Overview of the AD Prodrome: Implications for Patient Selection and Study Design

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Disclosure Statement (09-10)

- Sources of Research Support
  1. National Institute on Aging
  2. Anonymous Foundation
  3. Elan

- Consulting Relationships
  1. AstraZeneca
  2. Bristol-Myers Squibb
  3. Elan
  4. Genentech
  5. Lilly
  6. Merck
  7. Novartis
  8. Pfizer
  9. Schering Plough
  10. Wyeth

- Fees > $10,000

  None

- Stock Equity

  None

- Speaker's Bureaus

  None

- Editorial Boards

  Alzheimer's Disease & Associated Disorders

  Annals of Neurology

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Defining Alzheimer's Disease

- Alzheimer's disease (AD) refers to the neurodegenerative brain disorder regardless of clinical status

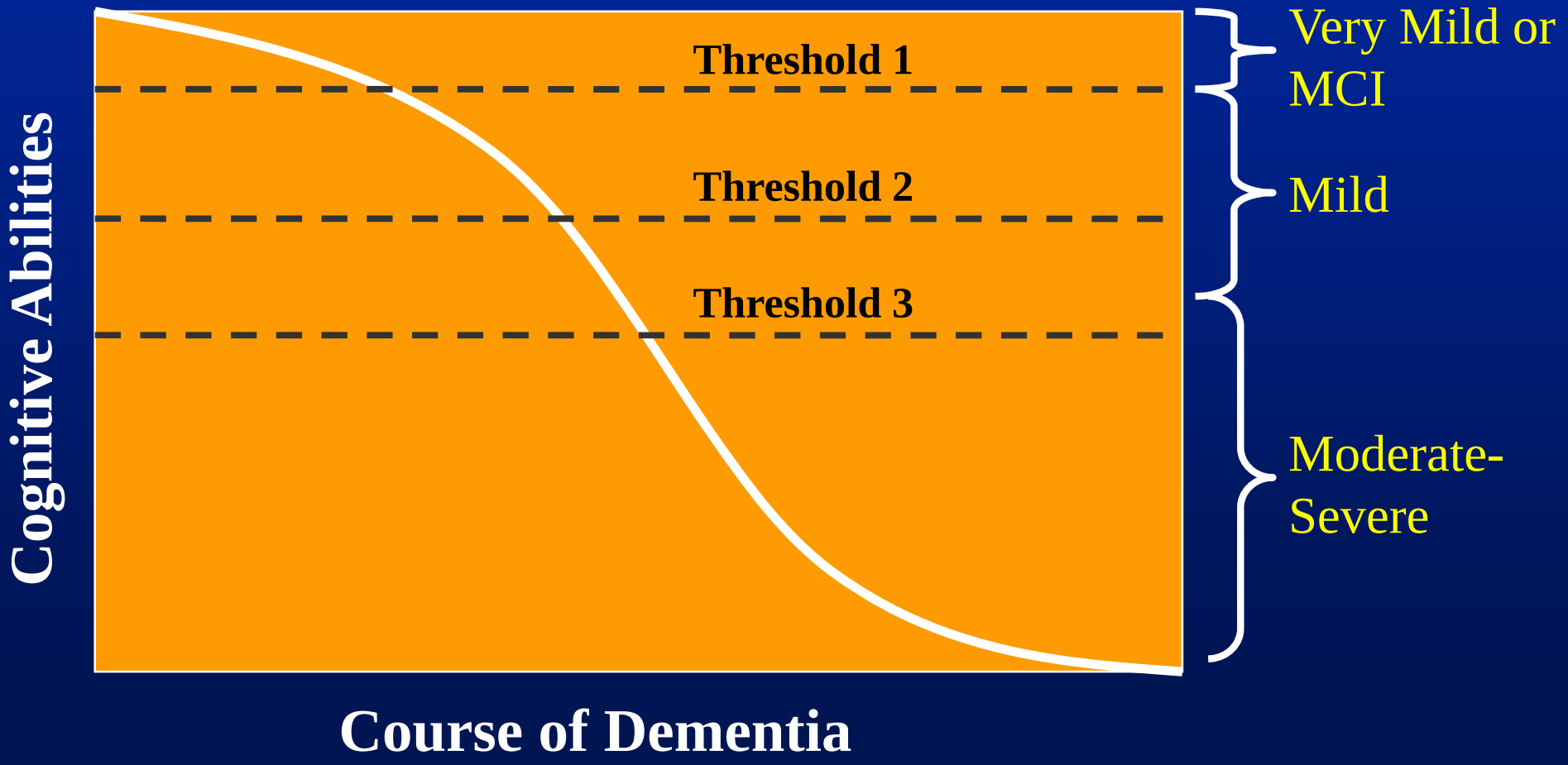
- AD can be conceptualized as having two major stages
  - Preclinical (presymptomatic)
  - Symptomatic
    - Prodromal (incipient)
    - Dementia of the Alzheimer type

Symptomatic AD

- Prodromal AD typically is distinguished from DAT by "failure to meet the threshold for dementia", implying a dichotomous condition of "no dementia" vs "dementia"
- BUT: AD is marked by continuous neuronal deterioration. Using a threshold to determine clinical status is arbitrary, ambiguous, and variably applied
- Dementia requires functional impairment caused by cognitive loss (ie, intraindividual decline, using one's previously attained level of function as the control)
  - "Impairment" depends on adequacy of information base and clinician's "threshold"

Diagnostic Thresholds for Dementia

Dementia results from progressive neuronal deterioration, from minimal to extensive. Conventional diagnosis draws a line in its course, labeling one side as demented and the other not.



Prodromal AD

- Generally staged as CDR 0.5; commonly characterized as “Mild Cognitive Impairment” (MCI) or “Cognitive Impairment, No Dementia” (CIND)
- “Impairment” for these conditions is determined by inter-individual comparison of cognitive test performance (often for episodic memory) rather than decline from previously attained levels; false positives and negatives
- Etiology not considered; MCI/CIND encompass nonAD dementias, reversible causes of cognitive impairment, and some low-performing normal individuals
- Hence, MCI/CIND define inherently heterogeneous samples

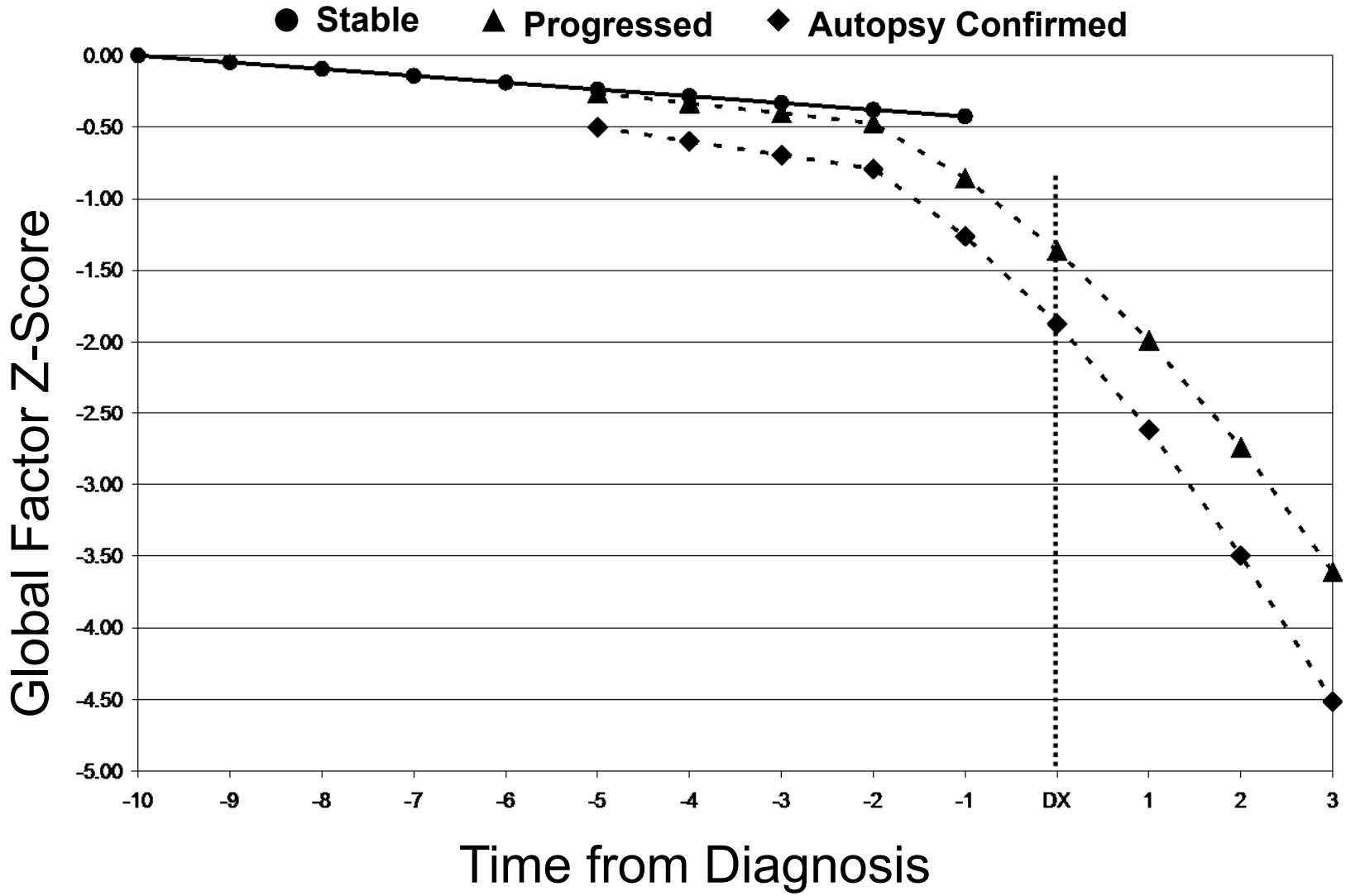
Two Approaches to Reduce Heterogeneity in Prodromal AD

- Use informant-based clinical assessment to capture intraindividual decline resulting in functional impairment (subtle) and provide etiologic diagnosis
  - Neuropathological confirmation of AD in 92% of CDR 0.5 individuals diagnosed with DAT (Storandt et al., Neurology 2006)
- Use arbitrary cognitive cut points to define “impairment” and incorporate biomarkers to establish likelihood that AD is causative (Dubois et al., Lancet Neurology 2007)

Ascertainment Bias in Prodromal AD

- Deleterious effects of preclinical AD on cognition lowers group norms used to determine impairment (Sliwinski et al., J Gerontol B Psychol Sci 2006)
- Reliance on divergence from group norms for diagnosis of prodromal AD fails to include persons in initial symptomatic stages (cutpoints are too lenient)
- Reliance on episodic memory deficit excludes persons in initial symptomatic stages with non-memory deficits (Johnson et al., Arch Neurol 2009)

Longitudinal Change in Global and Domain-specific Factor Scores



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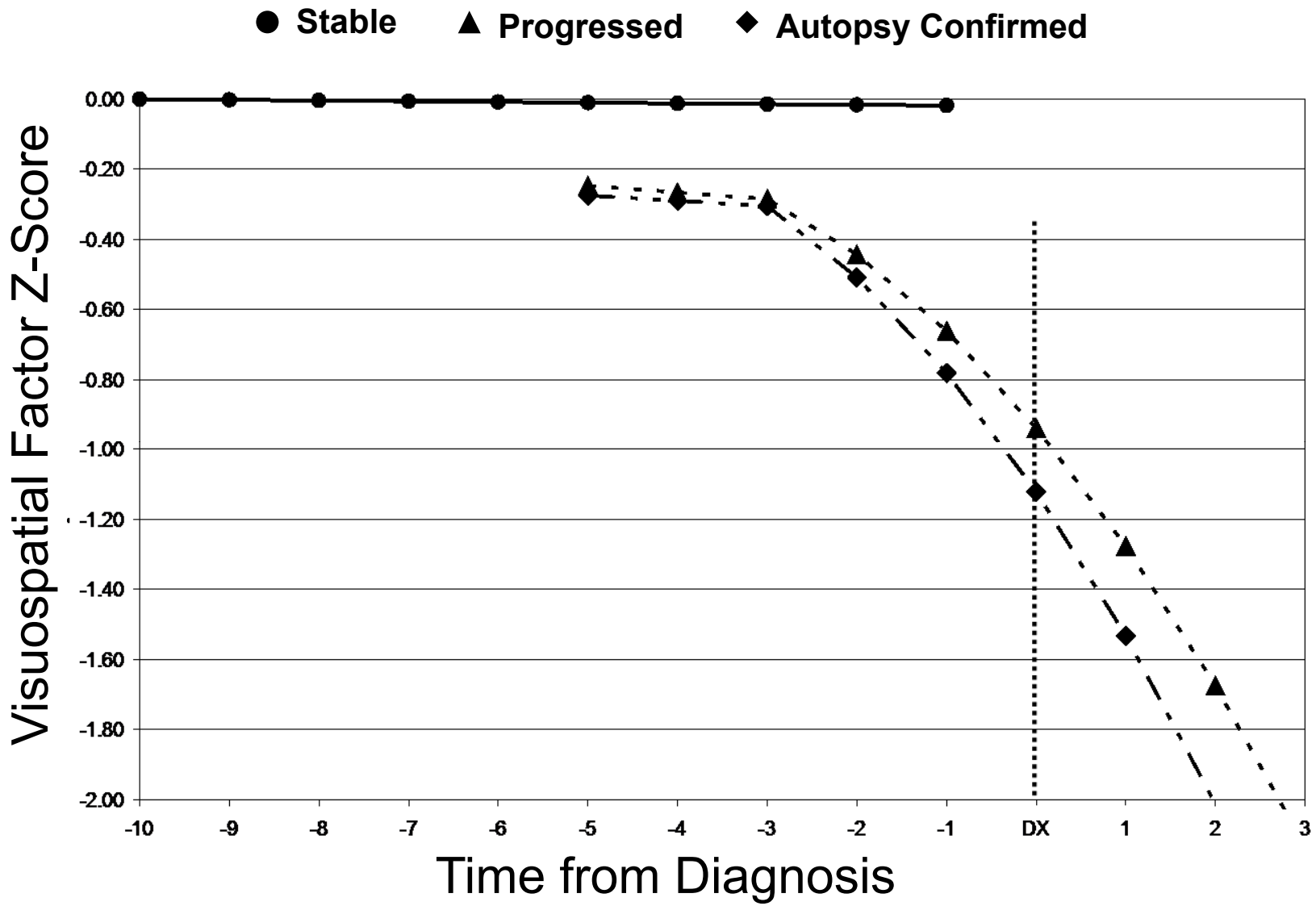


Hypothetical relationships of aging, preclinical AD, and AD

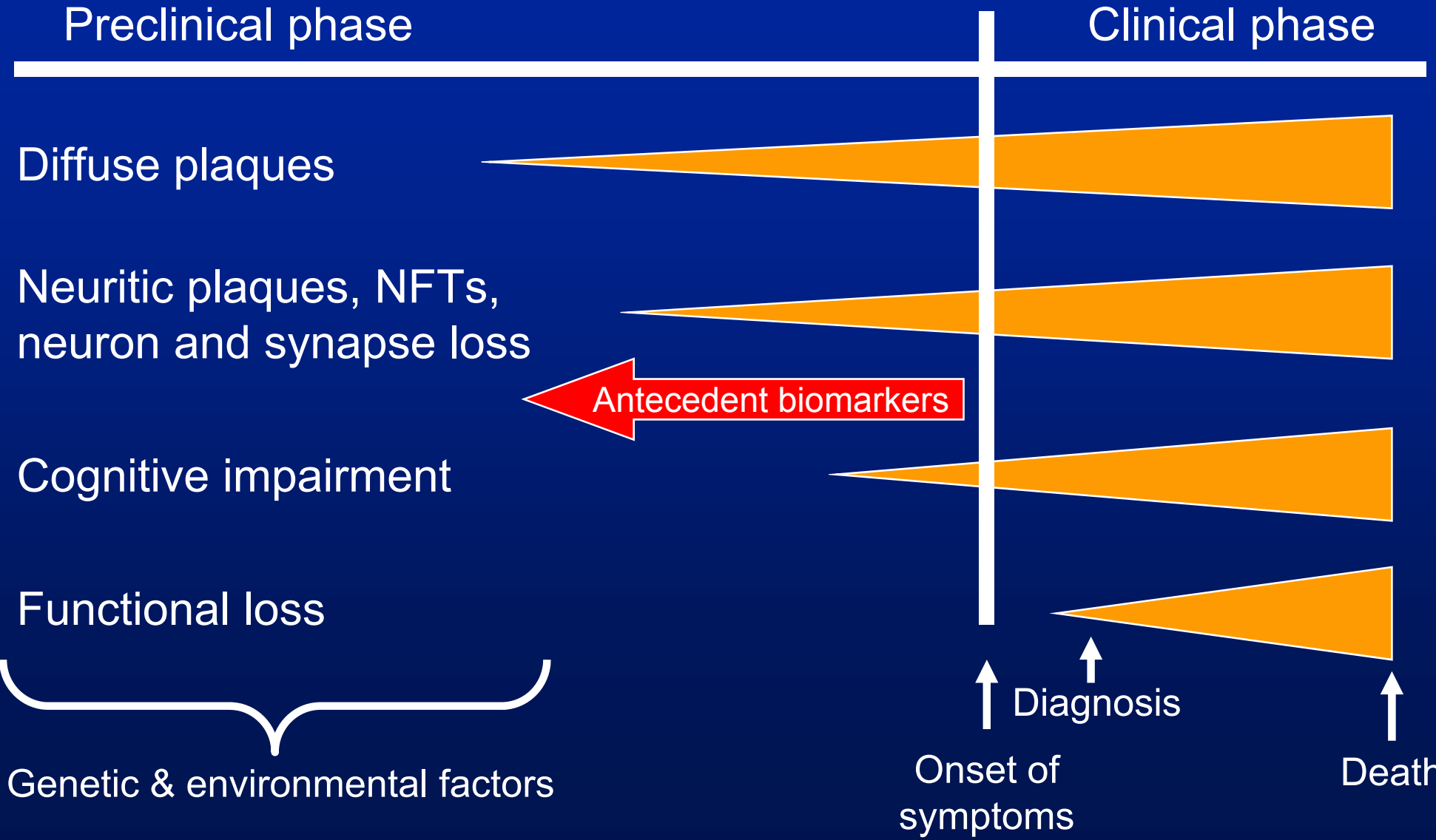
	Aging	Preclinical AD	Very Mild AD
Plaques in neocortex	None or a few diffuse plaques	Many neuritic & diffuse plaques	Many neuritic & diffuse plaques
Tangles in entorhinal cortex & hippocampus/CA1	Few to many (increases w/age)	Many	Many
Cell loss in entorhinal cortex & hippocampus/CA1	None	Little to none	Substantial (30%-60%)
Clinical diagnosis	Normal, CDR 0	Normal, CDR 0	Very mild dementia or MCI, CDR 0.5
Pathological diagnosis	Normal	AD	AD

Price and Morris, Ann Neurol 1999;45:358-368; Price JL et al, Arch Neurol 2001;58:1395-1402; Morris and Price, J Molecular Neurosci 2001;17:101-118

Preclinical Alzheimer's Disease

- Premise: AD pathologic process operates for many years before producing symptoms (i.e., dementia)
- Key corollary: Preclinical AD is not benign; affected individuals will develop symptomatic AD if they live long enough
- Time to symptomatic AD is influenced by brain and cognitive reserve and factors yet unknown

Chronic Disease Model of AD



Potential Indicators of Preclinical AD (Biomarkers)

- Cognitive – absence of learning effect; attentional profiles; response latency; intraindividual variability
- Personality – neuroticism; conscientiousness
- Genetics – apoE genotype; genomics
- Fluid biomarkers – assays for plasma and CSF Aβ40/42, tau, and p-tau; proteomics/metabolomics/lipidomics
- Neuroimaging – multiple modalities, including MRI (volume, shape, cortical thickness; whole brain and regional volumes) and PET imaging with amyloid tracers (e.g., PIB)

Molecular and Fluid Biomarkers Detect Preclinical AD

- CSF signature of AD: reduced $A\beta_{42}$, elevated tau and p-tau
- Amyloid imaging tracers (e.g., Pittsburgh Compound B, or PIB)
- Strong inverse relationship between CSF $A\beta_{42}$ and PIB amyloid burden
- PIB amyloid burden increases as a function of the 2 known risk factors for AD, age and APOE4?

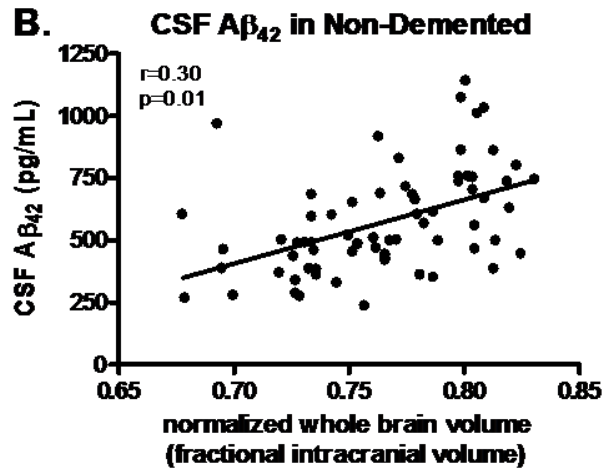
Fagan et al., Ann Neurol 2006; Fagan et al., Arch Neurol 2007; Fagan et al., Ann Neurol 2009; Morris et al., Ann Neurol 2010

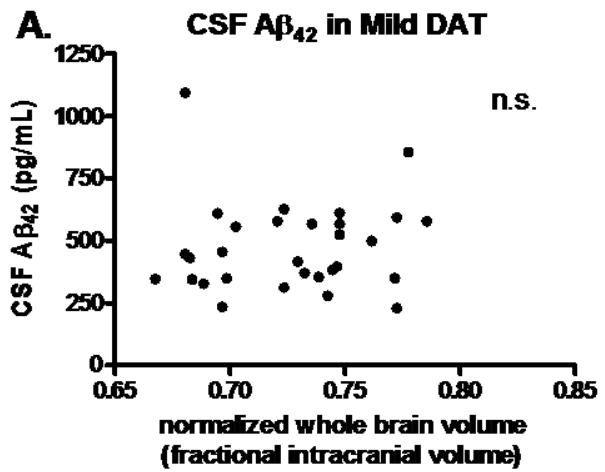
Preclinical AD is Not Benign

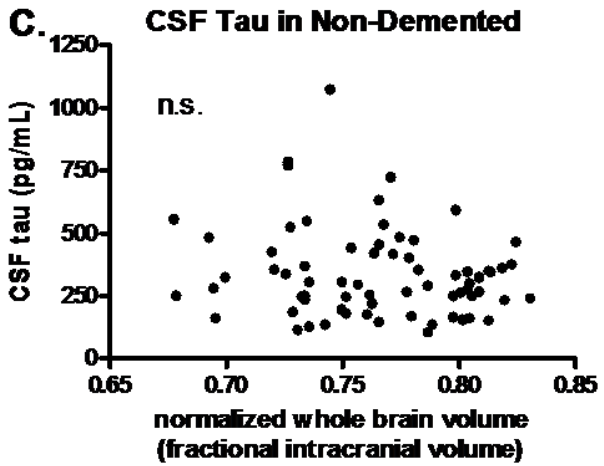
- Reduced CSF levels of $A\beta_{42}$ in cognitively normal people is associated with brain atrophy
- Elevated PIB amyloid burden is associated with
  - Longitudinal cognitive decline
  - Regional brain atrophy
  - Cortical thinning

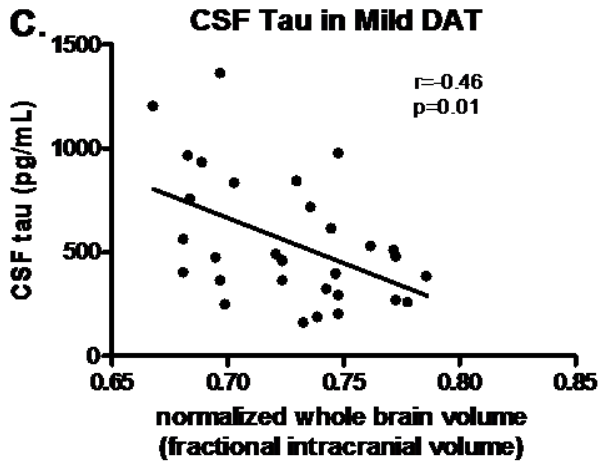
Fagan et al., Ann Neurol 2009; Dickerson et al., Cerebral Cortex 2009; Storandt et al., Arch Neurol, 2009

Structural Brain Change Correlates with CSF Aβ Levels in Nondemented Aging *Fagan AM et al, Ann Neurol 2009*



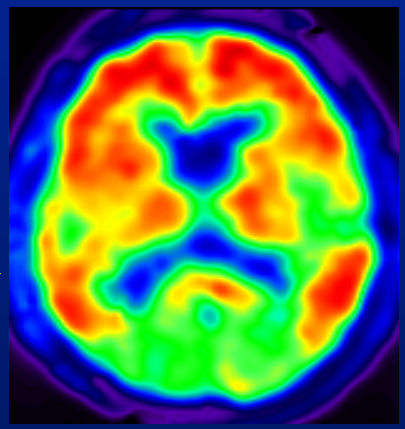


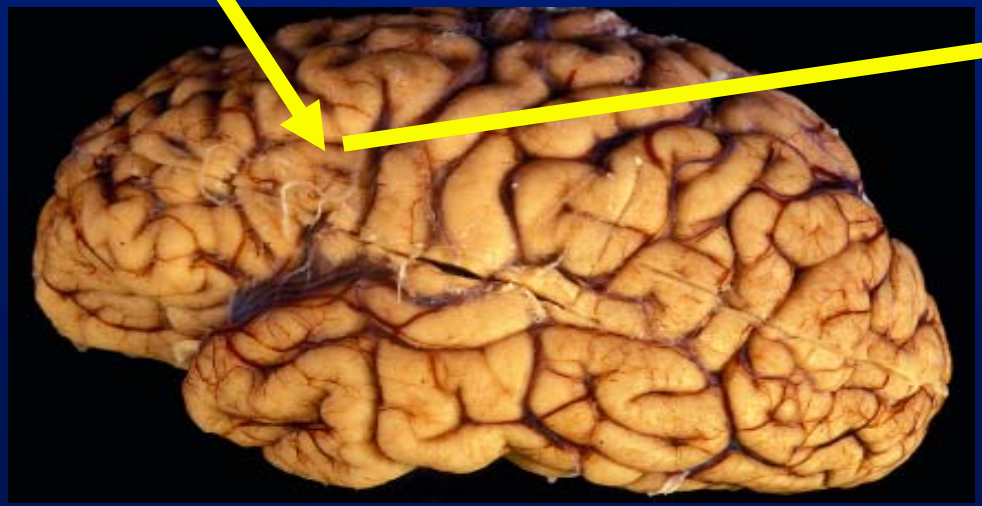




In vivo Amyloid Imaging with Pittsburgh Compound B (PIB) (Klunk et al, Ann Neurol 2004)

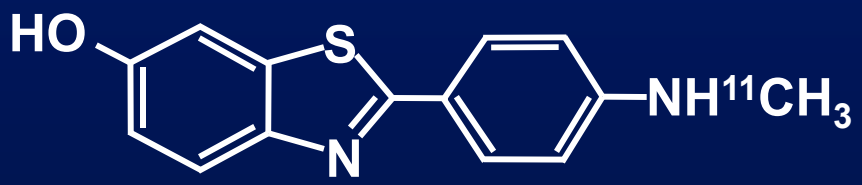
Histology - Thioflavin T



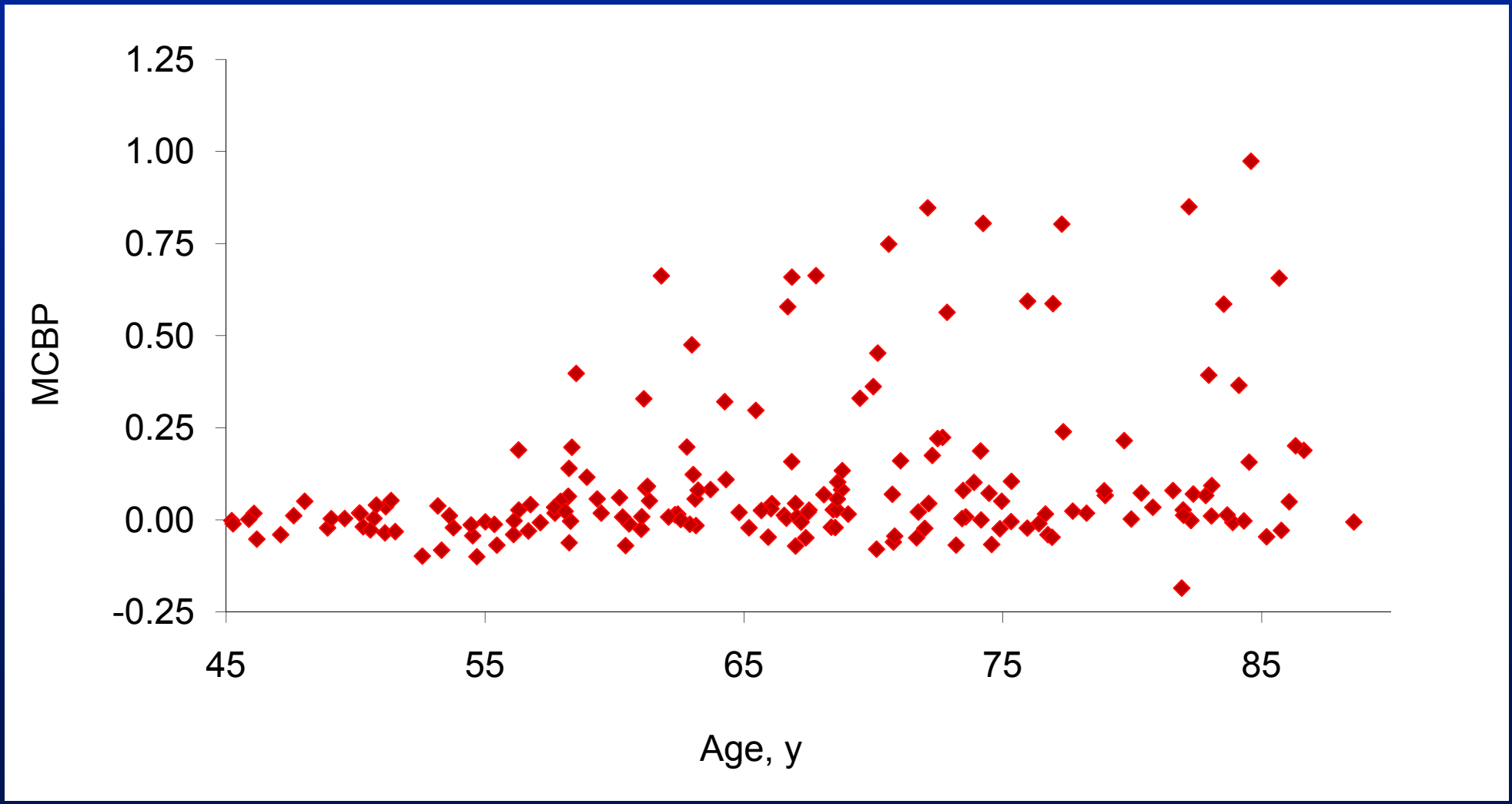


Courtesy of William Jagust

PET Imaging -
[^{11}C]6-OH-BTA-1 (PIB)



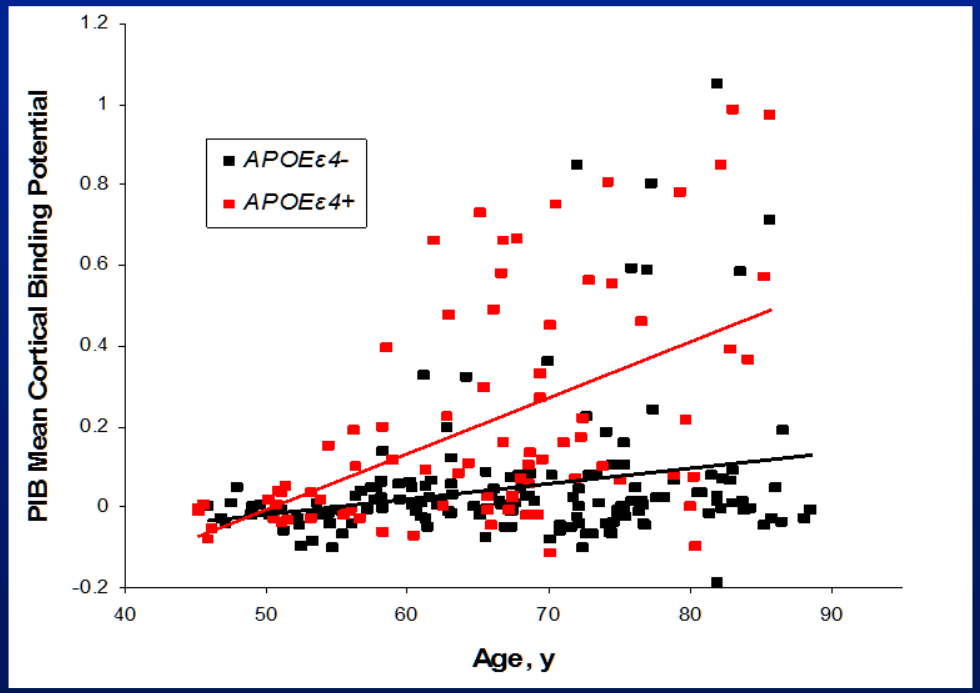
Scatter Plot of PIB Uptake by Age in Nondemented Aging (N=241)



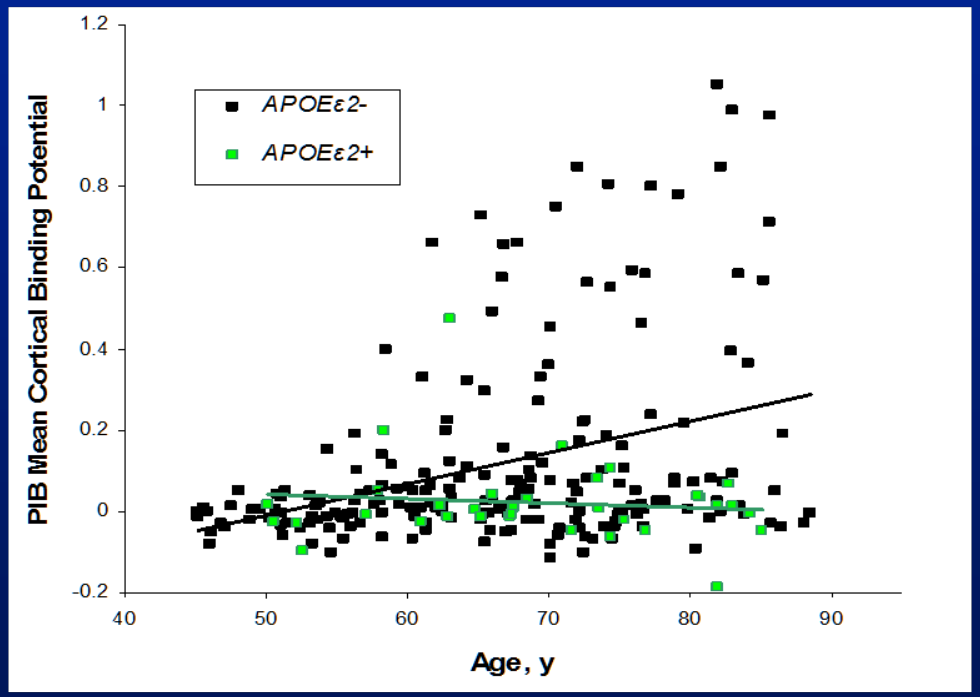
Morris et al, Ann Neurol 2010

MCBP values by age and APOE *status in 241 cognitively normal participants*

(A) *APOEε4*



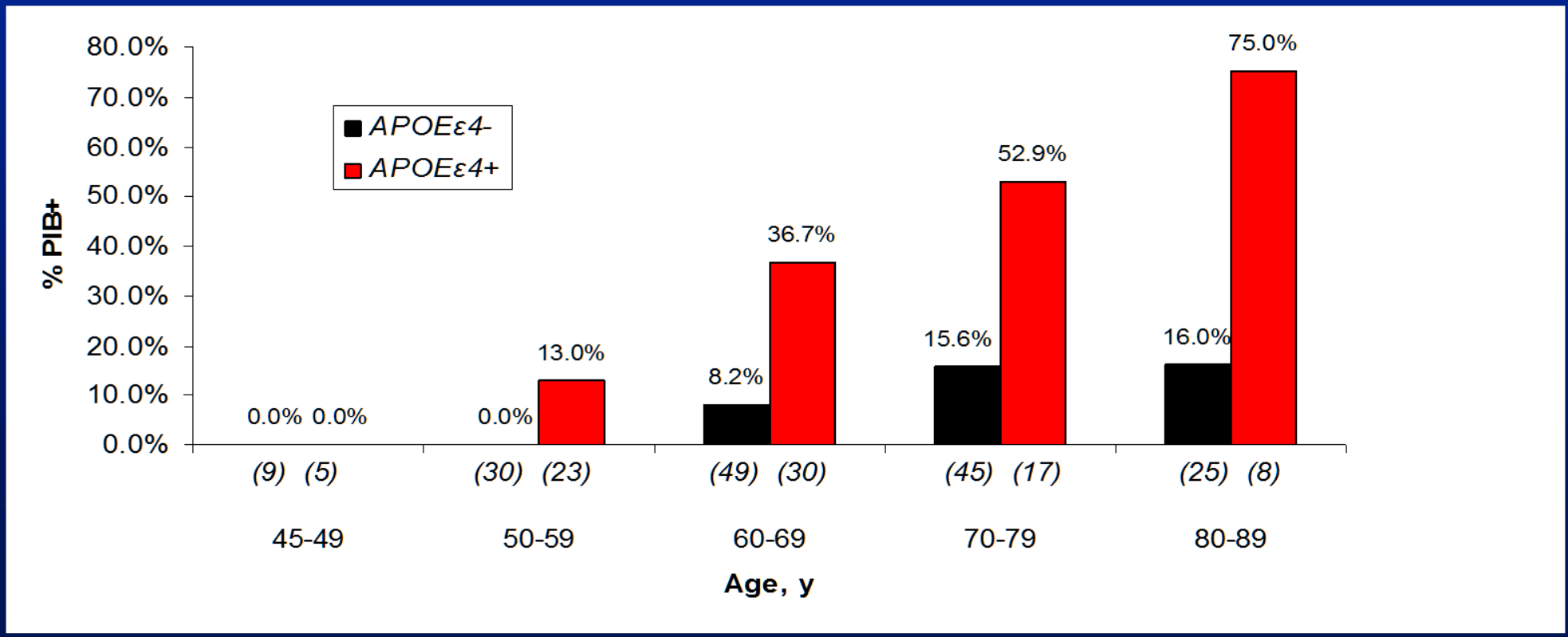
(B) *APOEε2*



Morris et al, Ann Neurol 2010

Frequency of biomarker-positive participants by APOEε4 status *The total number of participants with each APOEε4 status is indicated in italics for each age group*

(A) Percent PIB+ (MCBP > 0.18) by each age group for 241 participants



Morris et al, Ann Neurol 2010

Prediction of incident cognitive impairment in 114 cognitively normal persons

Model 1:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	
Model 2:	**$A\beta_{42}$**	**Age**	**Gender**	**Education**	***APOE4***	
Model 3:	**tau**	**Age**	**Gender**	**Education**	***APOE4***	
Model 4:	**$ptau_{181}$**	**Age**	**Gender**	**Education**	***APOE4***	
Model 5:	**$tau/A\beta_{42}$**	**Age**	**Gender**	**Education**	***APOE4***	
Model 6:	**$ptau_{181}/A\beta_{42}$**	**Age**	**Gender**	**Education**	***APOE4***	
Model 7:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	**$A\beta_{42}$**
Model 8:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	**tau**
Model 9:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	**$ptau_{181}$**
Model 10:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	**$tau/A\beta_{42}$**
Model 11:	**MCBP**	**Age**	**Gender**	**Education**	***APOE4***	**$ptau_{181}/A\beta_{42}$**

Cox proportional hazards models using stepwise selection: yellow = $p < .05$

Preliminary Biomarker Conclusions

- Cerebral $A\beta_{42}$ deposition is the pathobiological phenotype of APOE4 and increases as a function of age in preclinical AD
- $A\beta_{42}$ changes characterize preclinical AD; tau abnormalities occur later to mark symptomatic stages
- Reduction of CSF $A\beta_{42}$, and increased CSF tau identify very early symptomatic AD, in some instances prior to sufficient fibrillar Aβ for PIB detection
- Nonfibrillar cerebral Aβ deposits (diffuse SPs) and preclinical AD are not benign; both CSF and amyloid imaging Aβ markers in normal elders predict symptomatic AD

Incorporating Biomarkers into AD Clinical Trials

- Inclusion criteria (enrich patient selection)
  - Support accuracy of AD dx
  - Confirm presence of therapeutic target (e.g., Aβ deposits)
- Surrogate outcome measures
  - Preclinical AD (Aβ deposition): CSF $A\beta_{42}$; amyloid imaging (eg, PIB)
  - Symptomatic AD (neurodegeneration): CSF tau; regional and whole brain atrophy

Fagan et al., Ann Neurol 2009; Jack et al., Lancet Neurology 2010; Morris et al., Ann Neurol 2010

Paradigm Shift From Cure to Prevention

- Detect cognitively normal individuals with preclinical AD, intervene to prevent neurodegeneration and symptomatic AD
- Biomarkers are essential to detect preclinical AD
- Biomarkers may be used as surrogate outcome measures as they predict symptomatic AD
  - CSF levels of $A\beta_{42}$ and tau (Skoog et al., Dement Geriatr Cogn Disord 2003; Fagan et al., Arch Neurol 2007)
  - Amyloid imaging (Morris et al., Arch Neurol 2009
- Biomarkers will help determine when to intervene in preclinical AD to with primary prevention agents

The Dominantly Inherited Alzheimer Network: DIAN (U01 AG032438; JC Morris, PI)

- Build on ACS/FACS to establish an international registry of mutation carriers and noncarriers from families with *PSEN1*, *PSEN2*, or *APP* mutations
- Compare carriers and noncarriers to determine the chronology and order of imaging and biomarker changes that predict symptomatic AD
- Compare the clinical and pathological phenotypes of dominantly inherited AD with those of LOAD
- Maintain a publicly available resource of data and biospecimens

Initial sites: Washington Univ, B&W/MGH/Brown Univ, Columbia Univ, Indiana Univ, UCLA, ION/UCL, Australian Consortium

Hypothetical Progression of Alzheimer Changes

Mechanism	Biomarker
Upstream events (e.g., Aβ dimers, oligomers)	?
Aβ aggregation; deposition as cerebral diffuse plaques	↓ CSF $A\beta_{42}$ levels
Amyloid plaques become fibrillar	↓ CSF $A\beta_{42}$ levels; amyloid imaging
Amyloid plaques exert pathobiological signature	Brain volume loss; cognitive decline
Substantial neuronal/ synaptic damage	Dementia is manifested; dementia severity marked by increasing volume loss, ↑ CSF tau/ptau levels

Note: Other processes (e.g., inflammation; oxidative stress; vascular insufficiency) likely contribute