TOWARD EFFECTIVE ALZHEIMER'S THERAPY: PROGRESS AND COLLABORATION

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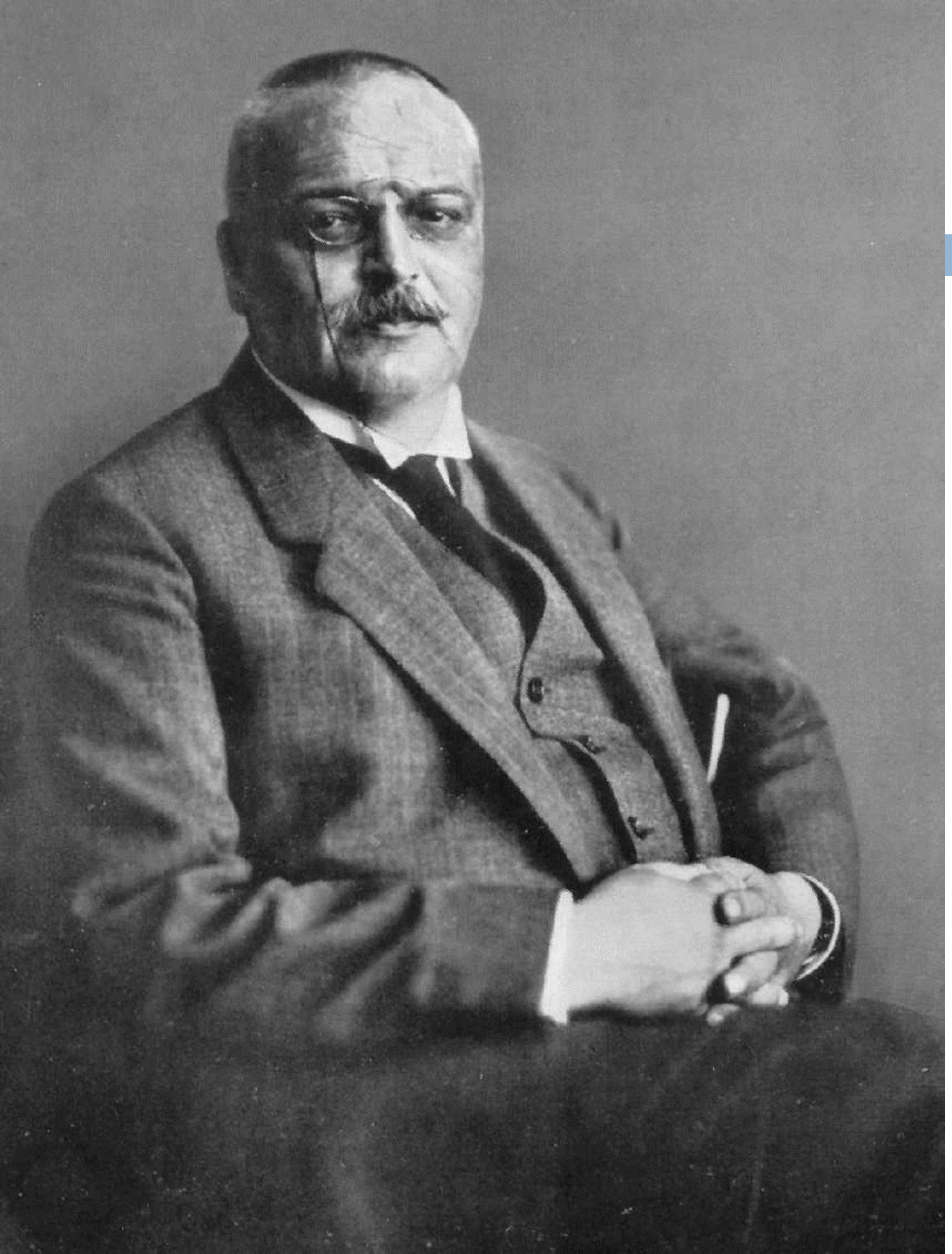
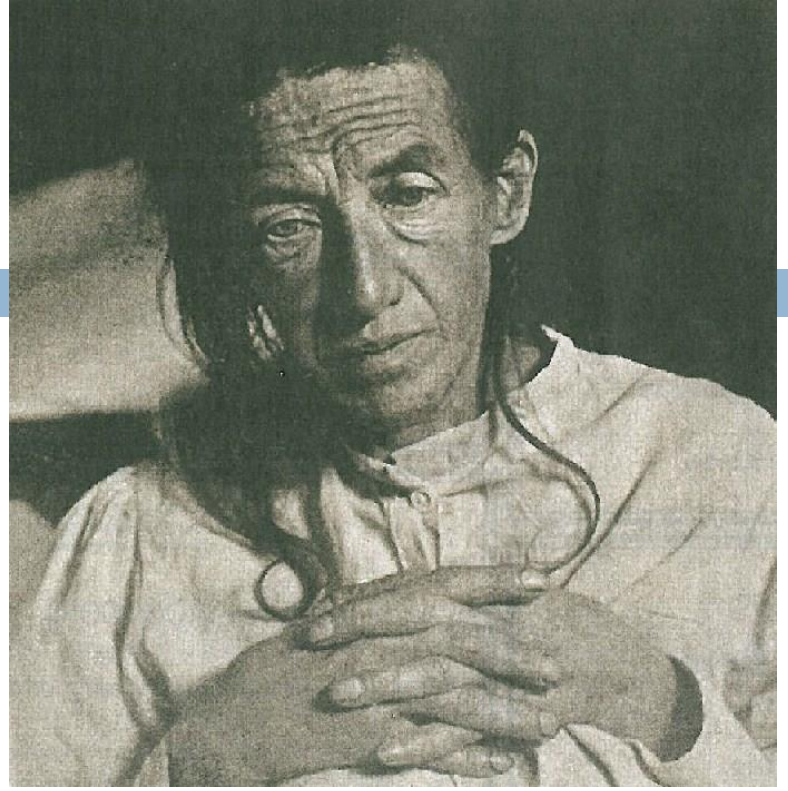




Brief History of AD Therapeutics

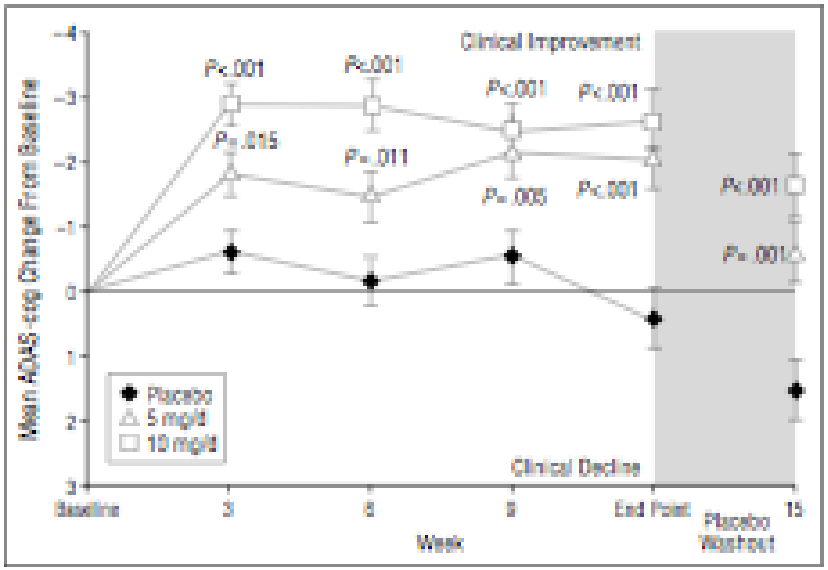
- 1906: Dr. Alois Alzheimer describes AD
- 1906-1970's: General assumption that this is an unusual and untreatable degenerative disease of middle age
- 1976: Dr. Robert Katzman editorial: The Prevalence and Malignancy of Alzheimer's Disease
- Late 1970's Cholinergic hypothesis suggests treatment possibilities
- 1984 Drs. Glenner and Wong purify and characterize brain amyloid
- 1985: First positive treatment study in AD
- 1993: Tacrine is approved; 3 other similar drugs follow
- PS1, PS2, APP and ADAD
- 2003: Memantine is approved, representing a second therapeutic class for AD
- And then a lost decade? What went wrong?

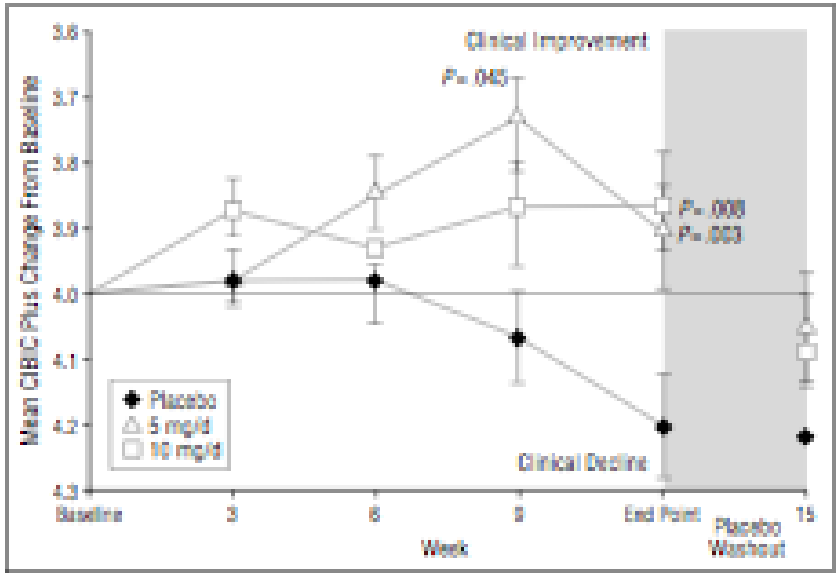
FDA Guidelines for AD Trials

- Co-Primary outcome measures
- Memory/cognition test, plus global or functional measure to establish clinical relevance
- ADAS-cog has worked well for cognitive enhancers in mild-moderate AD
- CIBIC-plus (CGIC) has worked well as a global
- CDR-SB, ADCS-ADL, DAD reasonable co-primaries for long trials

ADAScog change, CIBIC+ for assessment of cognitive enhancement

12 Week Phase II Donepezil Trial





Rogers et al, Arch Neurol, 1998

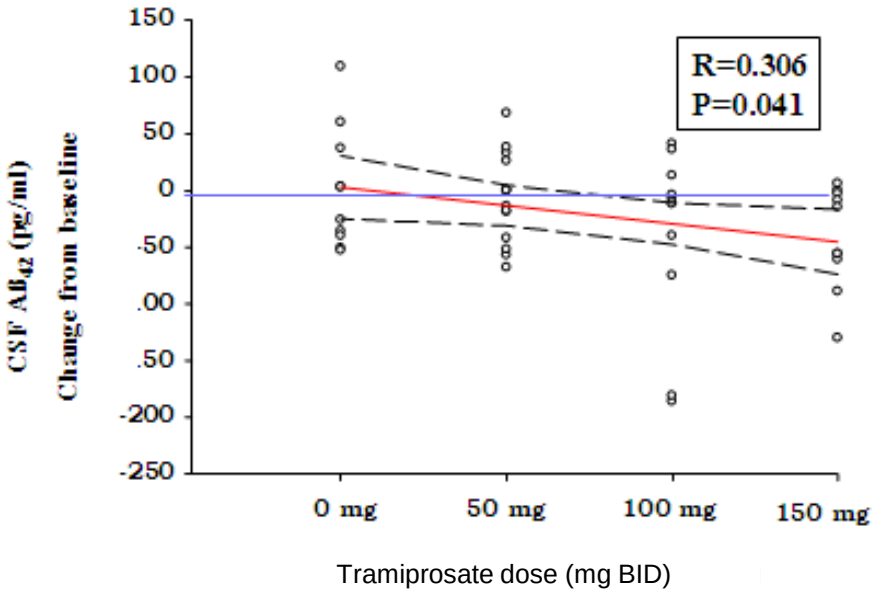
Disease-Modifying Drug Development: Phase II/III problems

- No short-term benefit expected, rather change in slope of decline
- Placebo groups in mild AD studies don't decline in 6 months; placebo decline minimal in 12 months
- To see effect on slope, need hundreds or thousands of subjects followed for 18 months

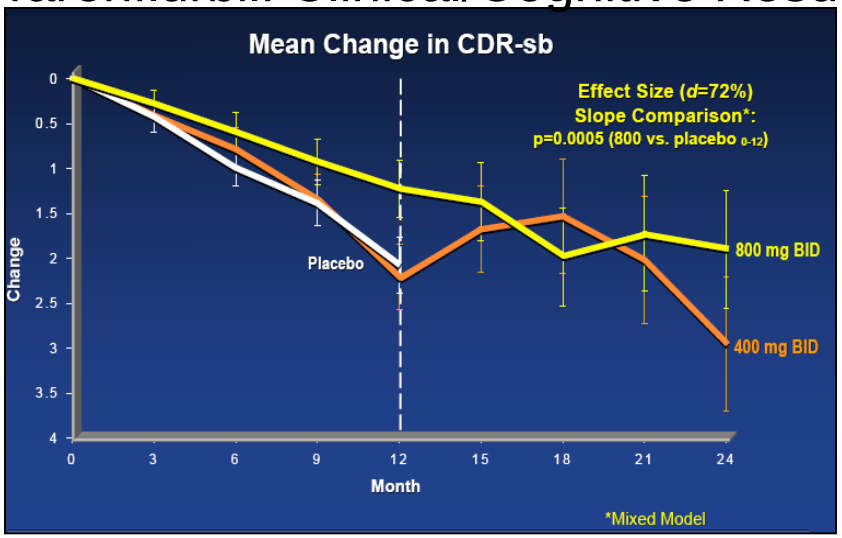
- Cannot see proof of efficacy in Phase II-type trial (in contrast to currently approved drugs)
- So we have lost a critical piece of the drug development process: the Phase II study

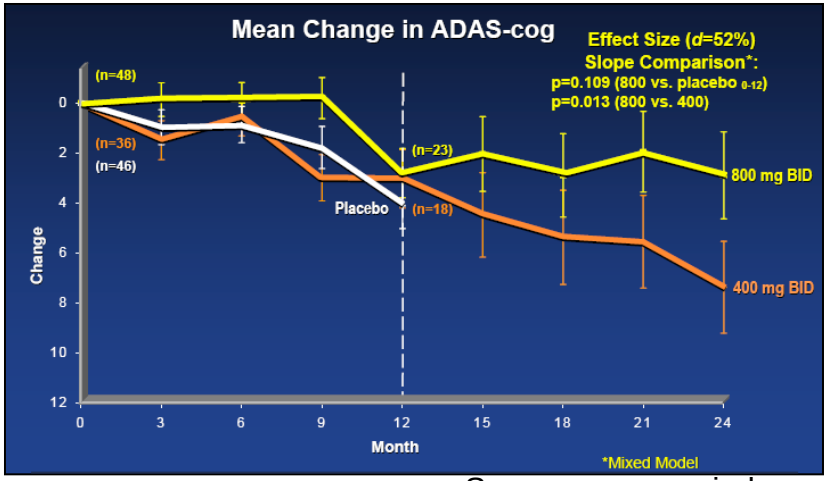
Comparison between Tramiprosate and Tarenflurbil Phase II trials

Tramiprosate: CSF-Aß Results



Tarenflurbil: Clinical/Cognitive Results

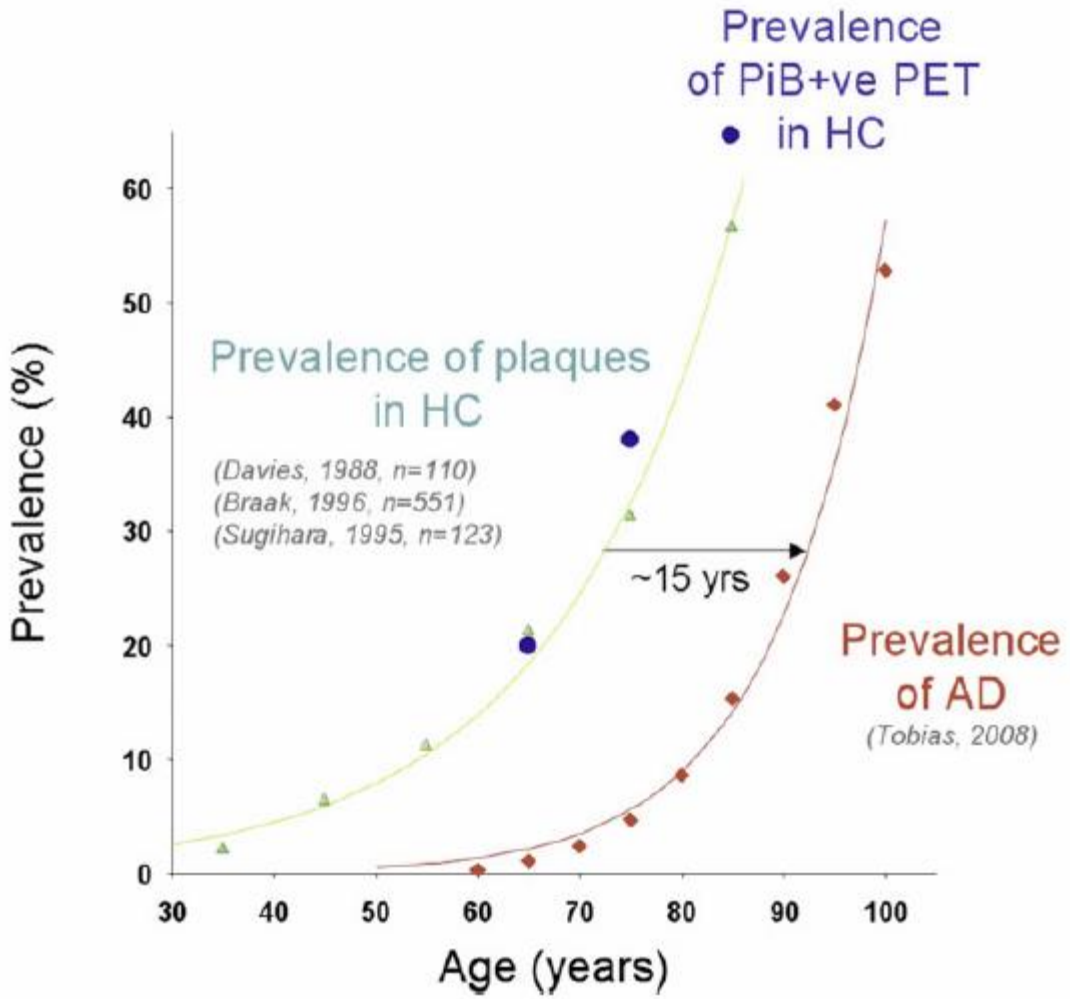




Source: www.myriad.com

- Even more important than the methodologic challenges, it is very plausible that the dementia stage of AD may be too late for disease-modification
- Especially for targeting amyloid

AIBL: Amyloid deposition by PIB and by autopsy precedes AD dementia by 15 years



CC Rowe et al, Neurobiol Aging, 2010

MCI Trials

- FDA, EMA never accepted MCI as a treatable entity for drug development
- Therefore, pre-dementia trials had to use time-to-dementia (a treatable entity) as outcome
- But MCI trials have not been successful

Issues with prior MCI trials

- Subject selection
- Variable conversion rate
- Subjective endpoint
- Artificiality of distinction between MCI and mild AD

Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease

Nicholas Kozauer, M.D., and Russell Katz, M.D.

N Engl J Med 2013; 368:1169-1171 | March 28, 2013 | DOI: 10.1056/NEJMp1302513

Kozauer and Katz, NEJM, 2013

- A specific suggestion … for trials focusing on patients in whom overt dementia seems imminent is the use of a single scale that combines assessment of both cognition and function, such as the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB).
- For patients whose disease is at an even earlier clinical stage, so that functional impairment would be more difficult to assess, it might be feasible to approve a drug through the FDA's accelerated approval pathway on the basis of assessment of cognitive outcome alone.

Better pre-dementia designs

- Now that FDA and EMA seem amenable to the idea of pre-dementia AD (eg, by Dubois criteria) we can abandon time-to-dementia design
- Operationalize Dubois criteria (eg MCI plus low CSF abeta42)
- Primary outcome: continuous measure such as CDR-SB (to capture effect on primary manifestations of disease and establish clinical relevance)
- Much more powerful than traditional MCI trial design

- So we have moved from successful symptomatic and unsuccessful disease-modifying drug trials in AD dementia to pre-dementia (prodromal) AD as a population for studies
  - Likelihood of success must be significantly greater
- Next: preclinical AD

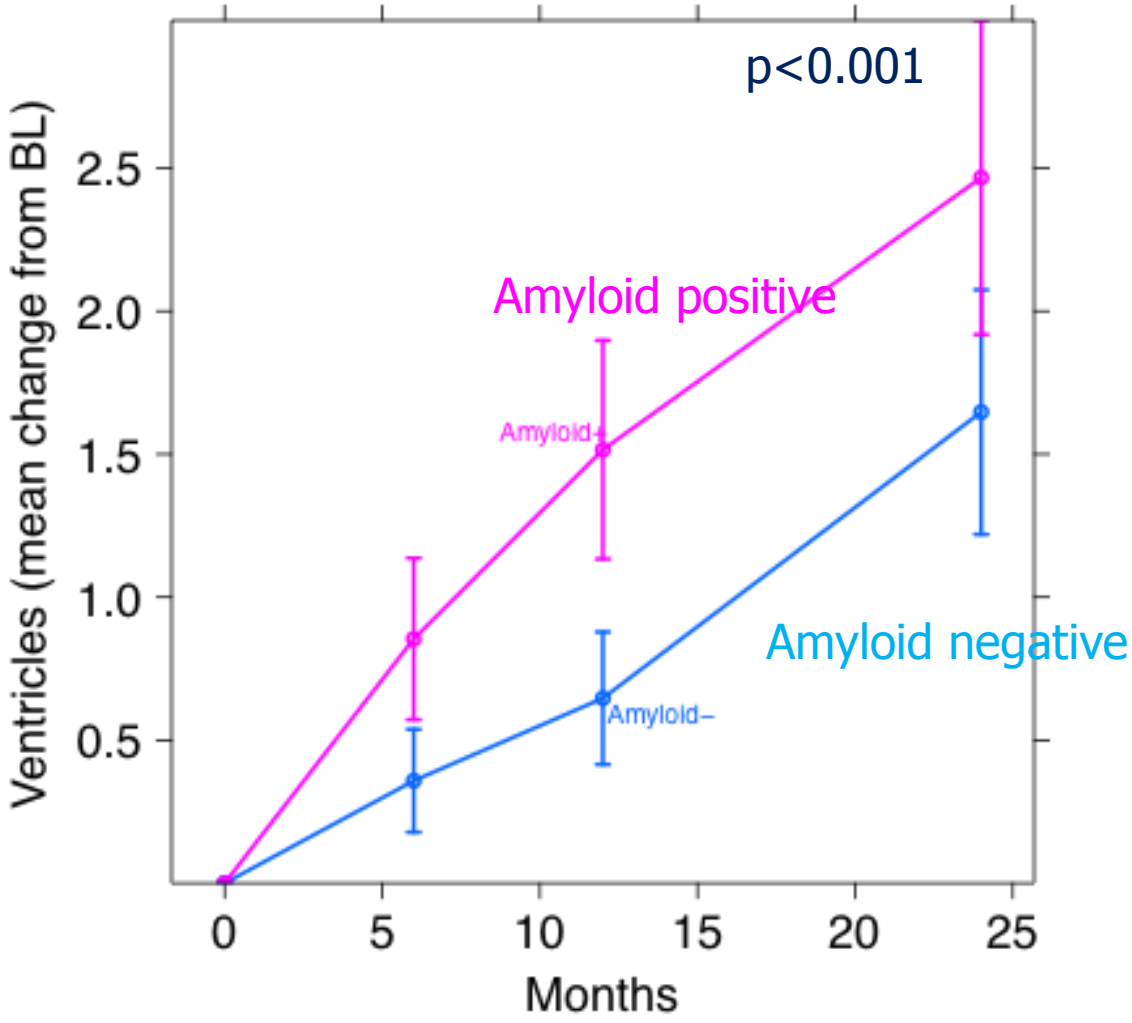
- (And someday: primary prevention)

Preclinical AD?

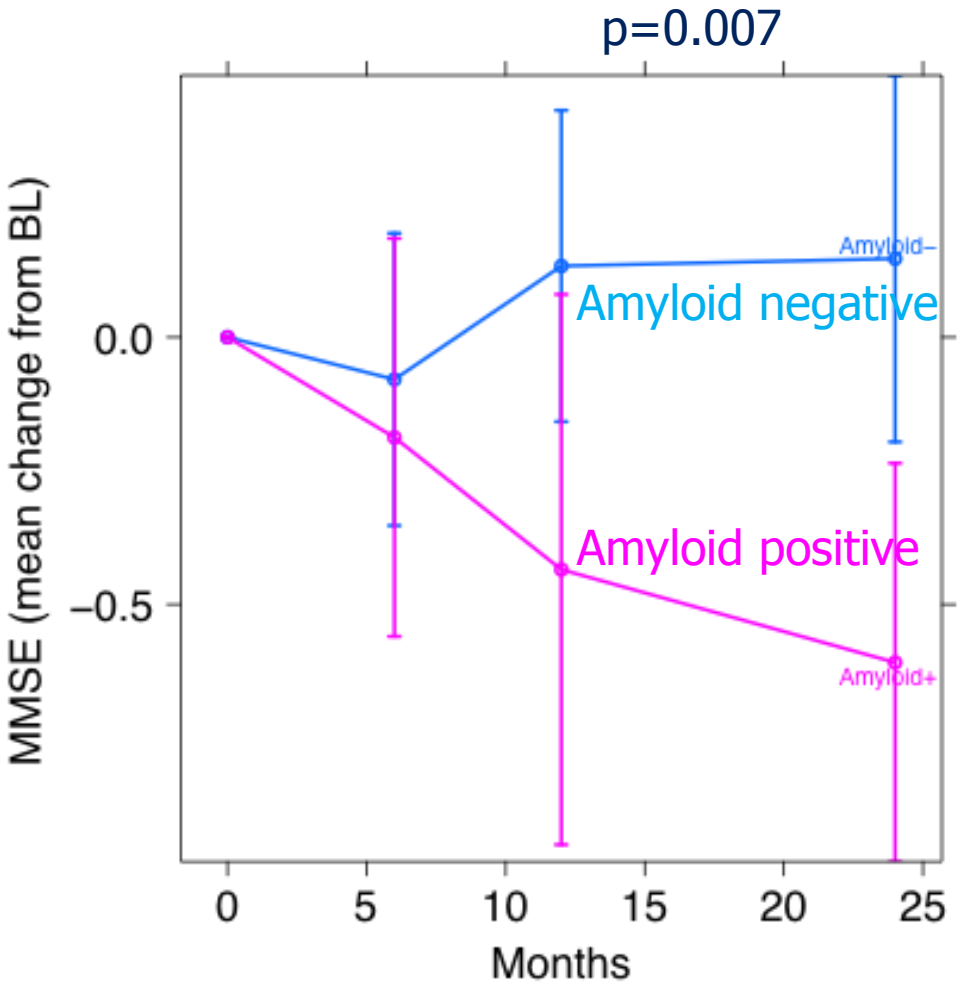
- One third of the ADNI normal control group (CDR=0) are amyloid positive by CSF or PET

- Is this “preclinical AD”?

Ventricular volume change in normals is linked to amyloid



MMSE change in normals is linked to amyloid



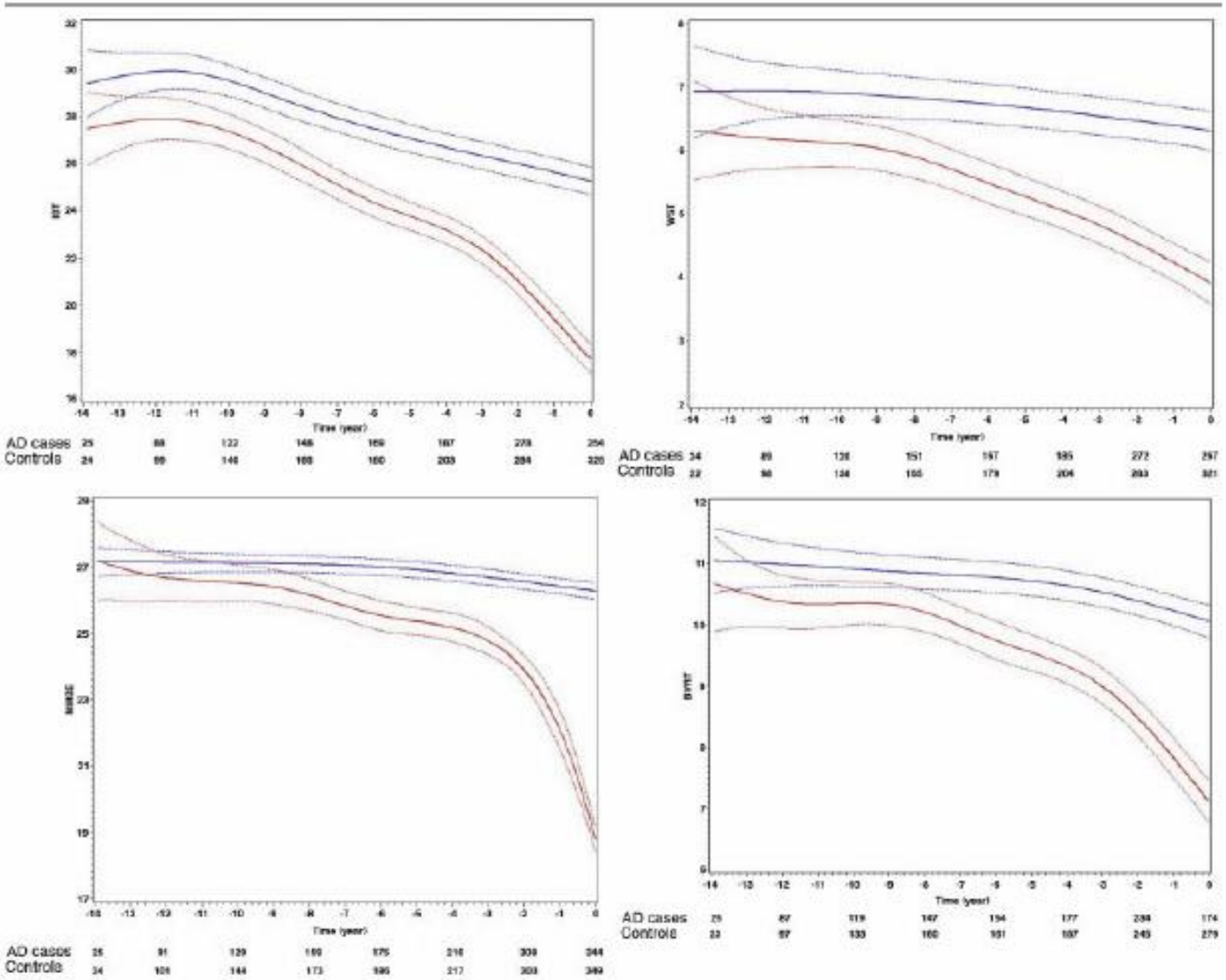
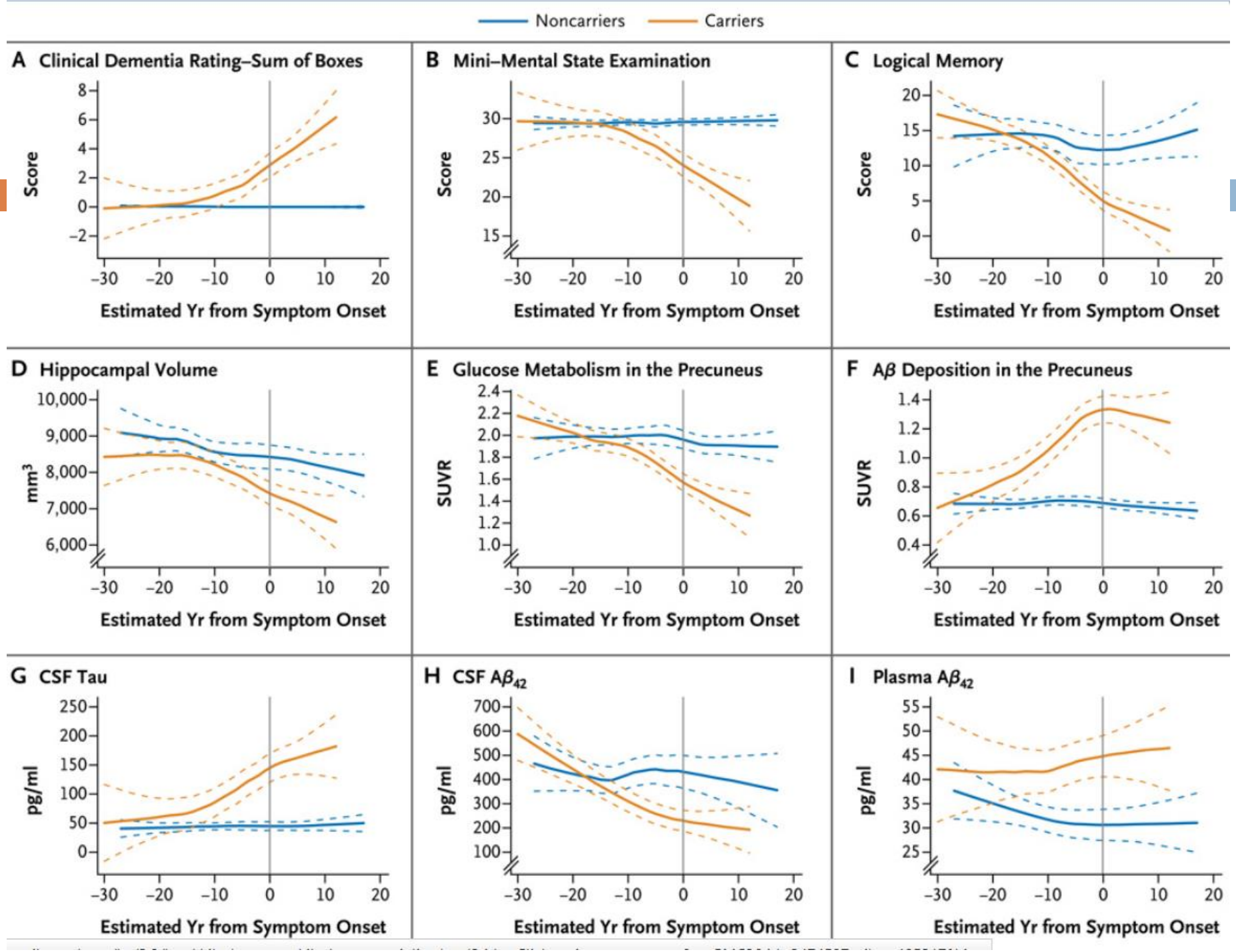


Fig 1. (A) Estimated evolution of the mean Isaacs Set Test (IST) score (and 95% confidence interval [CI]) during the 14 years preceding the diagnosis of Alzheimer's disease (AD; red curve *for future AD subjects;* blue curve *for healthy control subjects; scores ranging from 0–40). (B) Estimated evolution of the mean Wechsler Similarities test (WST) score (and 95% CI) during the 14 years preceding the diagnosis of AD (*red curve *for future AD subjects;* blue curve *for healthy control subjects; scores ranging from 0–10). (C) Estimated evolution of the mean Mini-Mental State Examination (MMSE) score (and 95% CI) during the 14 years preceding the diagnosis of AD (*red curve *for future AD subjects;* blue curve *for healthy control subjects; scores ranging from 0–30). (D) Estimated evolution of the mean Benton Visual Retention Test (BVRT) score (and 95% CI) during the 14 years preceding the diagnosis of AD (*red curve *for future AD subjects;* blue curve *for healthy control subjects; scores ranging from 0–15).*


Noncarriers
Carriers
A Clinical Dementia Rating–Sum of Boxes
Score
Estimated Yr from Symptom Onset
B Mini–Mental State Examination
Score
Estimated Yr from Symptom Onset
C Logical Memory
Score
Estimated Yr from Symptom Onset
D Hippocampal Volume
mm3
Estimated Yr from Symptom Onset
E Glucose Metabolism in the Precuneus
SUVR
Estimated Yr from Symptom Onset
F Aβ Deposition in the Precuneus
SUVR
Estimated Yr from Symptom Onset
G CSF Tau
pg/ml
Estimated Yr from Symptom Onset
H CSF Aβ42
pg/ml
Estimated Yr from Symptom Onset
I Plasma Aβ42
pg/ml
Estimated Yr from Symptom Onset

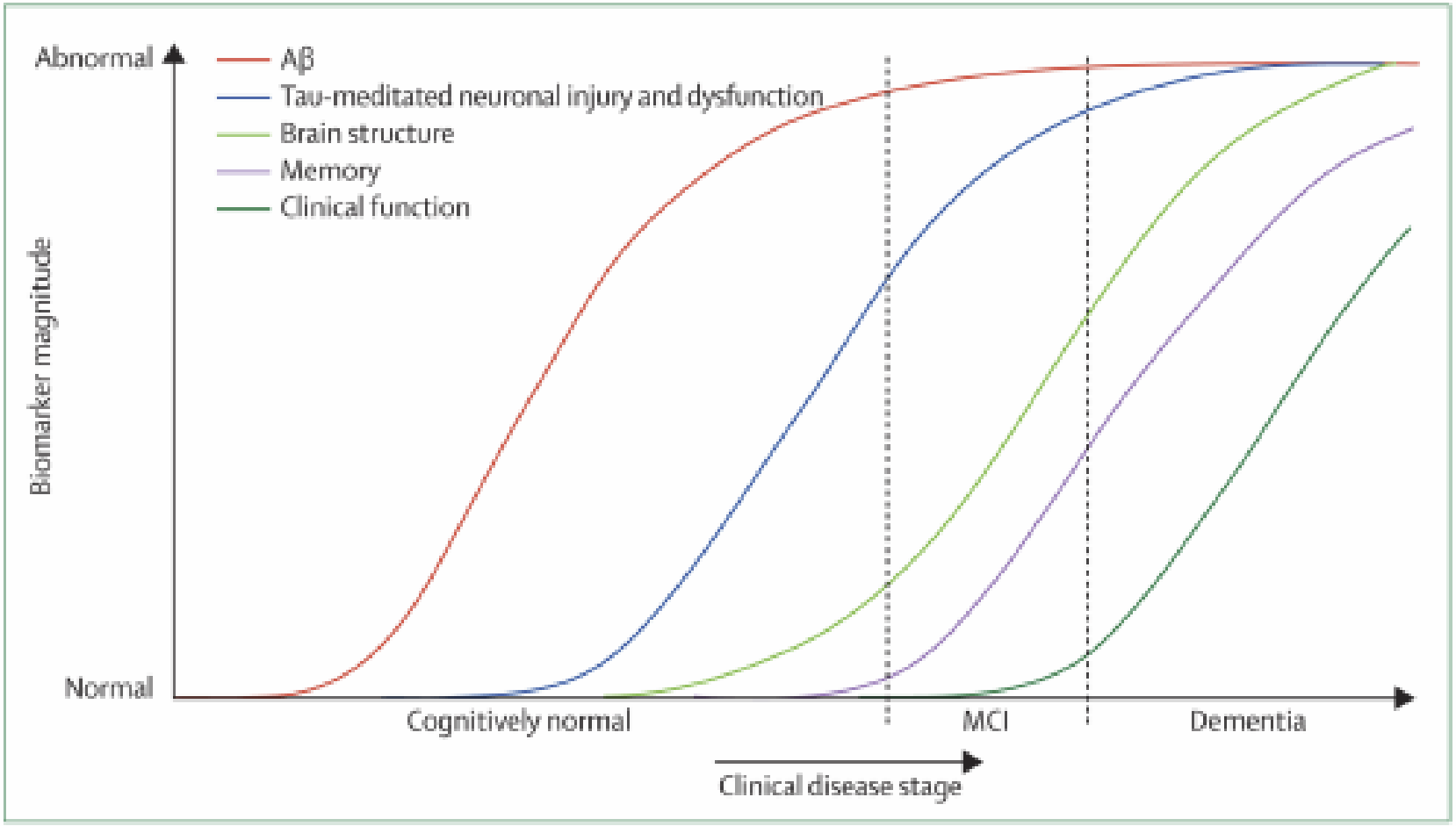
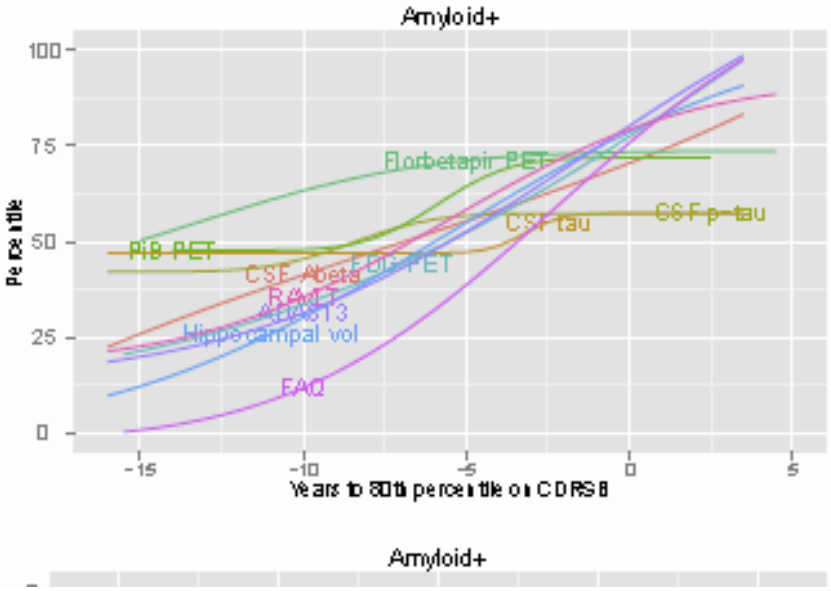
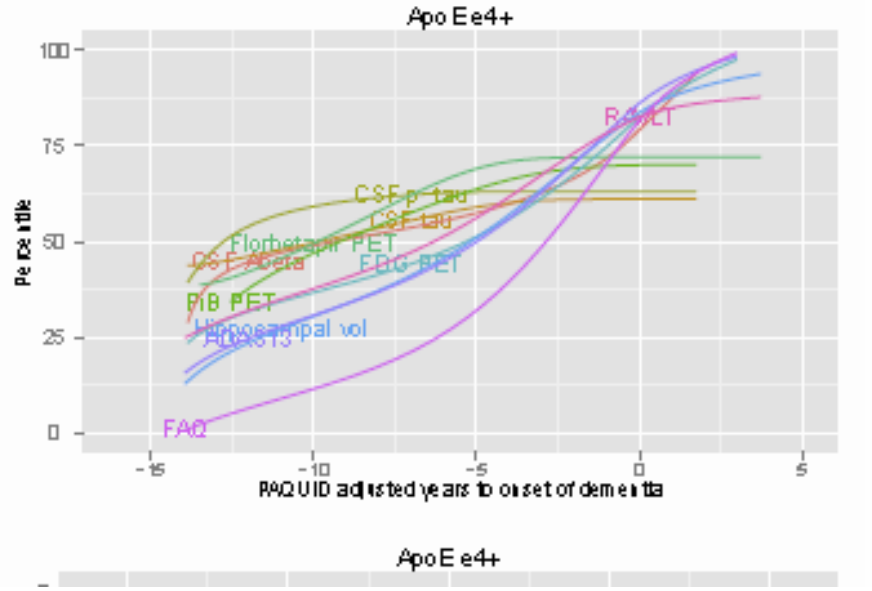


Figure 1: Dynamic biomarkers of the AD cascade hypothesized by Jack et al. [4]

Estimating long-term multivariate progression from short-term data. Donohue et al, Alzheimer's and Dementia, 2013:

Cognitive change occurs as early as functional/structural biomarker change





Secondary prevention (very early treatment of AD)

target *amyloid-related cognitive decline* in clinically normal older individuals

ADCS A4 Trial Design (Sperling, Aisen) Anti-Amyloid treatment in Asymptomatic AD

- Screen clinically/cognitively normal 65+ year-olds
- Select those with amyloid in brain by PET
- Enroll in a 3 year RCT of an anti-amyloid rx (solanezumab)
- Primary outcome: cognitive composite
- Broad secondaries including computerized cognitive composite, PRO, functional/structural MR, CSF

ADCS-PACC

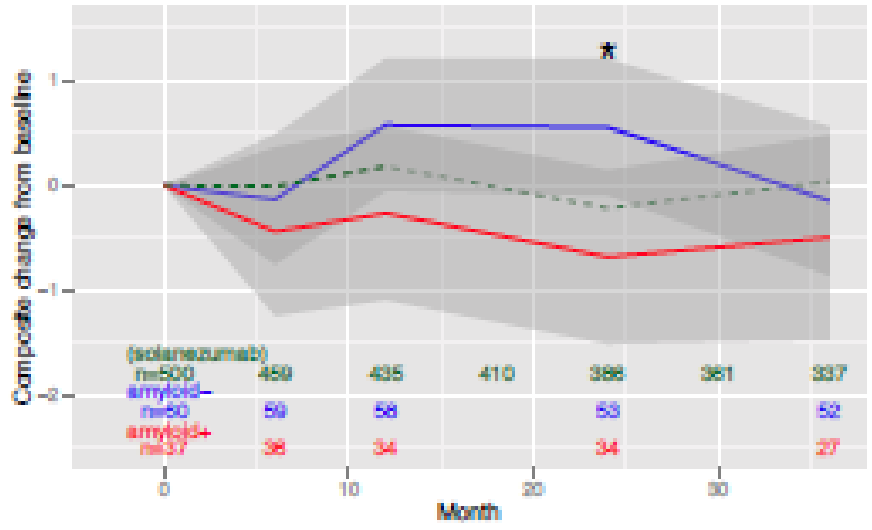
- Based on review of the literature from cohort studies data from “normal controls” who progressed to MCI or AD dementia, a composite measure sensitive to change in preclinical AD would likely require assessment of these key domains:
  - episodic memory
  - executive function
  - orientation

The ADCS-PACC includes:

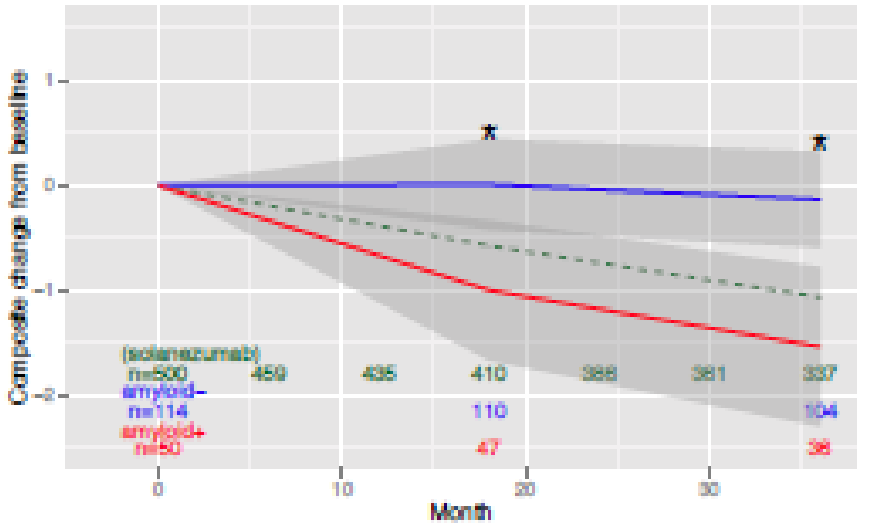
- Free and Cued Selective Reminding Test (FCSRT)
- Delayed Paragraph Recall
- Digit-Symbol Substitution test
- MMSE

- Sum of z scores

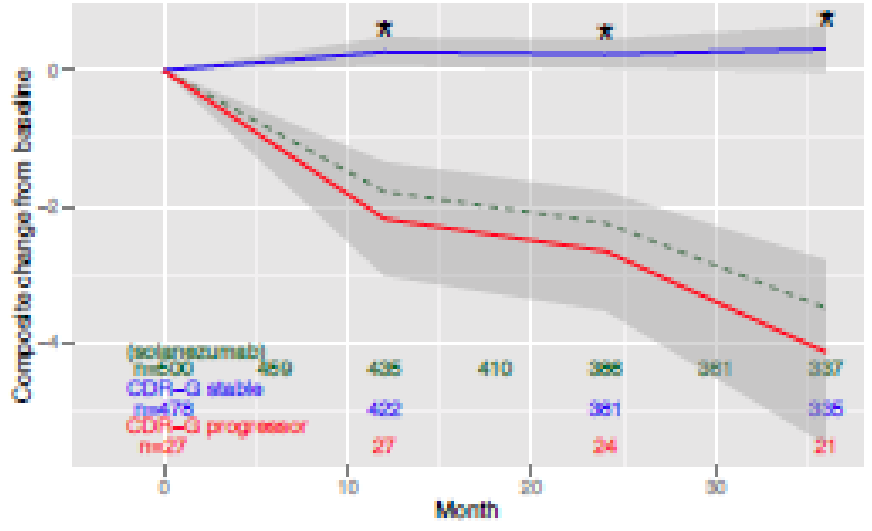
ADNI by Aβ



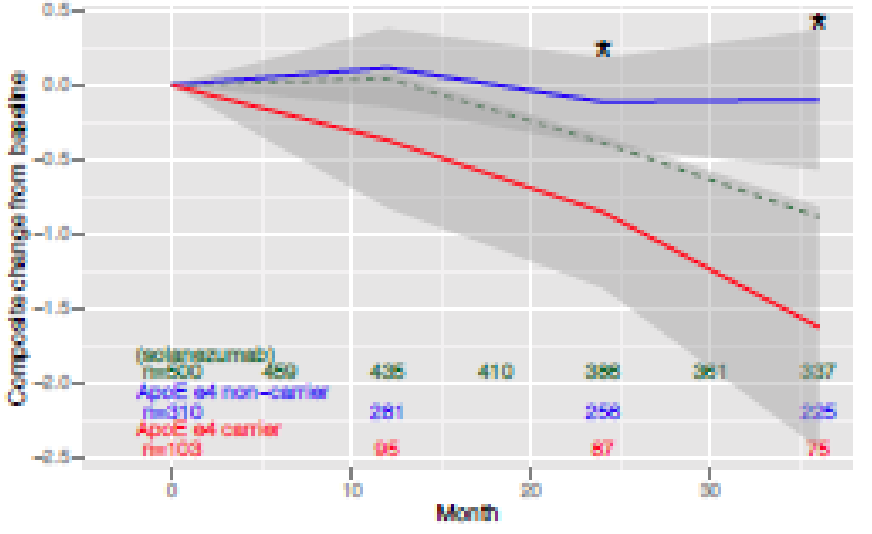
AIBL by Aβ



ADCS PI by CDR-G Progressor



ADCS PI by ApoE-ε4



Cognition is the best biomarker for AD trials

- Face validity
- Moves in the expected direction (in contrast to volumetric MR)
- Links early, middle and late stage disease- best for registration

- *Feasible primary outcome measure at the earliest identifiable stage of AD*

How will we get to primary prevention?

- Clarify the transition from normal aging to AD
- Identify those nearing that transition (epidemiology, genetics)
- Demonstrate impact of therapeutics on the transition

- Establish mid-life primary prevention

PET scanning will be the new colonoscopy

- Or LPs …
- Or plasma abeta may be the new cholesterol (once we figure out how to measure and analyze plasma abeta)

(Somewhat) controversial statement

- The amyloid therapeutic hypothesis is alive and well
- (Despite dozens of negative trials)

- The focus of trials on amyloid is appropriate
- (Even as we must continue to test other targets)

- We will get this right

Other therapeutic approaches

- Tau immunotherapies
- Glucose/insulin
- NGF, BDNF, exercise
- Anit-inflammatories? Target complement?
- APOE-related therapeutics
- Clues from new genes?

Justification for optimism

- So many brilliant basic and clinical scientists
  - We have very promising therapeutic candidates now, plus better trial designs
- So many, many generous volunteers in our trials

Justification for optimism: beyond the science and the trials

- Standardization and data sharing (M Weiner)
- Collaboration (M Carillo, Mike Weiner for WW-ADNI; B Vellas, J Touchon)
- National/international harmonization and vision (M Carillo, G Vradenberg, Z Khachaturian, N Buckholz)
- Regulatory vision (R Katz, C Sampaio)
- National leadership (R Petersen)
- Academic industry partnerships (DIAN, API, A4 …)

Conclusions: Lessons for AD trial design

- AD is a gradually progressive disorder lasting many years; MCI and AD dementia are artificial, fuzzy constructs, useful clinically but counter-productive in trials
- In prodromal AD, assessing treatment effects on continuous measures (eg CDR-SB) is much more powerful than time-to-dementia or other time-to-event designs
- Biomarkers are powerful but tricky
- Cognition may be the best biomarker (despite measurement challenges)

Conclusions: Lessons for AD trial design (continued)

- Probably wise to treat as early as possible
- Very early treatment trials, ie, secondary prevention trials targeting amyloid-mediated decline, are now feasible (with clear regulatory guidance)

- Primary prevention is the ultimate goal but we need more study of the transition between normal and preclinical AD (ADNI3?)

Final words

- *We will get there*

Acknowledgments

- NIA: ADCS, ADNI etc.
- Alzheimer's Association
- From the ADCS/UCSD: Debbie Tobias, Jeremy Pizzola, Devon Gessert, Tamie Sather, Sarah Walter, Ron Thomas, Rema Raman, Mike Donohue, Mike Rafii, Jim Brewer, Kristin Woods, Robert Rissman, Doug Galasko, David Salmon, Adam Fleisher, many others
- From ADNI: Mike Weiner, Ron Petersen, Laurel Beckett, Cliff Jack, Bill Jagust, Art Toga, John Trojanowski, Les Shaw, many others
- Many, many colleagues, individuals with (or at risk for) AD and their families