual clinical follow-ups
- Continue serial MRI scans
- Collect annual plasma/serum
- Perform 800 CSF's
- Perform 1200 FDG-PET scans
- Perform 1200 PiB PET scans

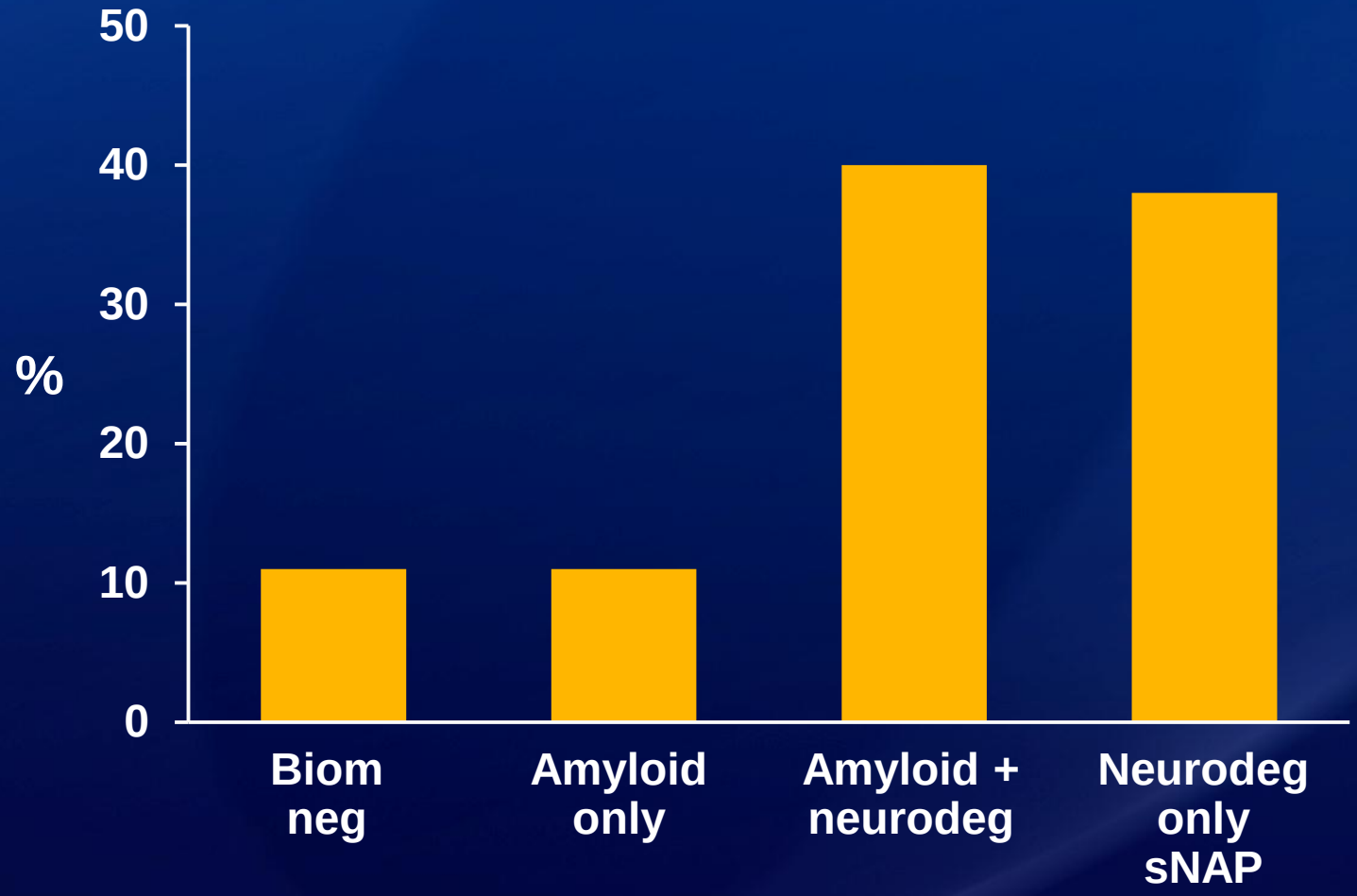
So, How Do the Criteria Fare in the General Population?

MCI Due to AD

Assessing Biomarkers in the Community

- **Biomarker negative**
  - Amyloid neg
  - FDG PET/MRI neg
- **Amyloid positive Neurodeg neg**
  - Amyloid pos
  - FDG PET/MRI neg
- **Amyloid pos Neurodeg pos**
  - Amyloid pos
  - FDG PET/MRI pos
- **Neurodegen only**
  - Amyloid neg
  - FDG PET/MRI pos

All MCI MCSA
Population Frequencies



Petersen et al: Ann Neuro, 2013

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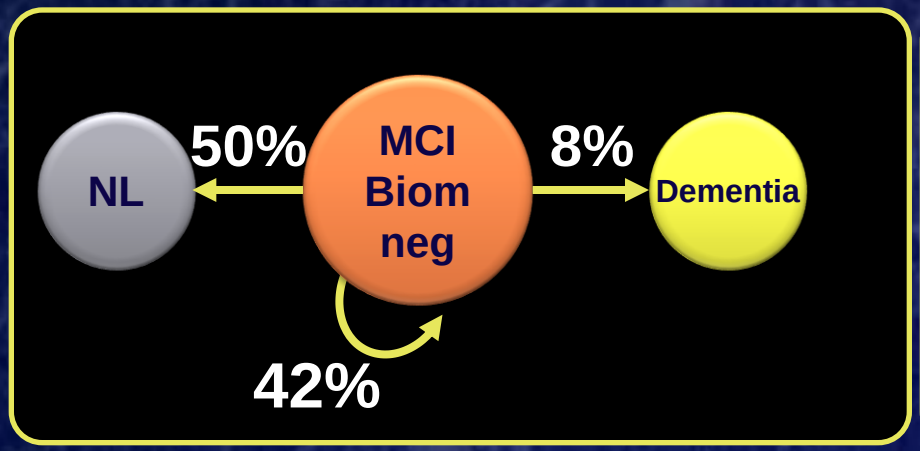
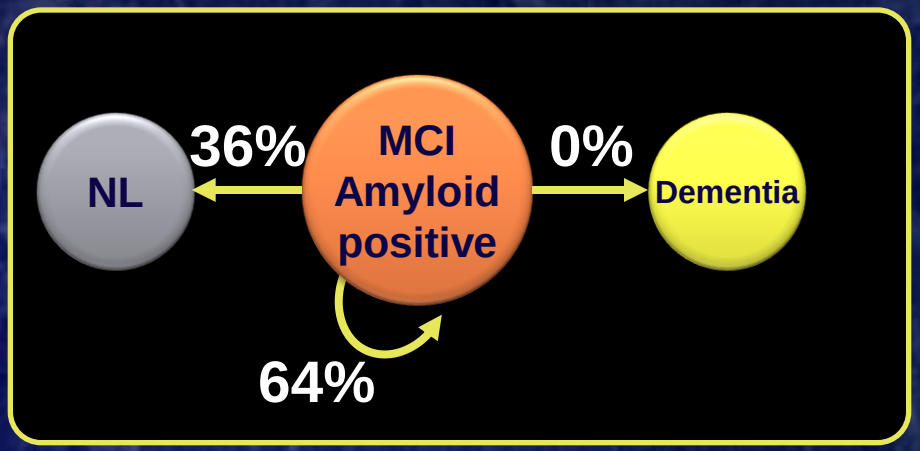
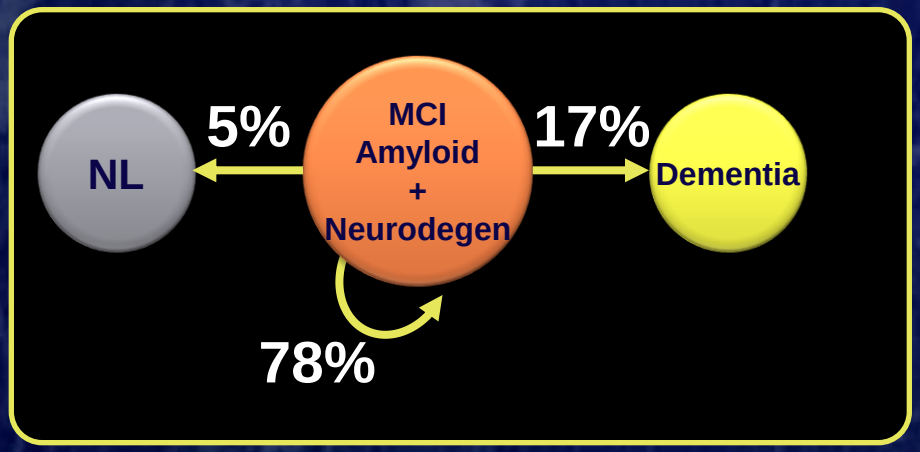
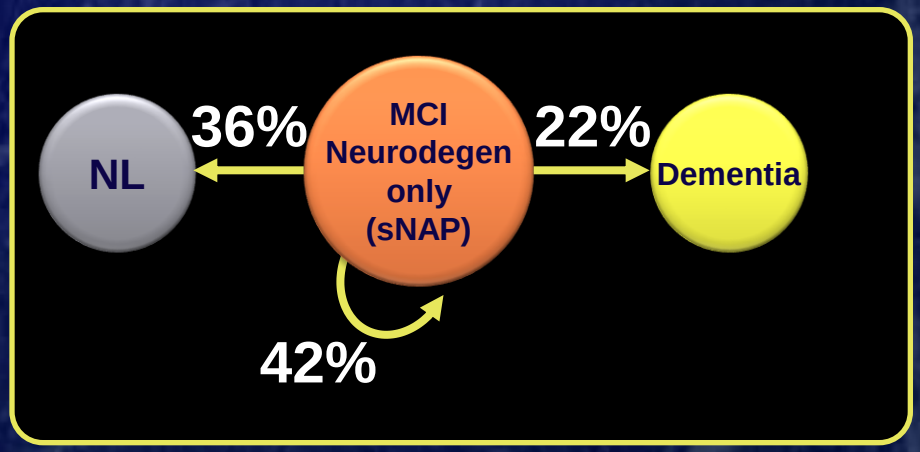
MCSA aMCI
Annual Rates of Change



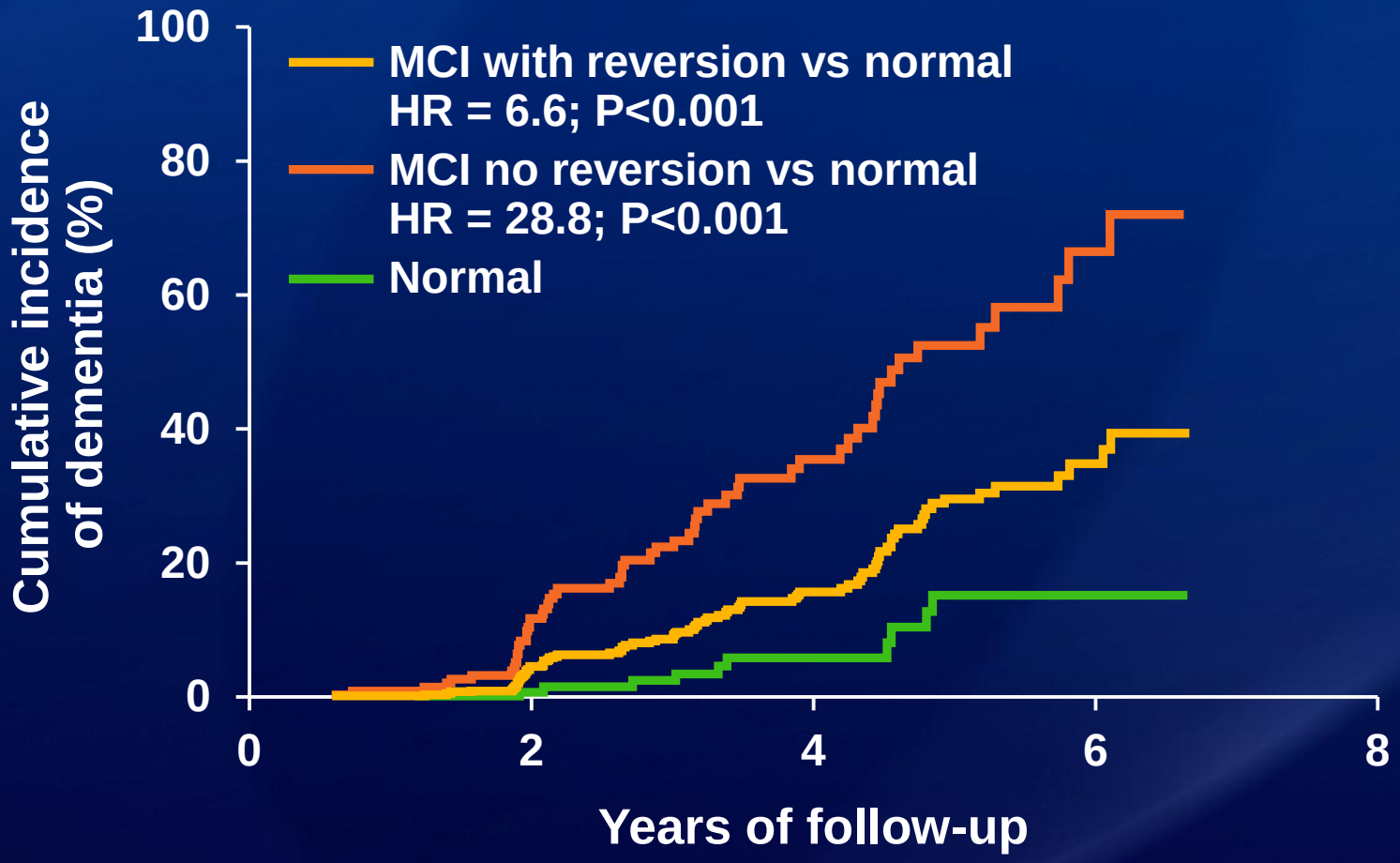






Petersen et al: Ann Neuro, 2013

Risk of Dementia Following Reversion to Normal



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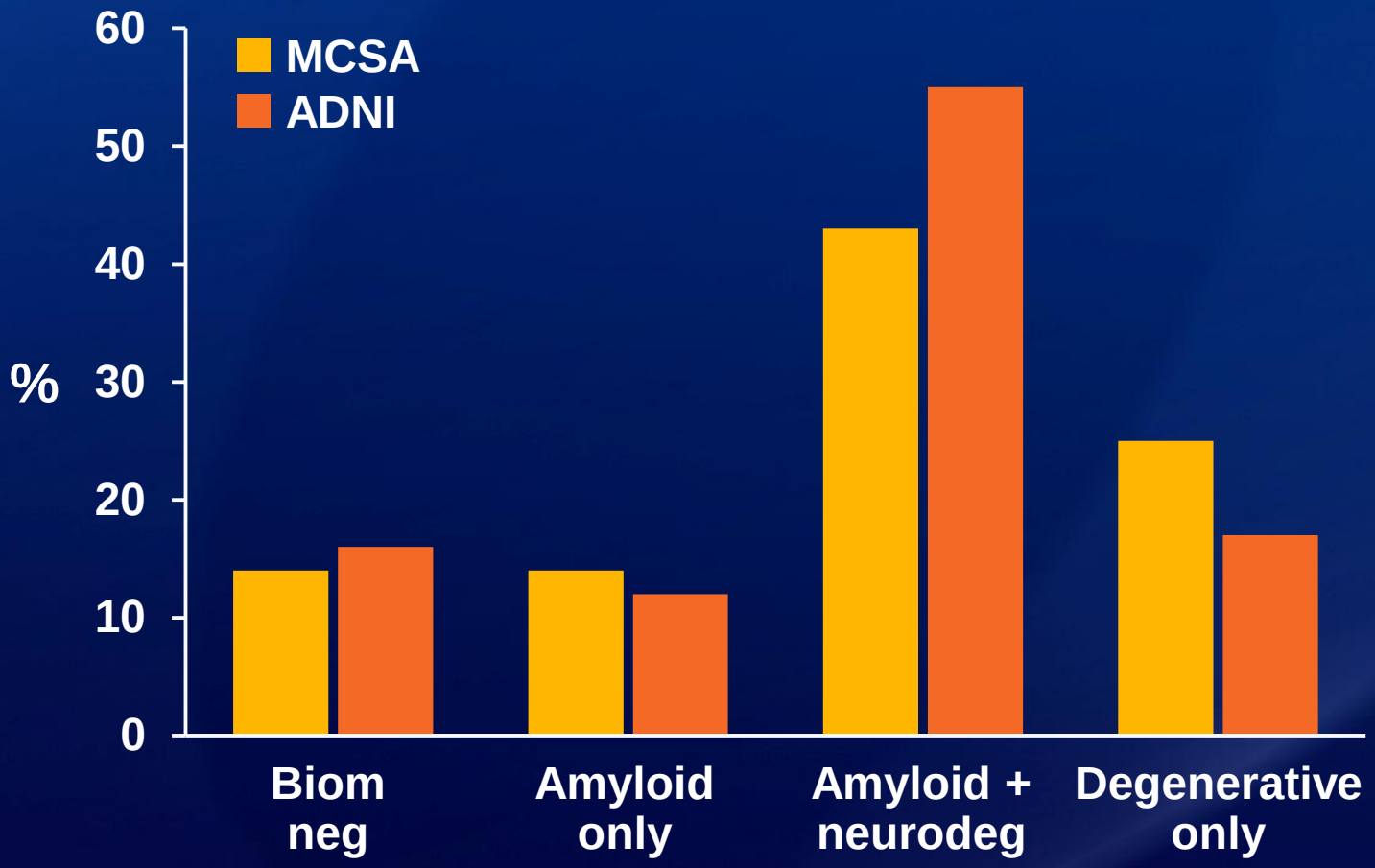
aMCI



Petersen et al: Ann Neuro , 2013

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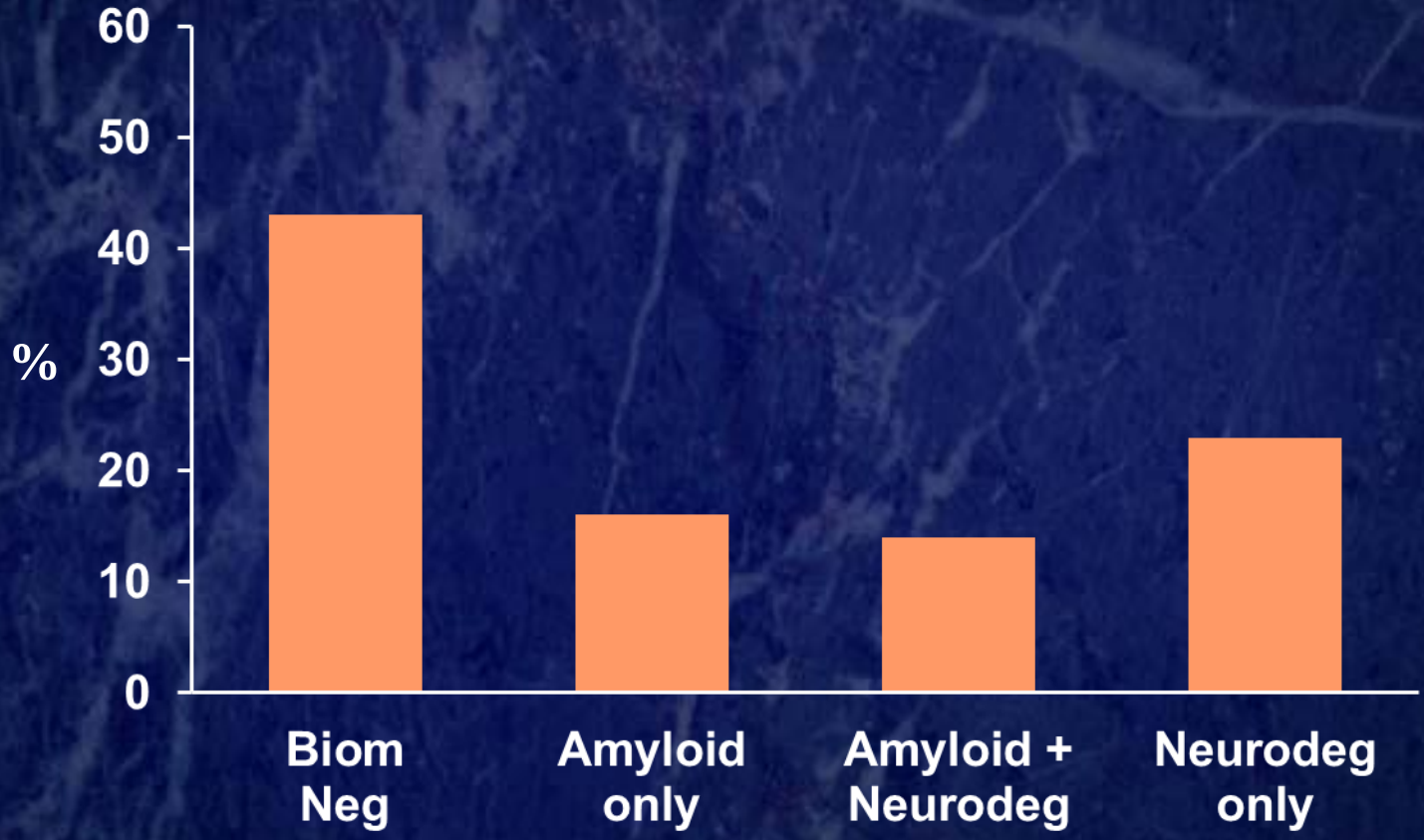
Preclinical AD

Preclinical AD

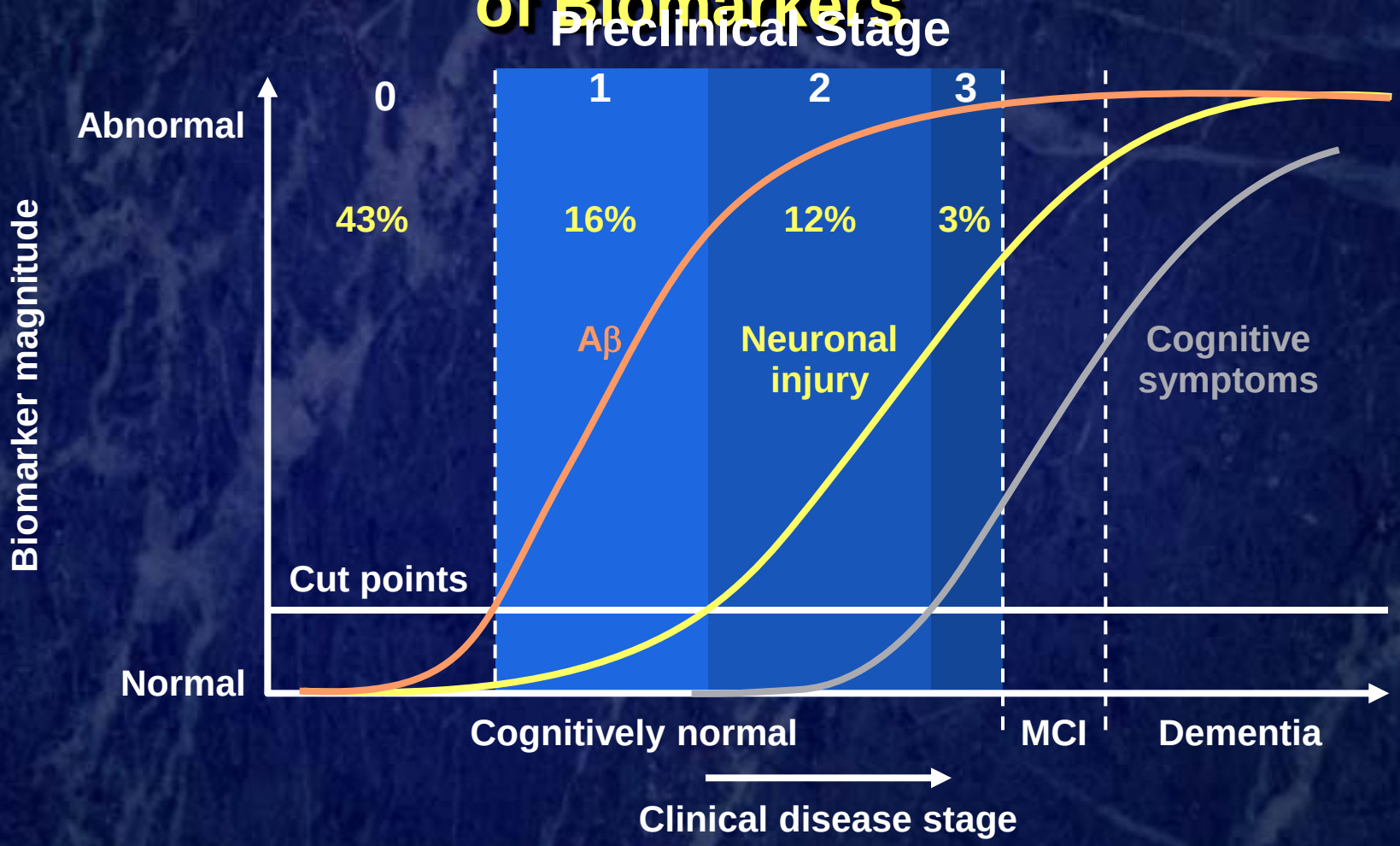
Diagnostic category	Aβ (PET or CSF)	Neuronal injury	Clinical
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive
Stage 0	Negative	Negative	Negative

Sperling et al: 2011

Pre-clinical Normal
Population Frequencies
Jack et al., Ann Neurol, 2012



NIA-AA Preclinical AD Staging in Relation to Our Hypothetical Model of Biomarkers



Jack et al: Lancet Neuro, 2010

Preclinical Alzheimer's Disease and Its Outcome

A Longitudinal Cohort Study

Stephanie J. B. Vos; Chengjie Xiong; Pieter Jelle Visser; Mateusz S. Jasielec; Jason Hassenstab; Elizabeth A. Grant; Nigel J. Cairns; John C. Morris; David M. Holtzman; Anne M. Fagan

Lancet Neurology 12:957, Oct 2013

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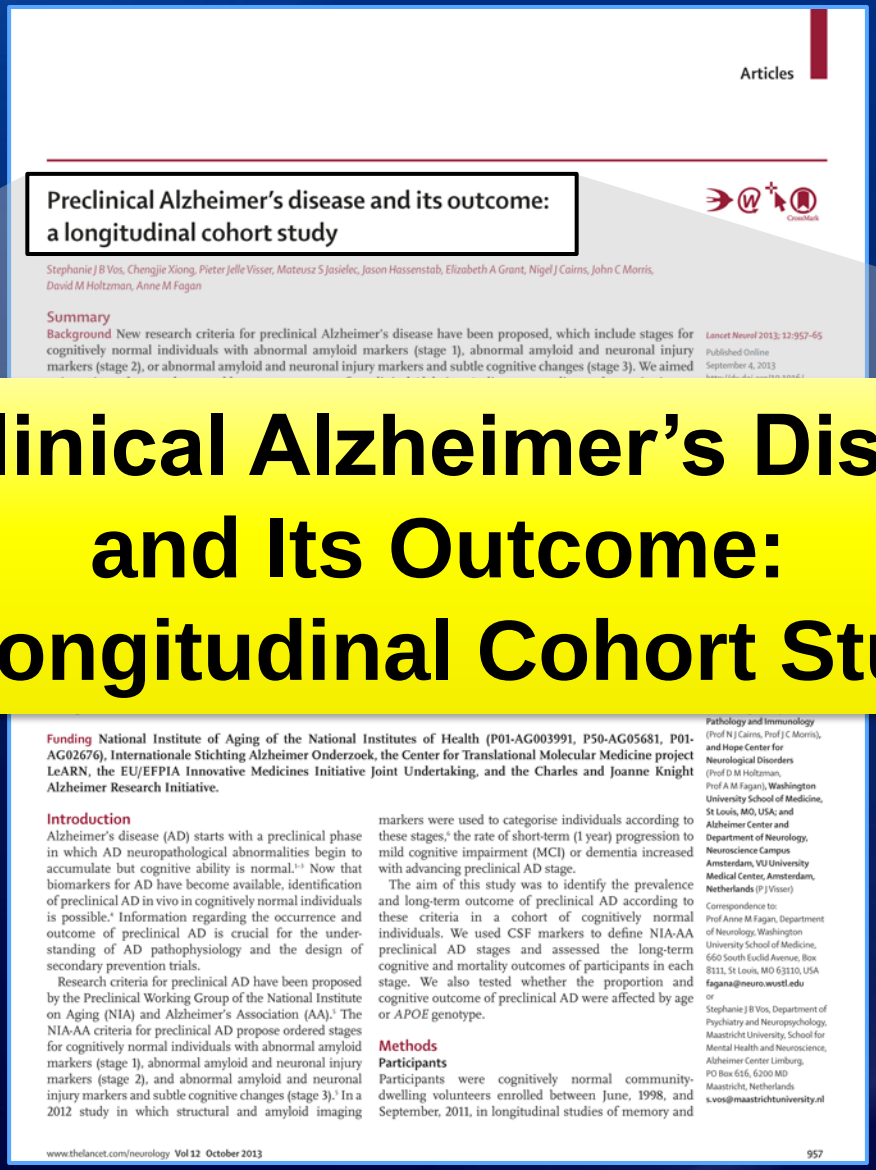

Articles

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

Stephanie J B Vos, Chengjie Xiong, Pieter Jelle Visser, Mateusz S Jasielec, Jason Hassenstab, Elizabeth A Grant, Nigel J Cairns, John C Morris, David M Holtzman, Anne M Fagan

Summary

Background New research criteria for preclinical Alzheimer's disease have been proposed, which include stages for cognitively normal individuals with abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), or abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3). We aimed

Lancet Neurol 2013; 12:957-65
Published Online September 4, 2013

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Introduction

Alzheimer's disease (AD) starts with a preclinical phase in which AD neuropathological abnormalities begin to accumulate but cognitive ability is normal.[1–3] Now that biomarkers for AD have become available, identification of preclinical AD in vivo in cognitively normal individuals is possible.[4] Information regarding the occurrence and outcome of preclinical AD is crucial for the understanding of AD pathophysiology and the design of secondary prevention trials.

Research criteria for preclinical AD have been proposed by the Preclinical Working Group of the National Institute on Aging (NIA) and Alzheimer's Association (AA).[5] The NIA-AA criteria for preclinical AD propose ordered stages for cognitively normal individuals with abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), and abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3).[5] In a 2012 study in which structural and amyloid imaging markers were used to categorise individuals according to these stages,[6] the rate of short-term (1 year) progression to mild cognitive impairment (MCI) or dementia increased with advancing preclinical AD stage.

The aim of this study was to identify the prevalence and long-term outcome of preclinical AD according to these criteria in a cohort of cognitively normal individuals. We used CSF markers to define NIA-AA preclinical AD stages and assessed the long-term cognitive and mortality outcomes of participants in each stage. We also tested whether the proportion and cognitive outcome of preclinical AD were affected by age or *APOE* genotype.

Methods

Participants

Participants were cognitively normal community-dwelling volunteers enrolled between June, 1998, and September, 2011, in longitudinal studies of memory and

Pathology and Immunology (Prof N J Cairns, Prof J C Morris), and Hope Center for Neurological Disorders (Prof D M Holtzman, Prof A M Fagan), Washington University School of Medicine, St Louis, MO, USA; and Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands (P J Visser)

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or
Stephanie J B Vos, Department of Psychiatry and Neuropsychology, Maastricht University, School for Mental Health and Neuroscience, Alzheimer Center Limburg, PO Box 616, 6200 MD Maastricht, Netherlands
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Preclinical Alzheimer's Disease and Its Outcome: A Longitudinal Cohort Study

Lancet Neurology 12:957, Oct 2013

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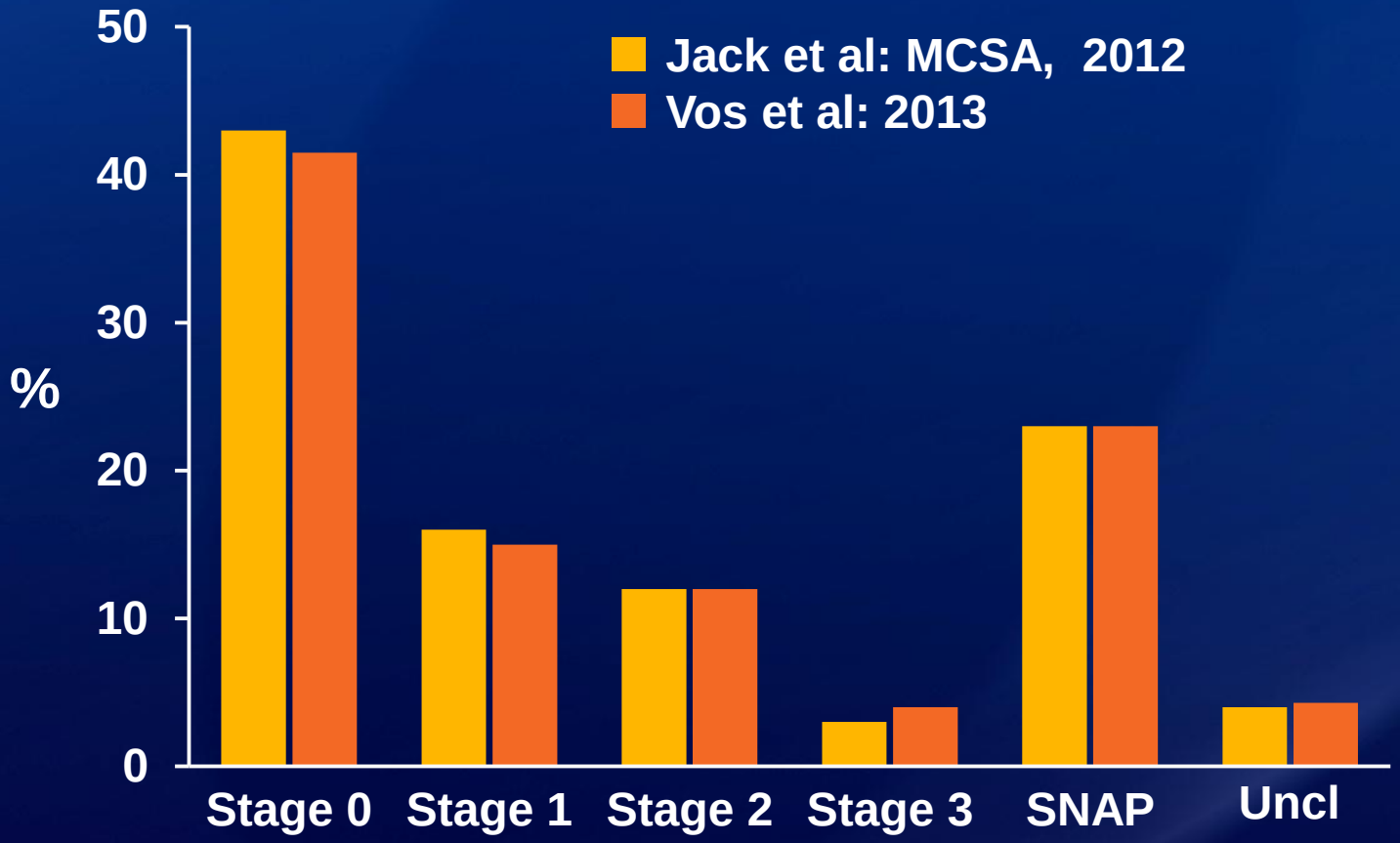
Pre-Clinical AD Stages

Neuroimaging vs CSF



Petersen, L Neur 2013

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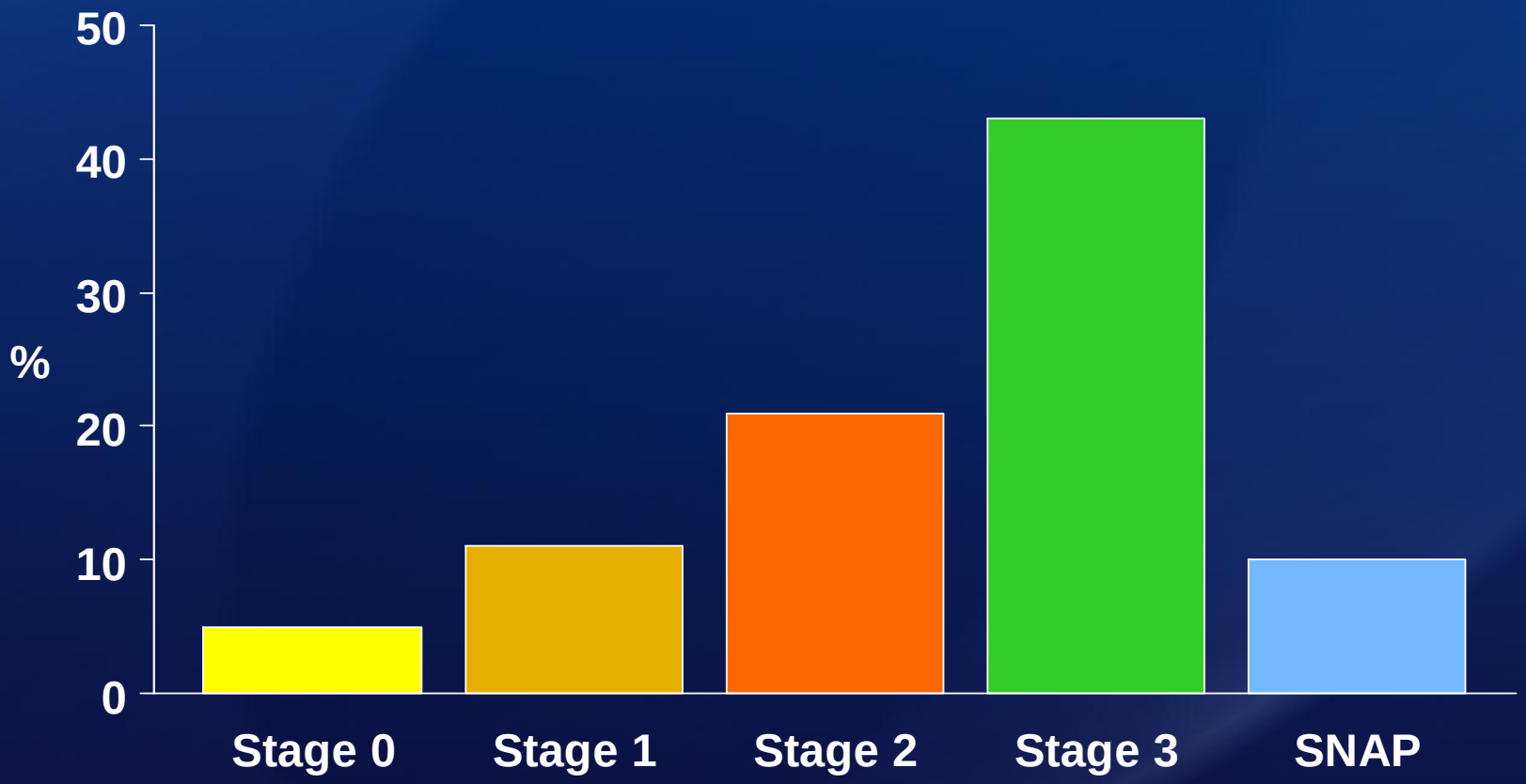
Preclinical Progression to MCI/Dementia

Mayo Clinic Study of Aging



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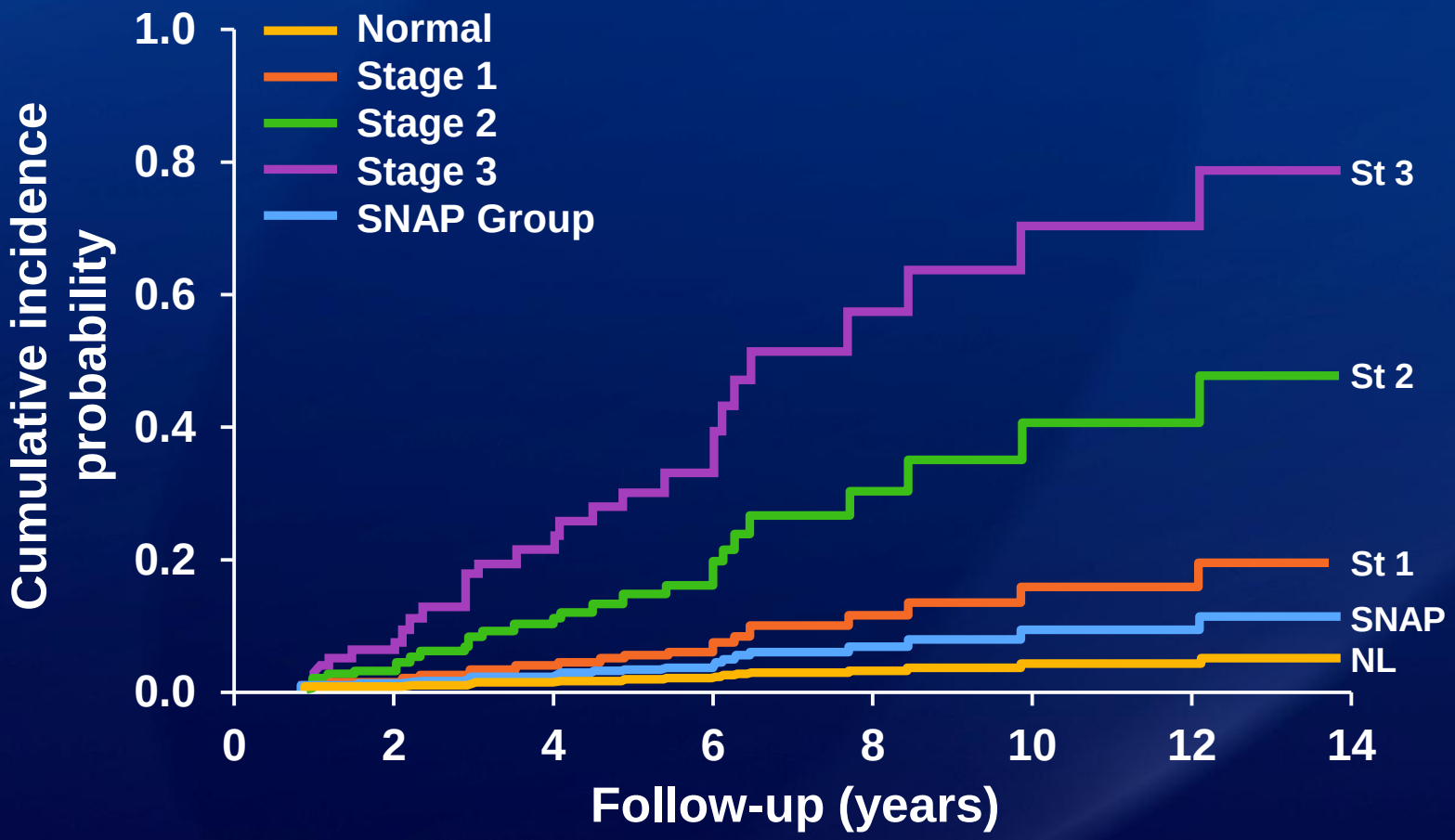
Knopman et al., 2012

Progression to CDR >/= 0.5 by Preclinical Alzheimer's Disease Stage



Vos et al: Lancet Neurol 12:957, 2013

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Amyloid-first and Neurodegeneration-first Profiles Characterize Incident Amyloid PET Positivity

Clifford R. Jack, Jr., Heather J. Wiste, Stephen D. Weigand, David S. Knopman, Val Lowe, Prashanthi Vemuri, Michelle M. Mielke, David T. Jones, Matthew L. Senjem, Jeffrey L. Gunther, Brian E. Gregg, Vernon S. Pankratz, Ronald C. Petersen

Neurology, 2013; 81: 1732-1740

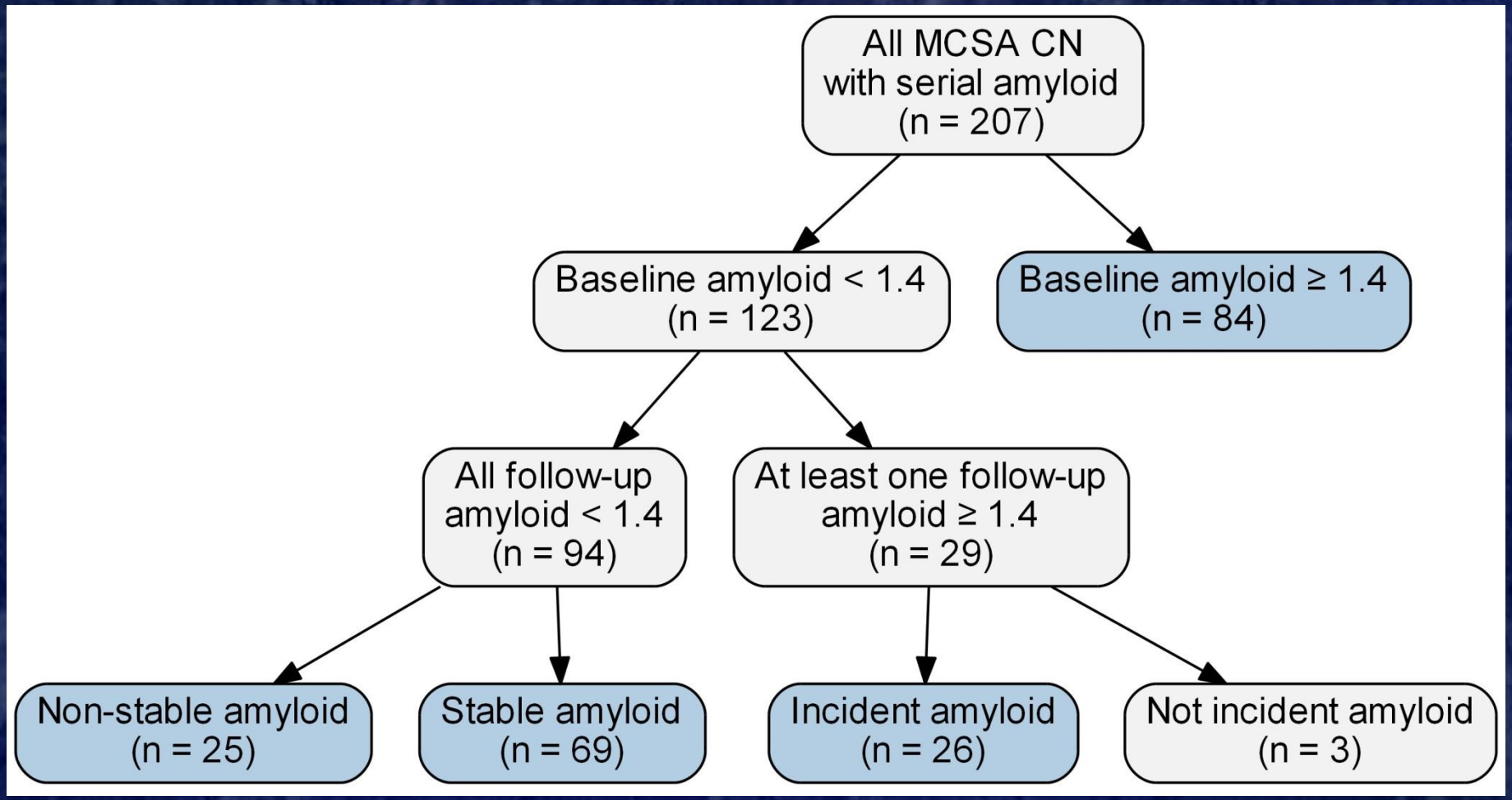
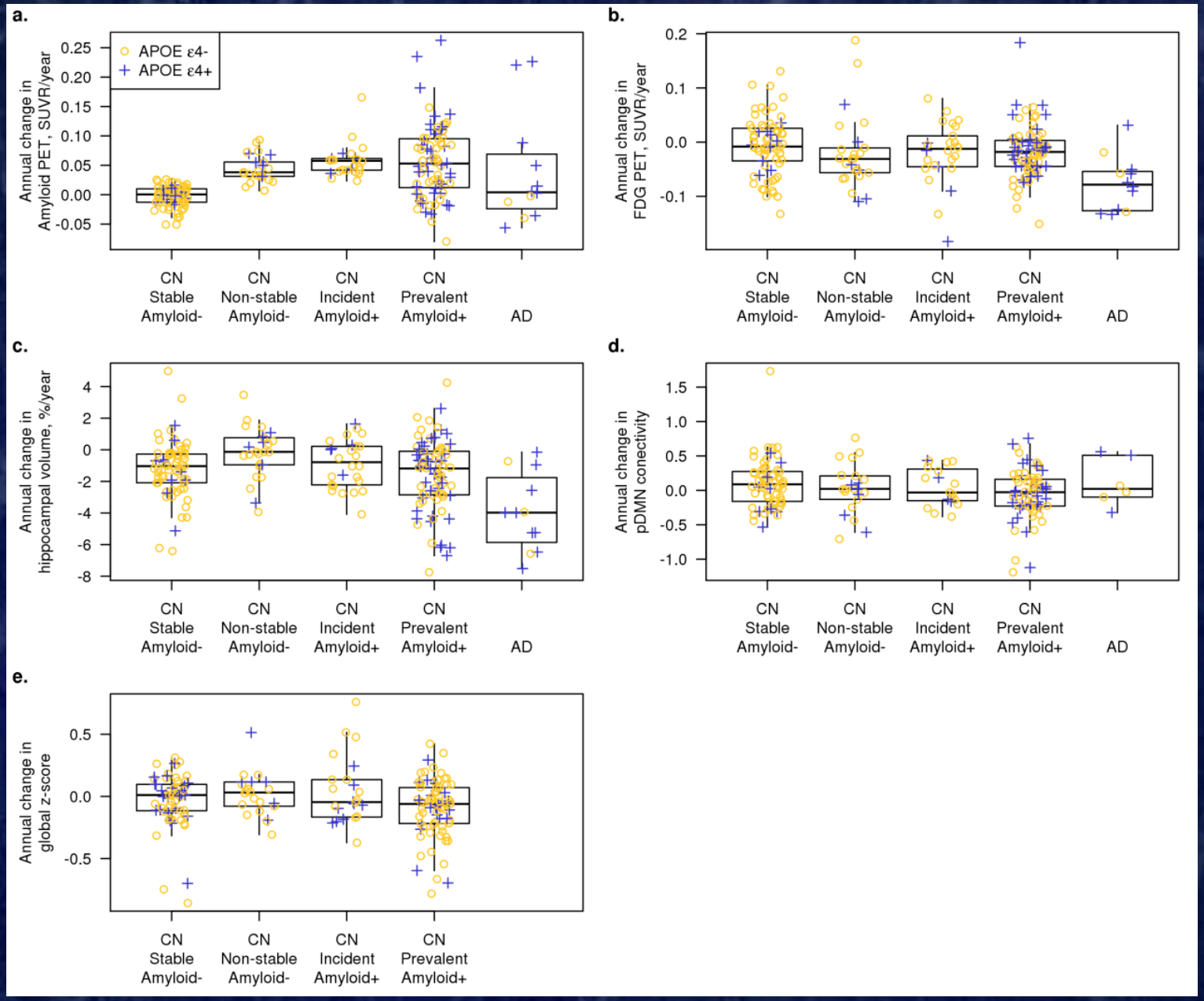


Figure 1. Flow chart.

The CN groups in blue are the focus of this paper.



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Jack et al, Neurology, 2013

Changes in Imaging and Clinical Measures By Amyloid Status

MAYO CLINIC

Brain Advance Access published October 30, 2013

doi:10.1093/brain/awt286 Brain 2013: Page 1 of 11 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease

Yen Ying Lim,[1] Paul Maruff,[1,2] Robert H. Pietrzak,[3] David Ames,[4,5] Kathryn A. Ellis,[1,4,5] Karra Harrington,[1] Nicola T. Lautenschlager,[4,6] Cassandra Szoeke,[5,7] Ralph N. Martins,[8] Colin L. Masters,[1] Victor L. Villemagne[1,9,10] and Christopher C. Rowe[9,10], for the AIBL Research Group

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2 CogState Ltd., Melbourne, Victoria, Australia
3 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
4 Academic Unit for Psychiatry of Old Age, St. Vincent's Health, Department of Psychiatry, The University of Melbourne, Kew, Victoria, Australia
5 National Ageing Research Institute, Parkville, Victoria, Australia
6 School of Psychiatry and Clinical Neurosciences and WA Centre for Health and Ageing, The University of Western Australia, Perth, Western Australia, Australia
7 CSIRO Preventative Health Flagship, Parkville, Victoria, Australia
8 Centre of Excellence for Alzheimer's Disease Research and Care, School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia
9 Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia
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High amyloid has been associated with substantial episodic memory decline over 18 and 36 months in healthy older adults and individuals with mild cognitive impairment. However, the nature and magnitude of amyloid-related memory and non-memory change from the preclinical to the clinical stages of Alzheimer's disease has not been evaluated over the same time interval. Healthy older adults ($n = 320$), individuals with mild cognitive impairment ($n = 57$) and individuals with Alzheimer's disease ($n = 36$) enrolled in the Australian Imaging, Biomarkers and Lifestyle study underwent at least one positron emission tomography neuroimaging scan for amyloid. Cognitive assessments were conducted at baseline, and 18- and 36-month follow-up assessments. Compared with amyloid-negative healthy older adults, amyloid-positive healthy older adults, and amyloid-positive individuals with mild cognitive impairment and Alzheimer's disease showed moderate and equivalent decline in verbal and visual episodic memory over 36 months (d's = 0.47–0.51). Relative to amyloid-negative healthy older adults, amyloid-positive healthy older adults showed no decline in non-memory functions, but amyloid-positive individuals with mild cognitive impairment showed additional moderate decline in language, attention and visuospatial function (d's = 0.47–1.12), and amyloid-positive individuals with Alzheimer's disease showed large decline in all aspects of memory and non-memory function (d's = 0.73–2.28). Amyloid negative individuals with mild cognitive impairment did not show any cognitive decline over 36 months. When non-demented individuals (i.e. healthy older adults and adults with mild cognitive impairment) were further dichotomized, high amyloid-positive non-demented individuals showed a greater rate of decline in episodic memory and language when compared with low amyloid positive non-demented

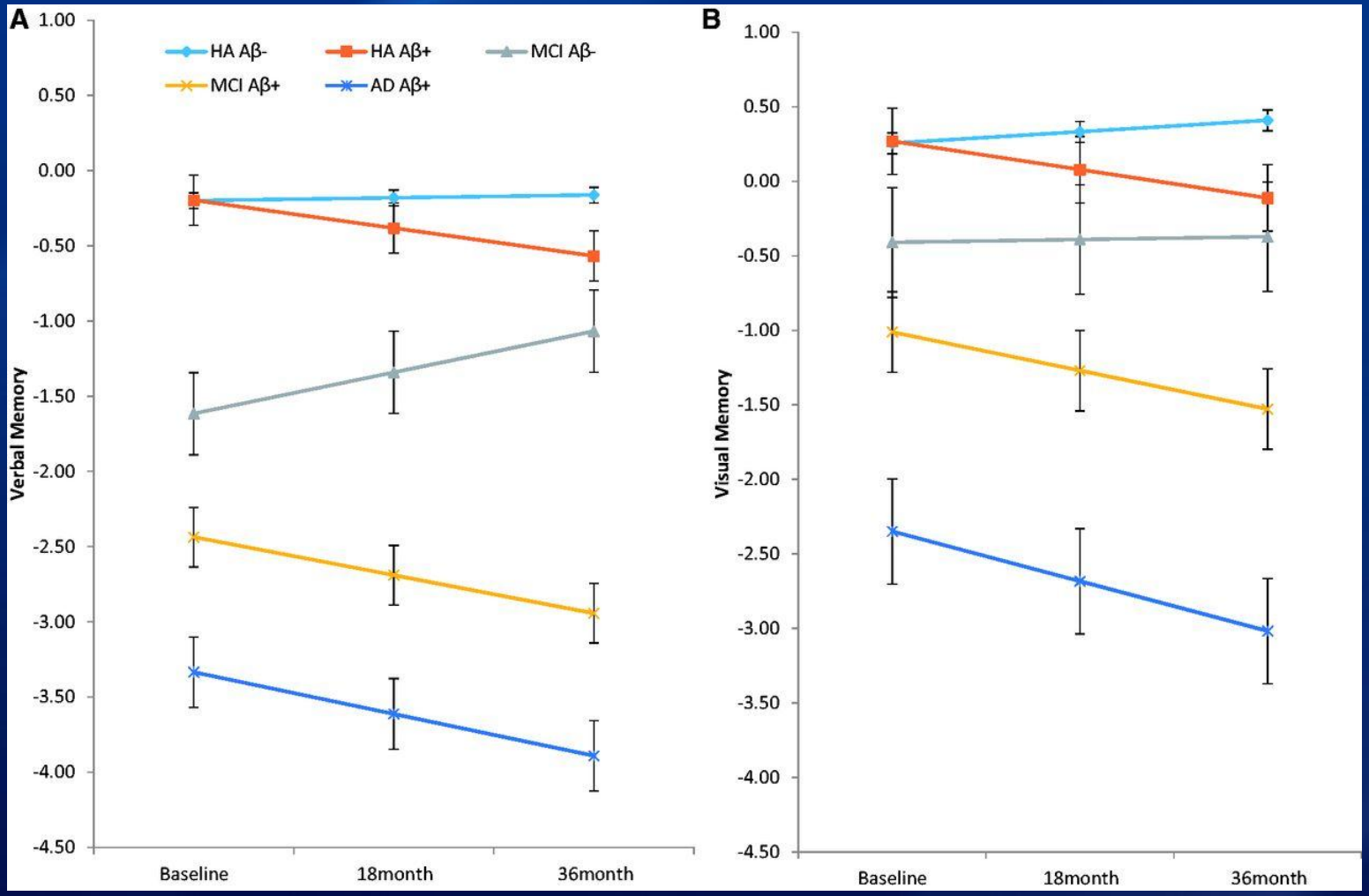

Figure 1.

Linear trend of performance on the verbal memory composite (A) and the visual memory composite (B) for HA-Aβ−, HA-Aβ+, MCI-Aβ−, MCI-Aβ+, and AD-Aβ+ groups, from baseline to 36 months.

Lim YY et al, Brain 2013.

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Mayo Clinic Study of Aging

Role of amyloid status in progression from healthy control to MCI in the general population

MAYO CLINIC

Role of Amyloid in Predicting Progression in Imaging and Cognitive Biomarkers

- Amyloid positive vs. amyloid negative
  - Imaging biomarkers
    - PiB PET
    - FDG PET
    - MR ventricular volume
  - Cognitive measures
    - Global
    - 4 cognitive domains

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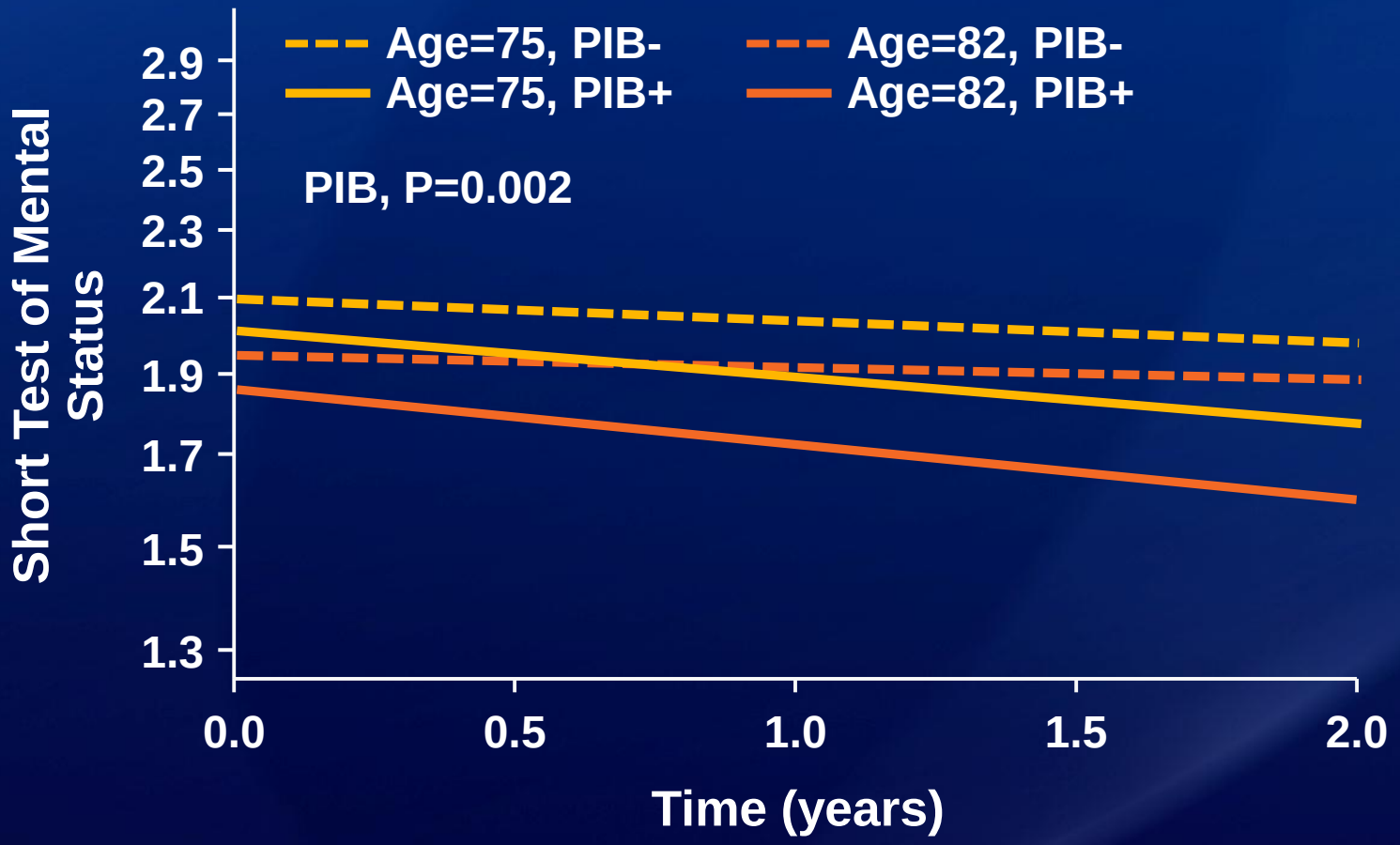
Baseline Characteristics of Subjects with Serial Data

Characteristic	Serial Cognitive Data (n = 484)	Serial Imaging Scans (n = 200)
Age, years, median (IQR)	78 (75, 82)	78 (75, 82)
Male, no. (%)	269 (56)	121 (60)
APOE e4 carrier, no (%)	120 (25)	57 (28)
Education, years, median (IQR)	14 (12, 16)	14 (12, 16)
Short Test Score, median (IQR)	35 (34, 37)	35 (33, 37)
Cognitive domain z-scores, median (IQR)		
Global	0.75 (0.16, 1.25)	0.71 (0.13, 1.23)
Memory	0.70 (0.02, 1.38)	0.70 (-0.04, 1.32)
Language	0.50 (-0.02, 1.02)	0.47 (-0.04, 0.99)
Attention	0.59 (-0.00, 1.11)	0.59 (0.02, 0.99)
Visuospatial	0.64 (0.02, 1.22)	0.61 (0.00, 1.20)
PIB ratio, median (IQR)	1.38 (1.31, 1.63)	1.38 (1.30, 1.61)
FDG ratio, median (IQR)	1.40 (1.30, 1.50)	1.40 (1.30, 1.50)
Hippocampal volume, cm3, median (IQR)	7.0 (6.4, 7.5)	7.0 (6.4, 7.5)
Hippocampal volume/TIV, median (IQR)	0.47 (0.43, 0.52)	0.47 (0.42, 0.52)
Number of follow-up visits, %		
1	261 (54)	171 (86)
2	181 (37)	28 (14)
3	29 (6)	1 (0)
4	10 (2)	0 (0)
5	3 (1)	0 (0)

Change in STMS by PiB Over Time



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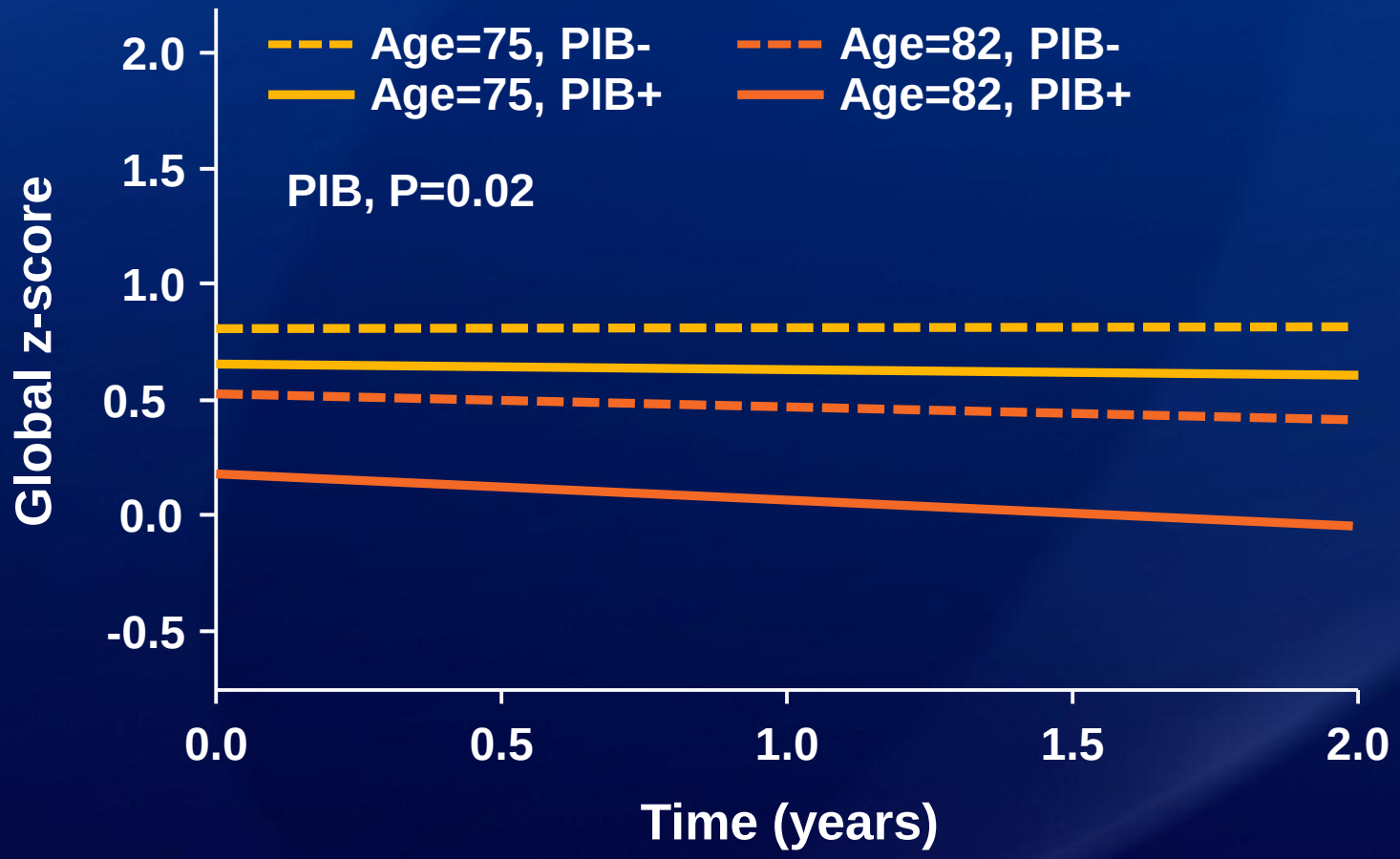
Change in Global Cognition by PiB Over Time



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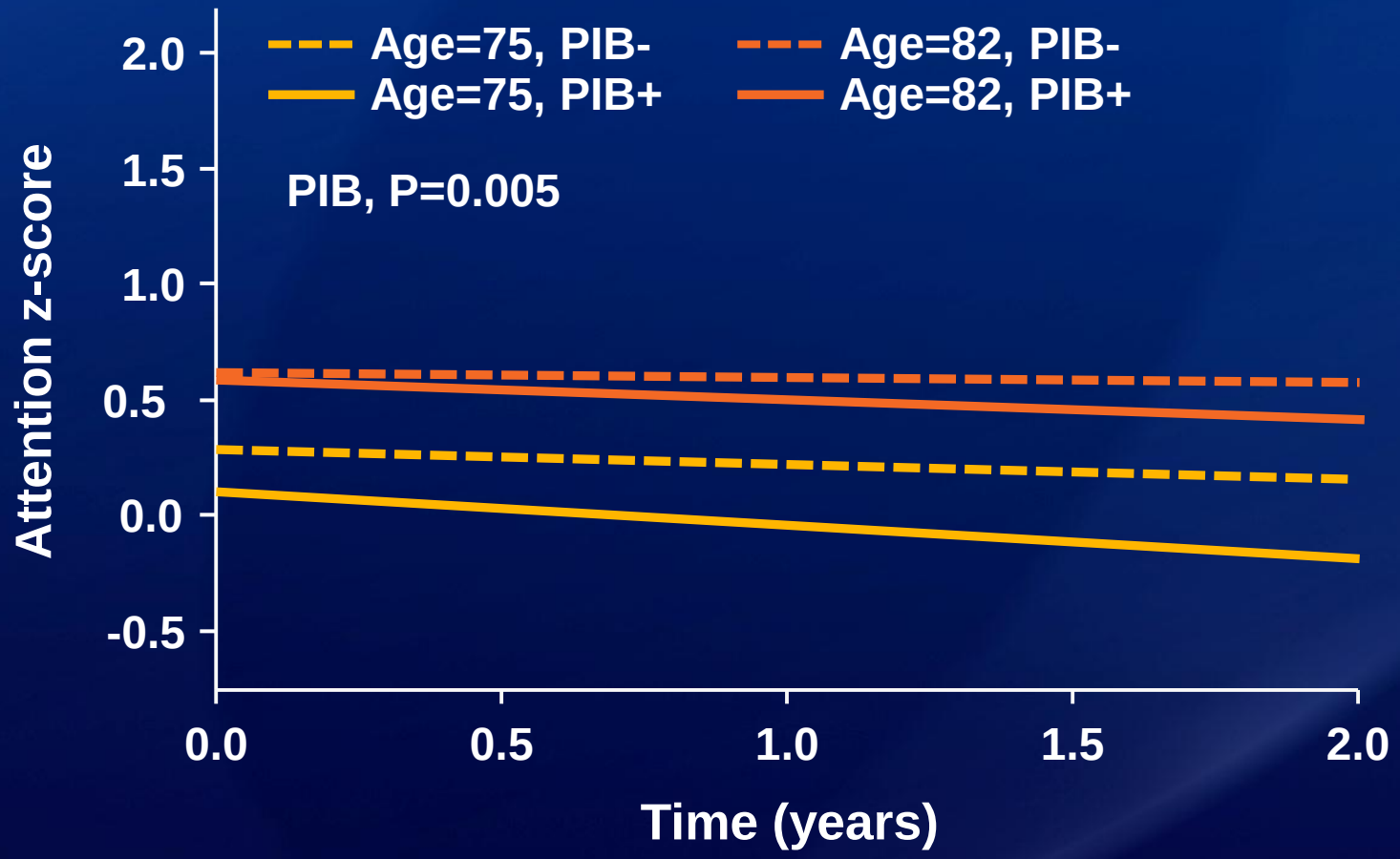
Change in Attention by PiB Over Time



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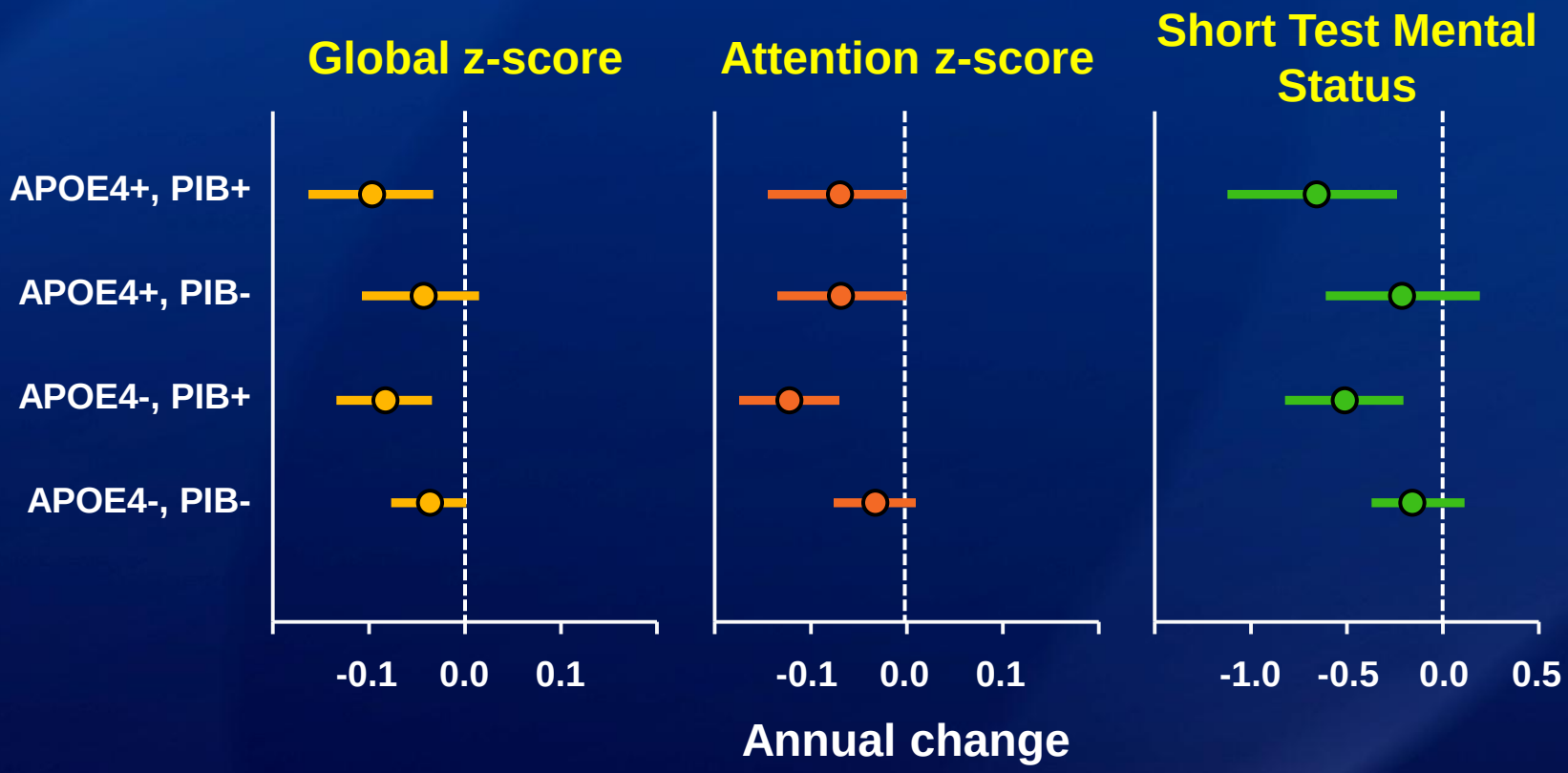
ApoE and PiB
Cognitive Measures



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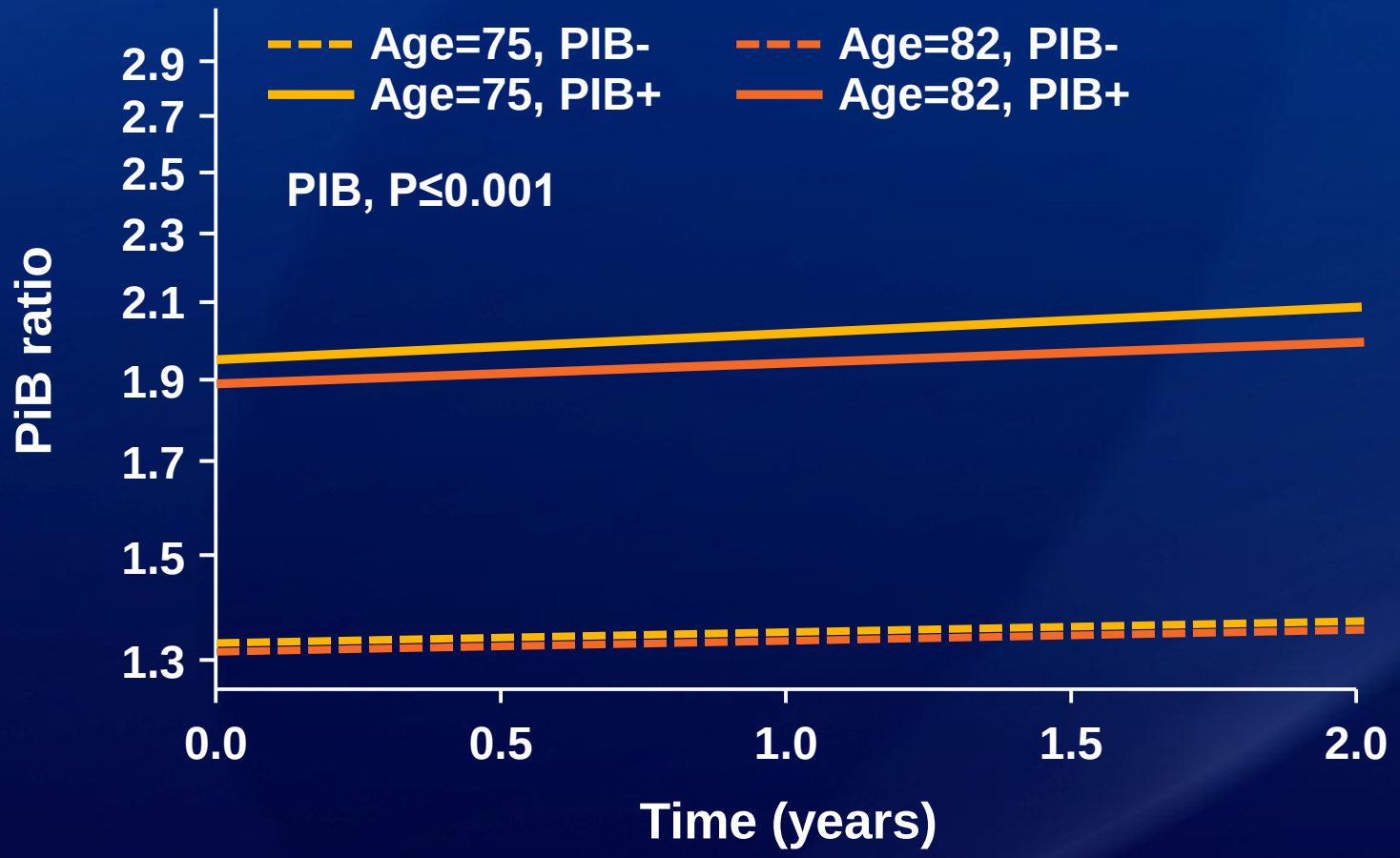
Change in PiB Levels by PiB Over Time



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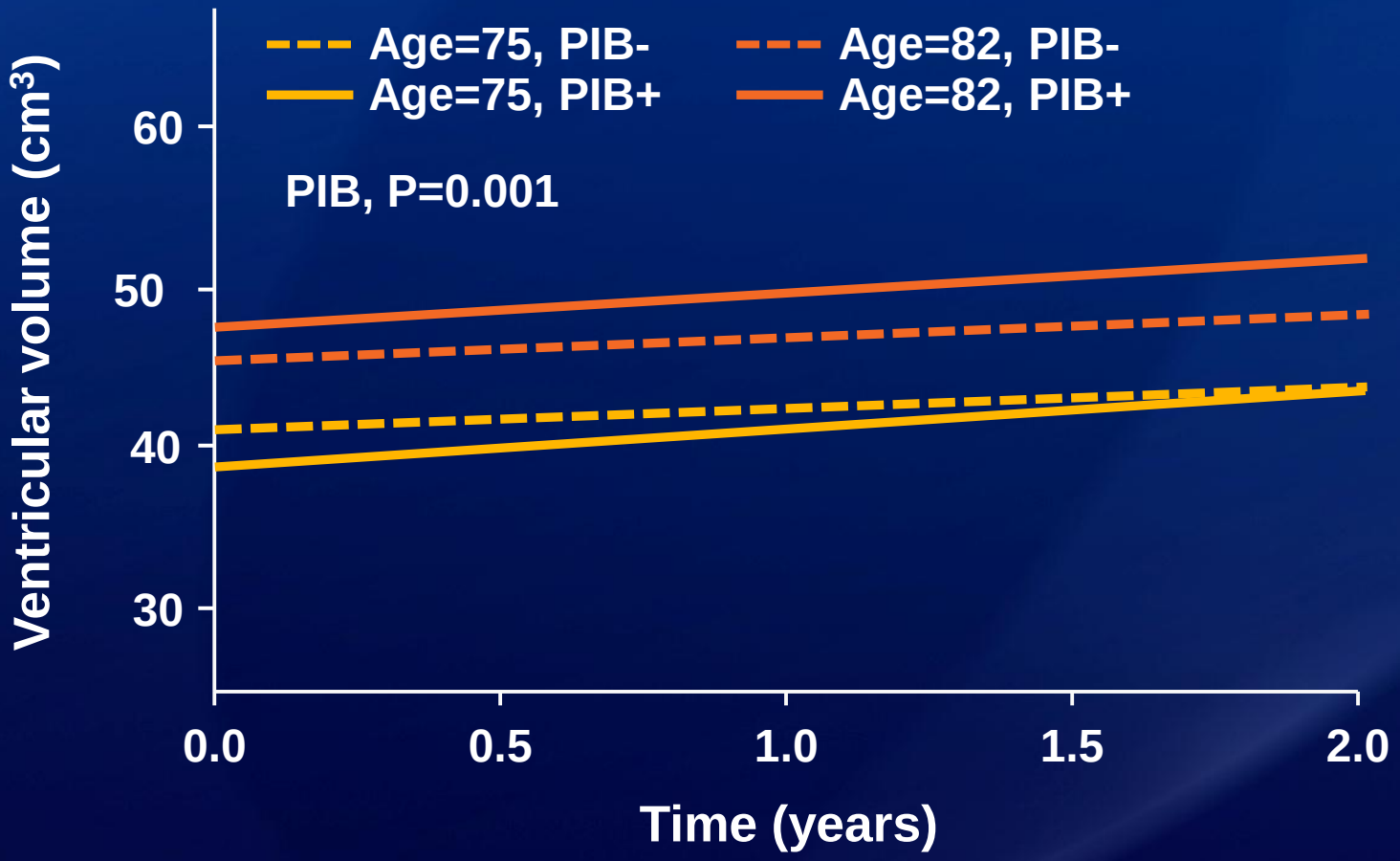
Change in Ventricular Volume by PiB Over Time



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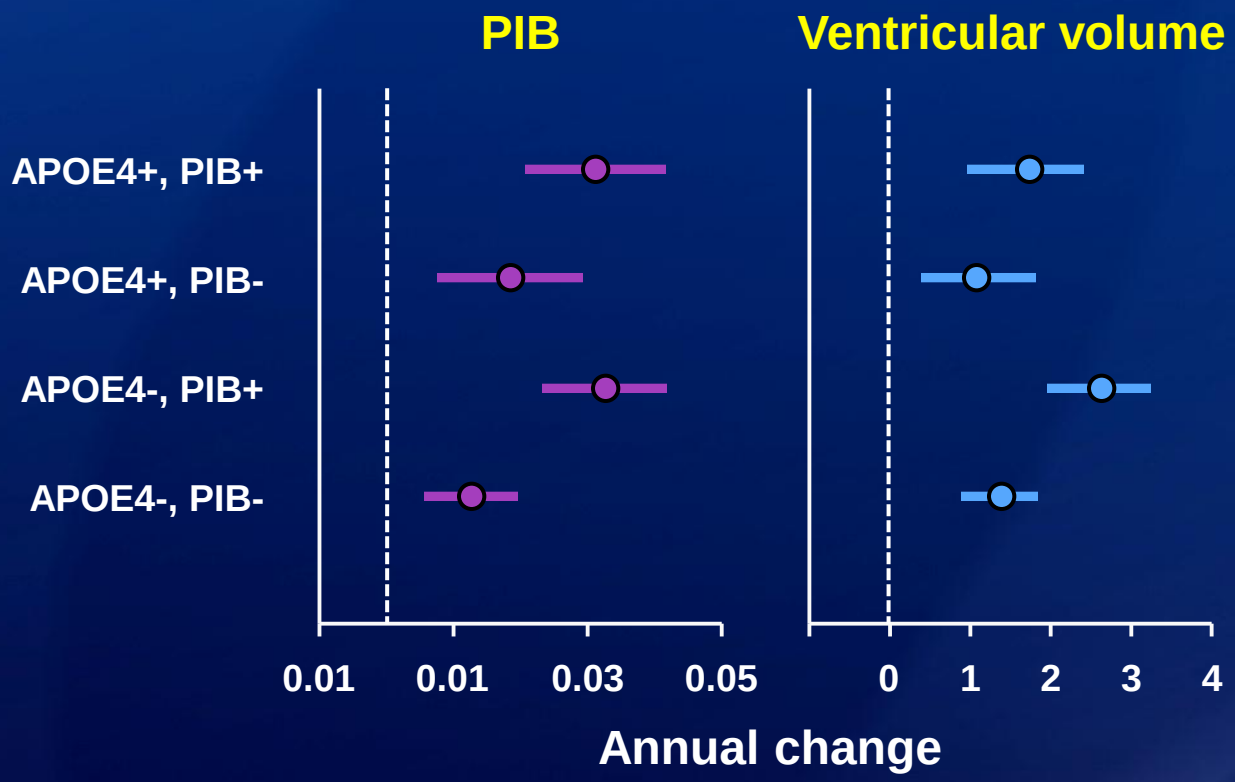
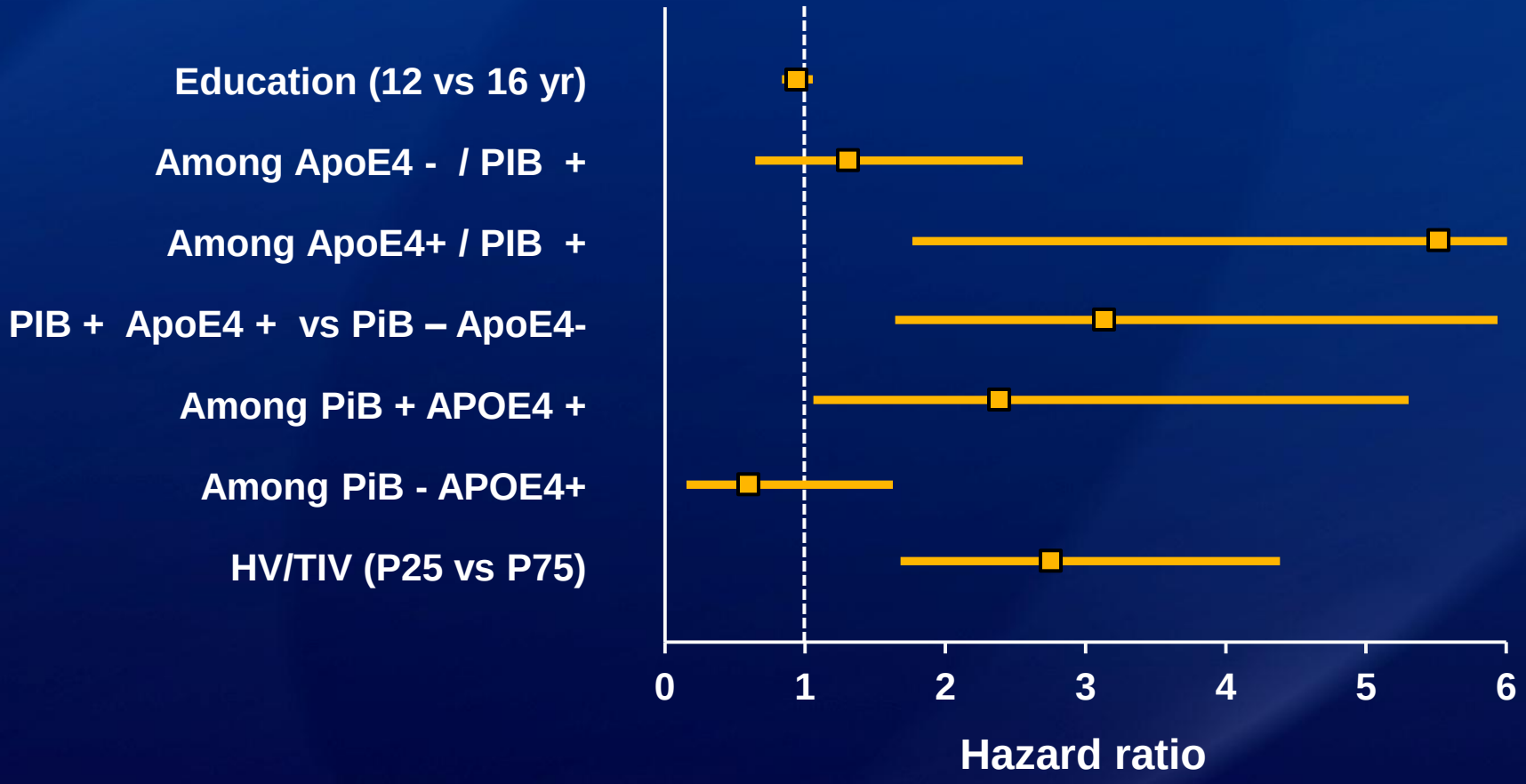
ApoE and PiB Imaging Biomarkers



Education, PBI by ApoE Interaction and Hippocampal Volume



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Evolving Field on Biomarkers

- **Pre-clinical**
  - Amyloid alone slow progression
  - Amyloid plus neurodegeneration
  - Amyloid plus ApoE4 additive
- **MCI**
  - Amyloid alone slow progression
  - Amyloid plus neurodegeneration

Mayo Clinic AD Research

Rochester

Brad Boeve

Dave Knopman

Cliff Jack

Val Lowe

Bob Ivnik

Mary Machulda

Michelle Mielke

Rosebud Roberts

Walter Rocca

Shane Pankratz

Jenny Whitwell

Kejal Kantarci

Joe Parisi

Eric Tangalos

Jacksonville

Neill Graff-Radford

Steve Younkin

Dennis Dickson

John Lucas

Tanis Ferman

Rosa Rademakers

Nilufer Taner-Erketin

Len Petrucelli

Guojin Bu

Otto Pedraza

Scottsdale

Rick Caselli

Bryan Woodruff

Yonas Geda

Thank You

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