# Long-Term Studies in Alzheimer disease: Evidence of Progression?

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# Overview

- Alzheimer's disease is a condition that progresses over years with observable deterioration in:
  - Cognition
  - Function
  - Behavior
- We have sensitive instruments which yield predictable change
- Expanded AD definition permits observation of progression other conditions
  - MCI
  - Cognitive healthy elders

# Dementia of the Alzheimer type (DSM-IV-TR) 294.1X

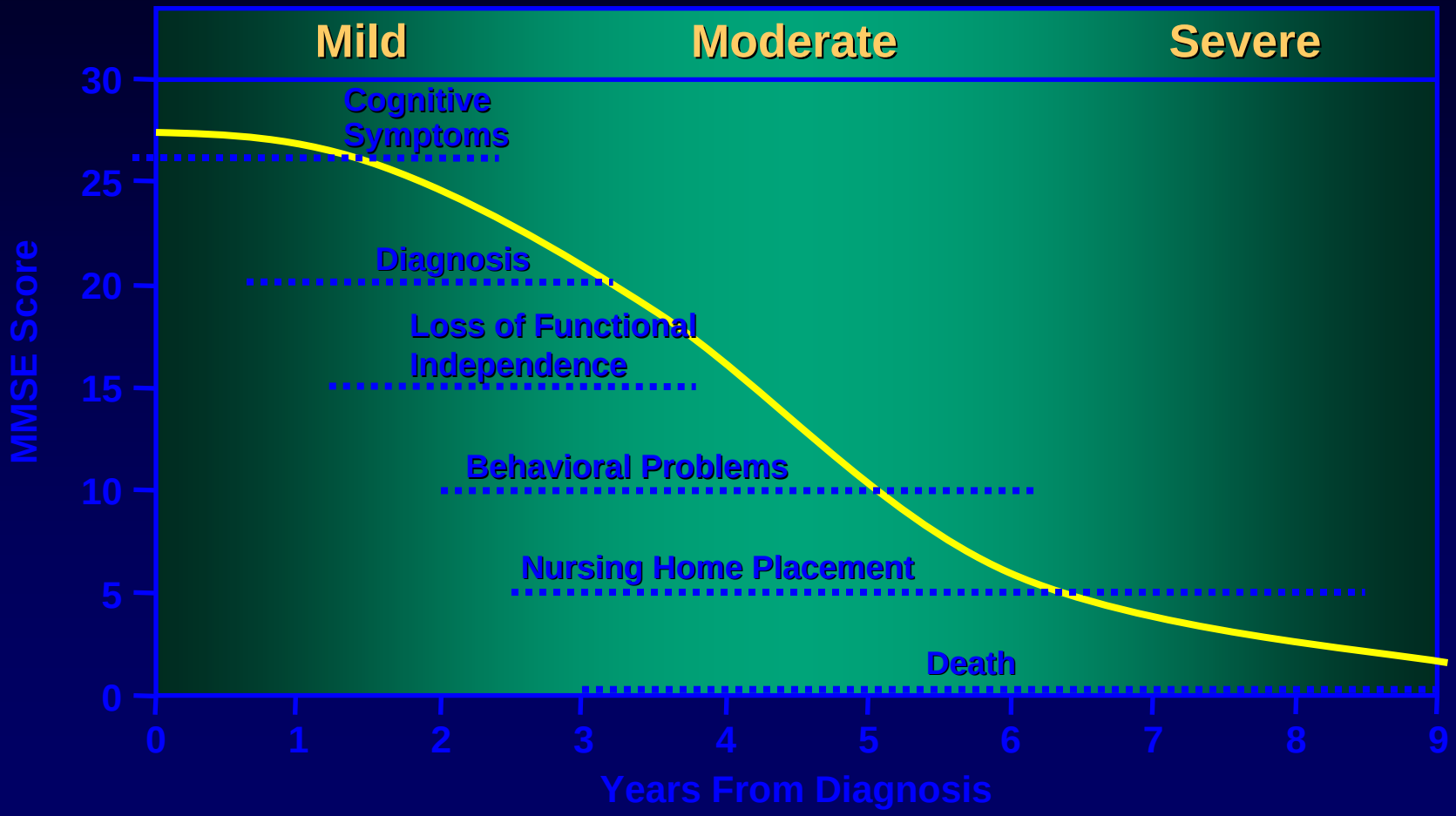
- Memory impairment and :
  - Aphaisa, apraxia, agnosia, executive function
- Impairment in social or occupational functioning
- Gradual onset
- Impairment not due to CNS, systemic or substance induced
- Deficits not exclusively during the course of a delirium
- Not due to other Axis I disorder

# Criteria for AD (NINCDS/ADRDA)

- Definite AD
  - Histologic confirmation of the disorder
- Probable AD
  - Characteristic clinical course and findings
  - Insidious onset
  - Continuous progression
  - Deficits in 2 or more areas of cognition
  - Absence of other disorders that could account for dementia
- Possible AD
  - Patients with an atypical course or concurrent illnesses

McKhann et al. 1984.

# Clinical Disease Progression



# Progression of Cognitive Impairment is Measurable

- MMSE progression predictable from mild to moderate AD
- ADAScog demonstrates progression from MCI through Mild and Moderate AD
- Severe Impairment Battery (SIB) demonstrates worsening over a year even in those with very low MMSE scores

# Efficacy of Long-Term Use

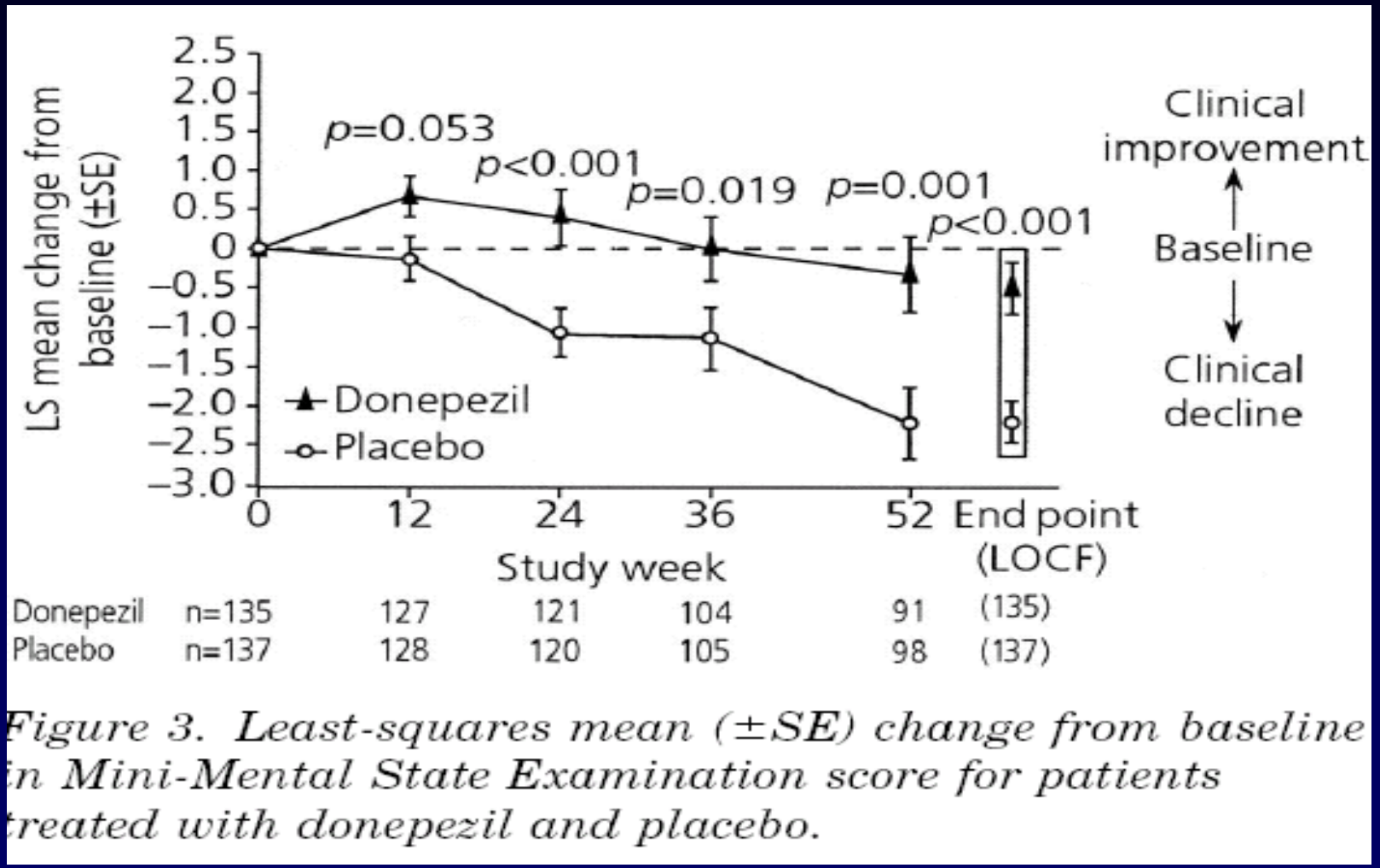


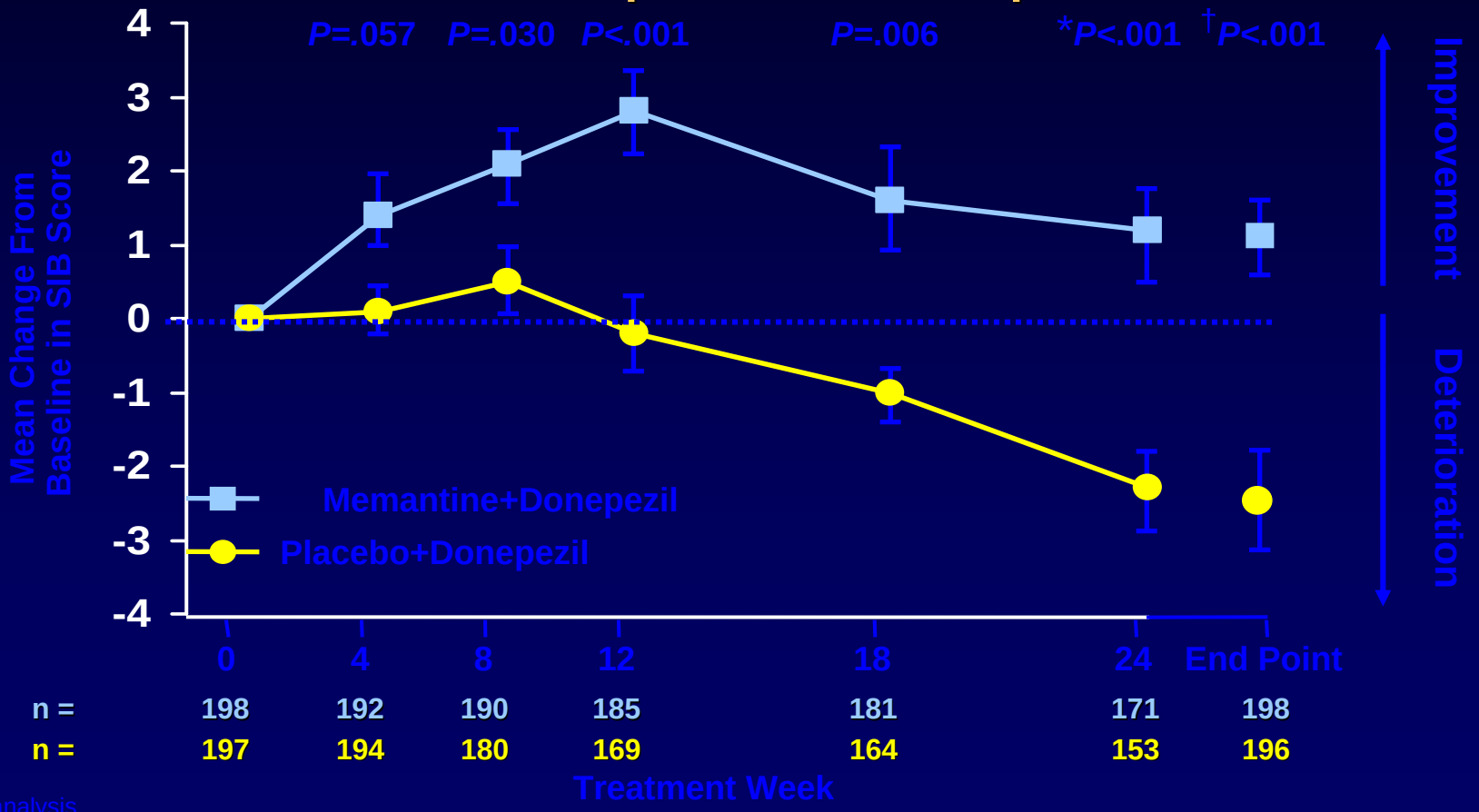

*Figure 3. Least-squares mean (±SE) change from baseline in Mini-Mental State Examination score for patients treated with donepezil and placebo.*

*Winblad et al 2001*

*Memantine + Donepezil in Moderate to Severe AD Study*

# Results: Cognition—SIB

**Memantine + Donepezil Produced Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone**




*OC analysis. †LOCF analysis.

Adapted from Tariot P, et al. *JAMA*. 2004;291:317-324.

Data on file, Forest Laboratories, Inc.

# Trial Designs for Slowing Progression/Prevention

- Assess treatments over extended time period: one or more years
- Compare slope of performance over time
- Survival analysis:
  - Requires discrete events
  - Compares the time to reach events in treatment and placebo group

# Progression in outcomes

## Courtney, et al;Lancet 2004

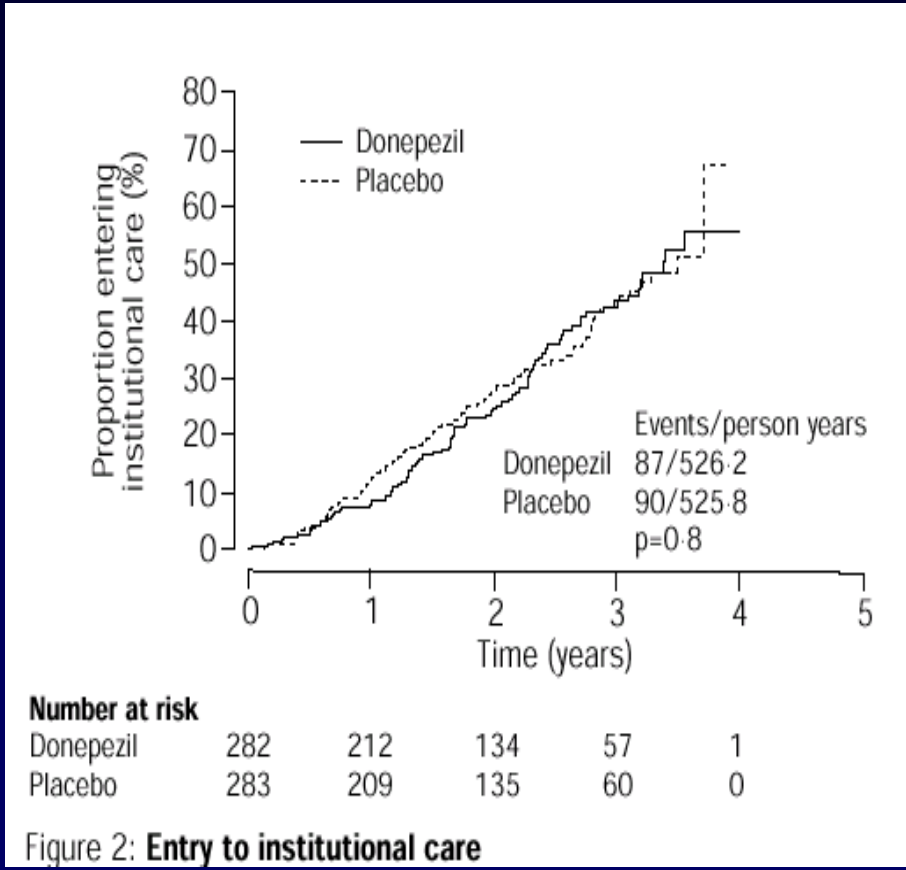
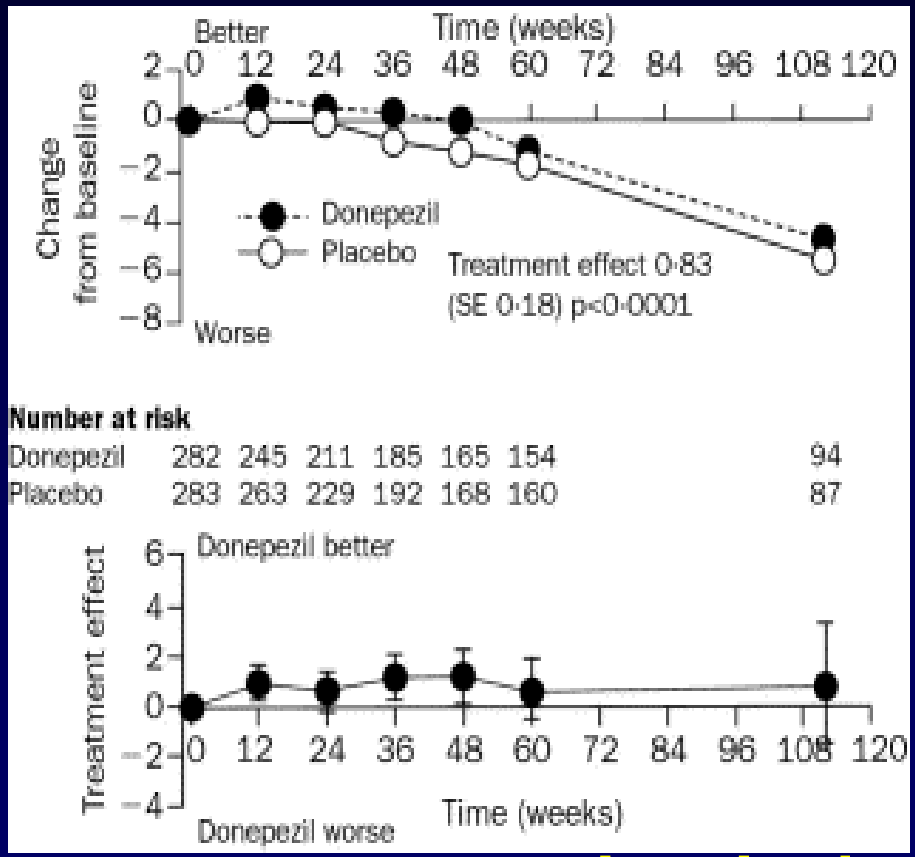


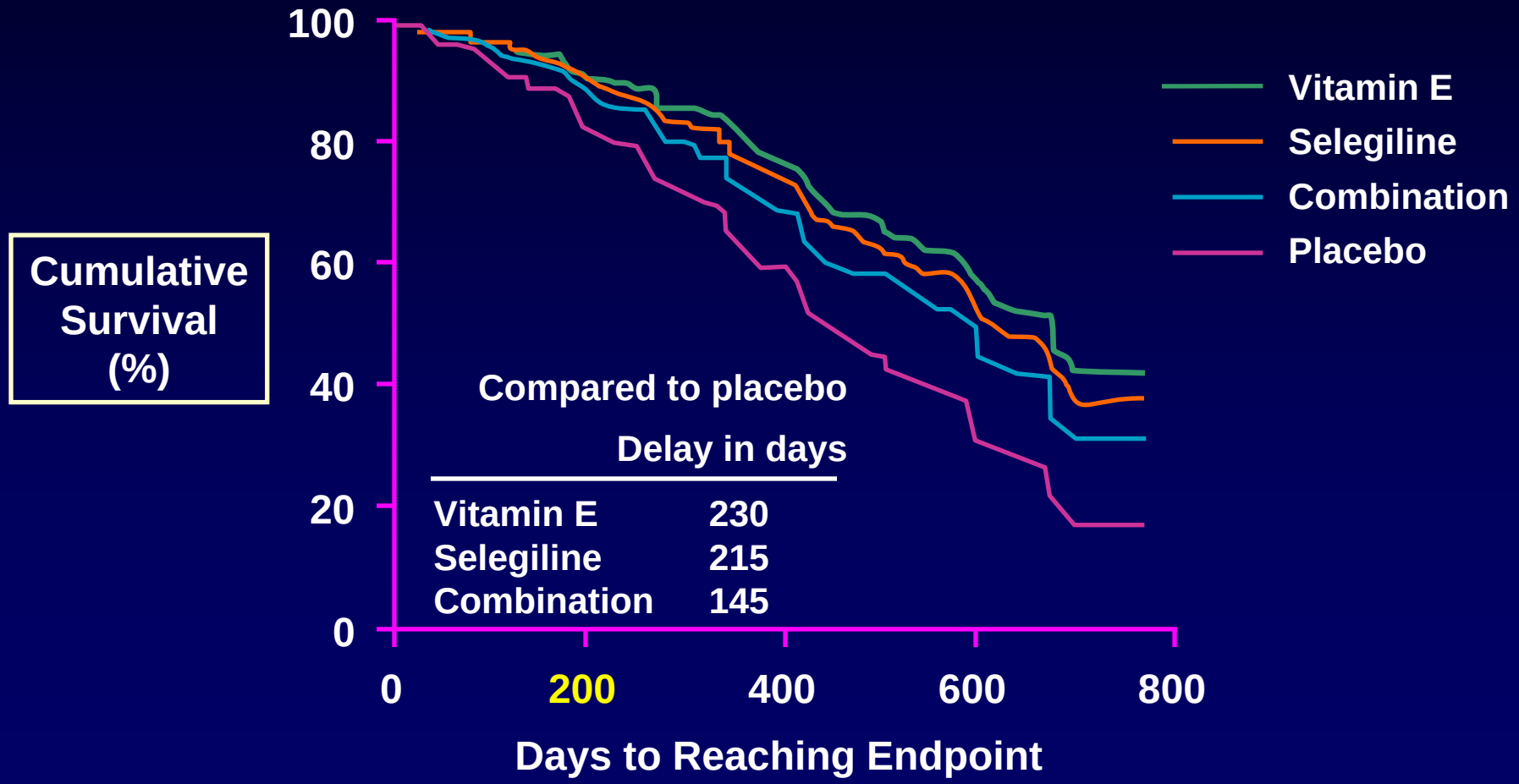

Figure 2: **Entry to institutional care**

No effect on institutionalization




MMSE: Donepezil vs placebo (95% CI 0·5–1·2, p<0·0001)

# What about Vitamin E: Delay in Clinical Progression of AD or Not?




Sano M, et al. *N Engl J Med.* 1997;336:1216-1222.

# Measuring Progression in AD

- Placebo rate of change is available in recently reported studies
  - One year:
    - Dimebon Rember
  - 18 Months:
    - Tarenflurbil, VITAL
    - CLASP LEAD

# Challenges to Measuring Progression Timing: How Long

- Those with disease and symptoms progress rapidly; consequently shorter trial periods.
- At-risk individuals require longer observation periods.
- Balance with the desire for lasting benefit and longer life.

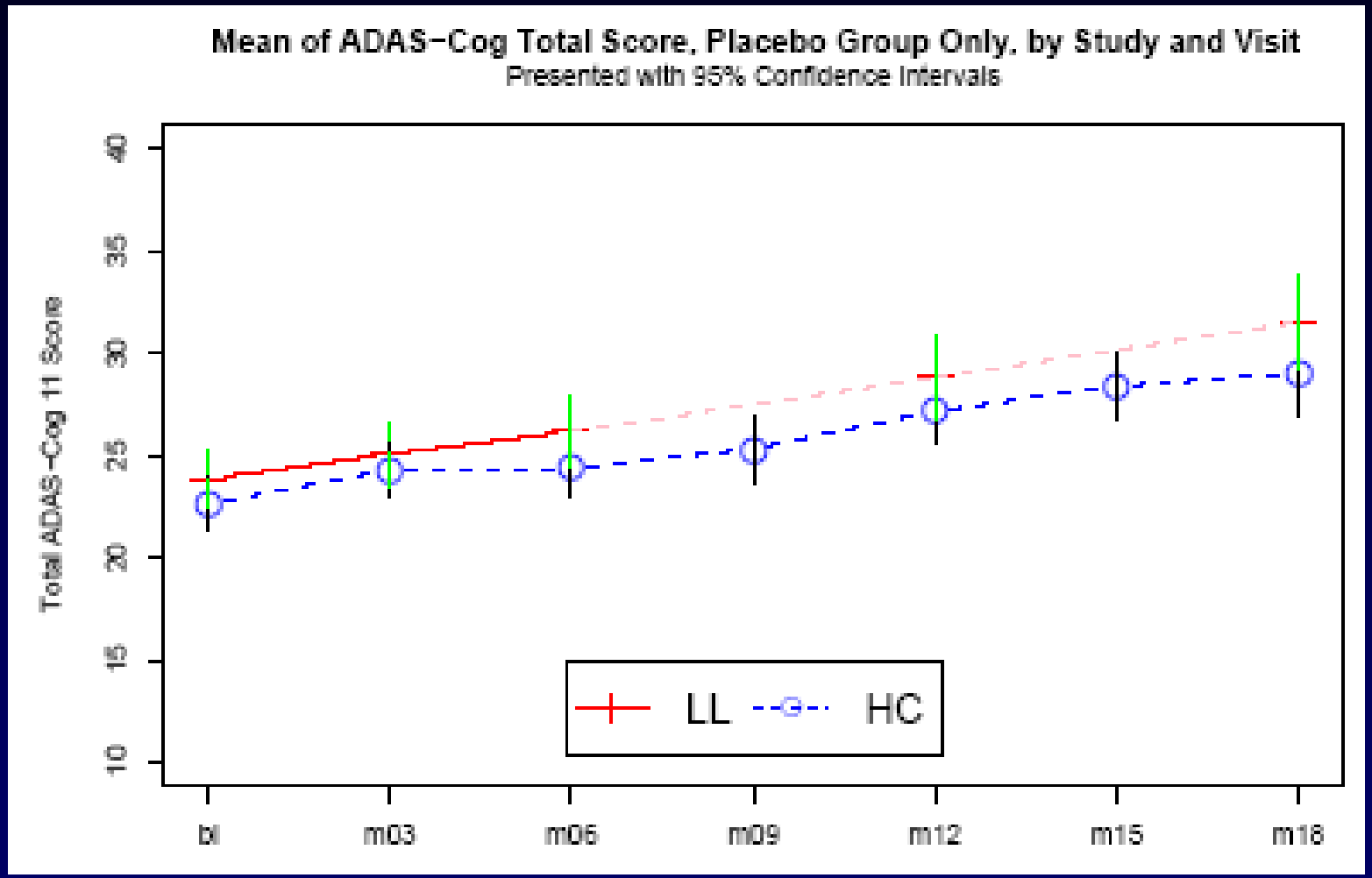
# ADAScog change

| Study | Baseline MMSE | 1 yr change | 18 mo change |
|---|---|---|---|
| Dimebon | 18.3 | 6.9 | - |
| Rember | ? | 7.0 (e) | - |
| Tarenflurbil | 23.30 | - | 7.1 |
| VITAL | 20.91 | 4.46 | 6.54 |
| CLASP | 20.70 | 5.30 | 7.97 |

# Challenges to Measuring Progression Timing: How Often

- Frequency of assessment must balance sensitivity with feasibility and subject acceptability
- Frequent assessment provides
  - stable measure, smaller measurement error
  - Increased drop-out and missing data
- Cognitive testing is a common reason for non-compliance

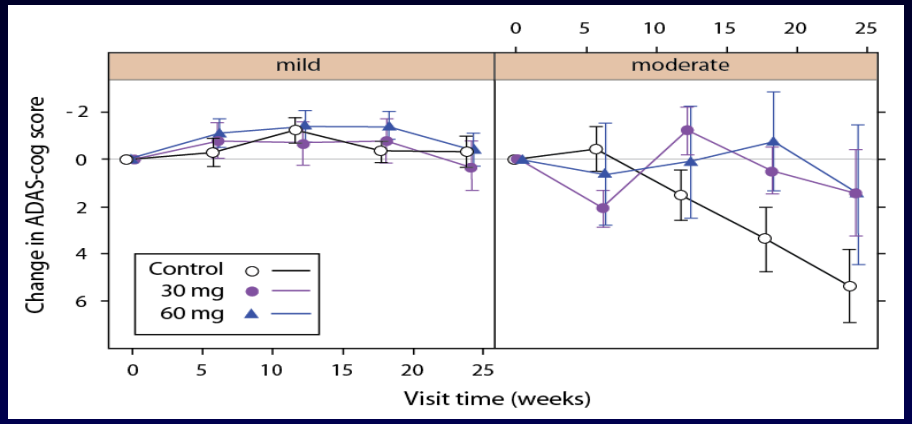
# Comparison of ADAS-cog Placebo Score



# ADL change

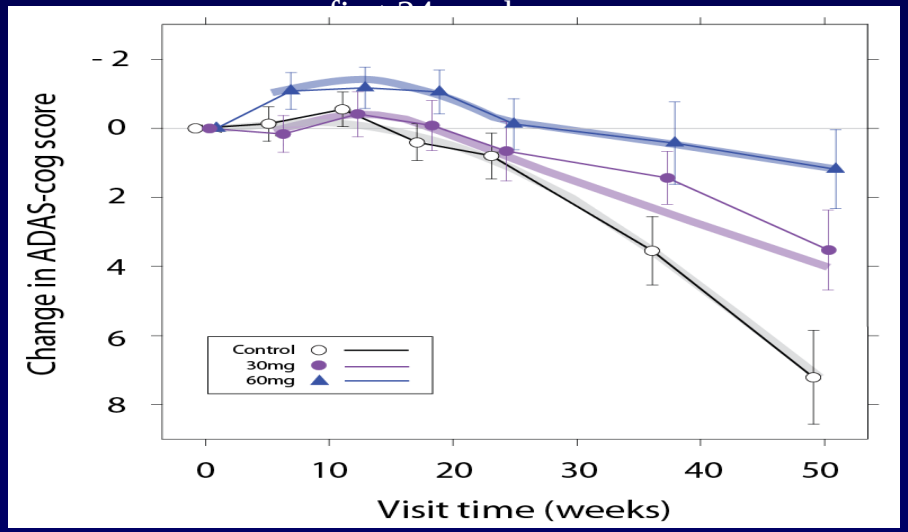
| Study | Baseline MMSE | 1 yr change | 18 mo change |
|---|---|---|---|
| Dimebon | 18.30 | 5.20 | - |
| Tarenflurbil | 23.30 | - | 9.8 |
| VITAL | 20.91 | 7.82 | 10.0 |
| CLASP | 20.7 | 6.11 | 9.51 |

# REMBER Trial Outcomes at 24 and 50 weeks




- **50-WEEK OUTCOME**
  - ADAS-cog effect at 50 weeks positive in pooled mild & moderate subjects (and in mild separately)
    - **81% reduction in rate of decline relative to controls**
    - **Mild and moderate: decline from baseline not significant**
    - 6.8 ADAS-cog unit units difference relative to controls ($p < 0.0001$)
    - Effect size at 50 weeks greater than effect size at 24 weeks ($p = 0.0091$)

- **PRIMARY OUTCOME AT 24 WEEKS**
  - **ADAS-cog effect at 24 weeks positive in moderate subjects in prespecified primary outcome analysis:**
    - 5.5 ADAS-cog unit difference relative to controls in moderates ($p = 0.021$)
    - **Moderates: decline from baseline not significant**
    - Mild controls did not decline over



# Timing
# How Long- Some Facts

- AD: current 1 yr observed change is 50% less than that reported a decade ago *(Comparison to IB for ACHI)*
- MCI conversion to AD:
  - 3yr: 45 % with impairment (-2 SD) *(ADCS MCI)*
  - 4 yrs 25% with less impairment (-1.5 SD) *(ADRC)*
- Healthy Elders
  - 65 yrs + Mean annual change on a cognitive measure Placebo: .213 (improvement) over 5 years *(WHIMS)*
  - 80 yr 7% worsen over or .250 (worsening ) over 2 yrs *(PI)*

# NINCDS-ADRDRD-revised

**Terms**

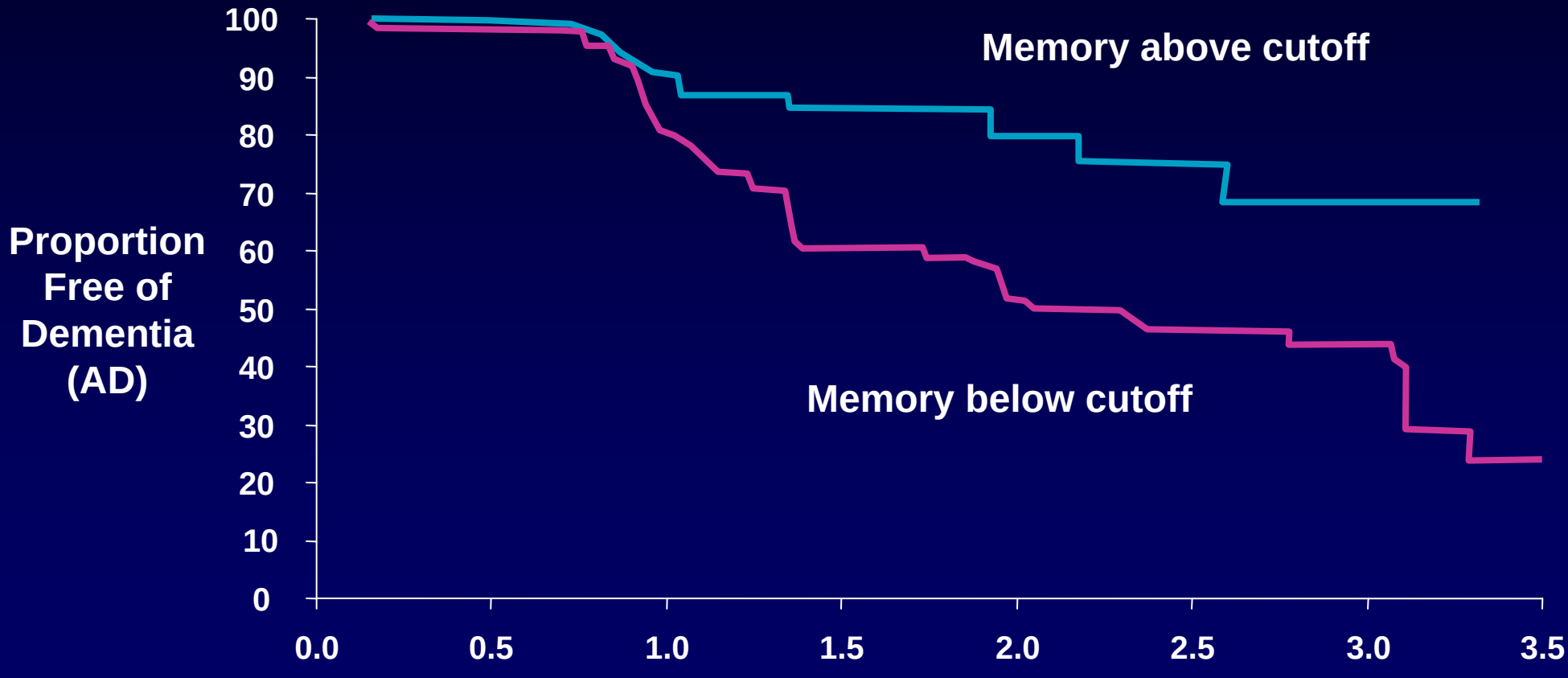
- Mild cognitive impairment
- Preclinical AD
- Prodromal AD
- AD dementia

**Probable AD**

- **Core features**
  - Memory deficit with or without othr cognitive deficit, gradual progressive
- **Supportive Features**
  - Medial temporal lobe atrophy
  - Abnormal CSF biomarker
  - Specific PET pattern (glucose metabolism or PIB or equivalent
  - Proven autosomal dominant mutation
- **Exclude by history, focality, atypicality**
- **Definite AD: pathology or genetics**

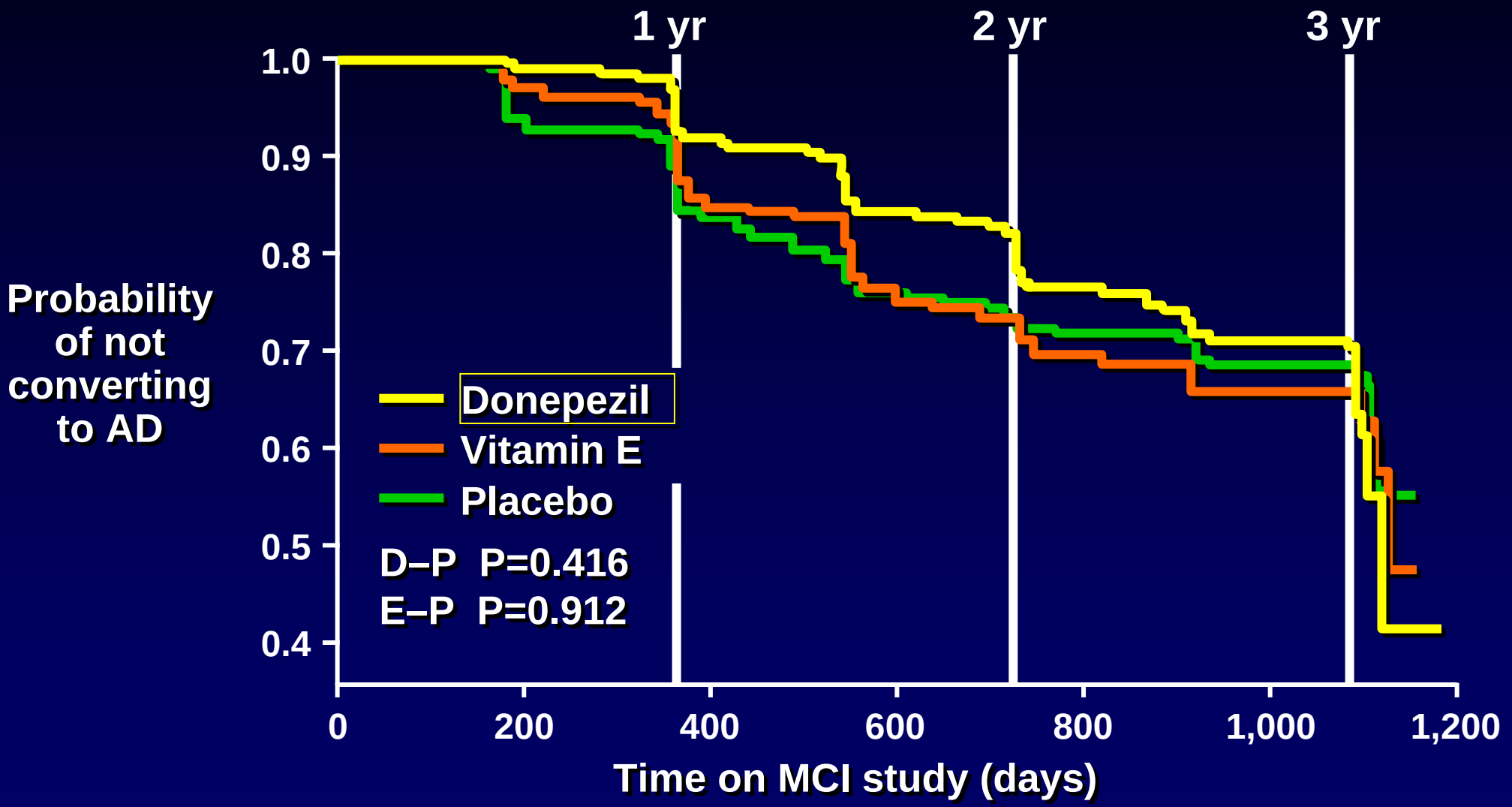
*****Dubois et at Lancet Neurology 2007***

# Memory Impairment and the risk of Alzheimer's Disease



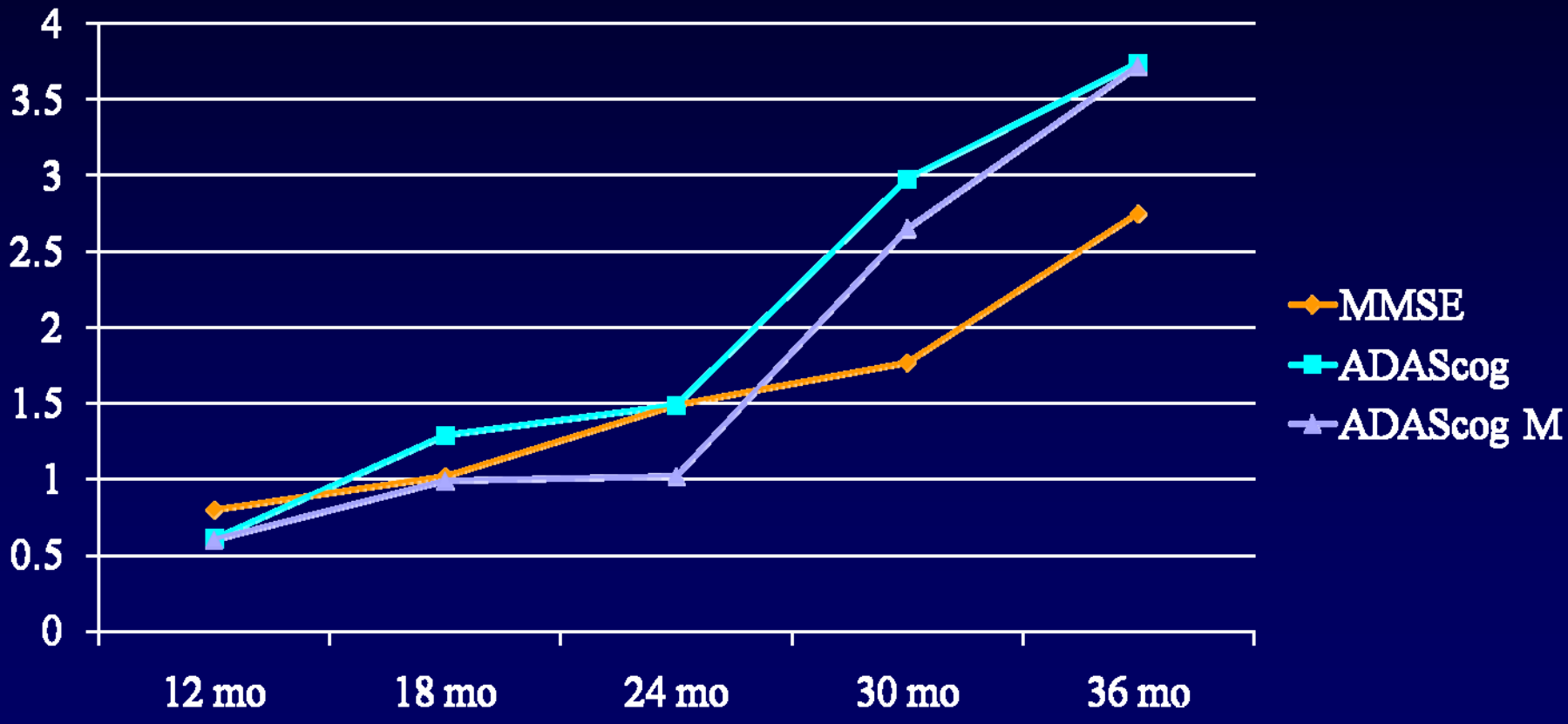

*Grundman, Peterson et al 1996*

# Conversion to AD by Treatment Group

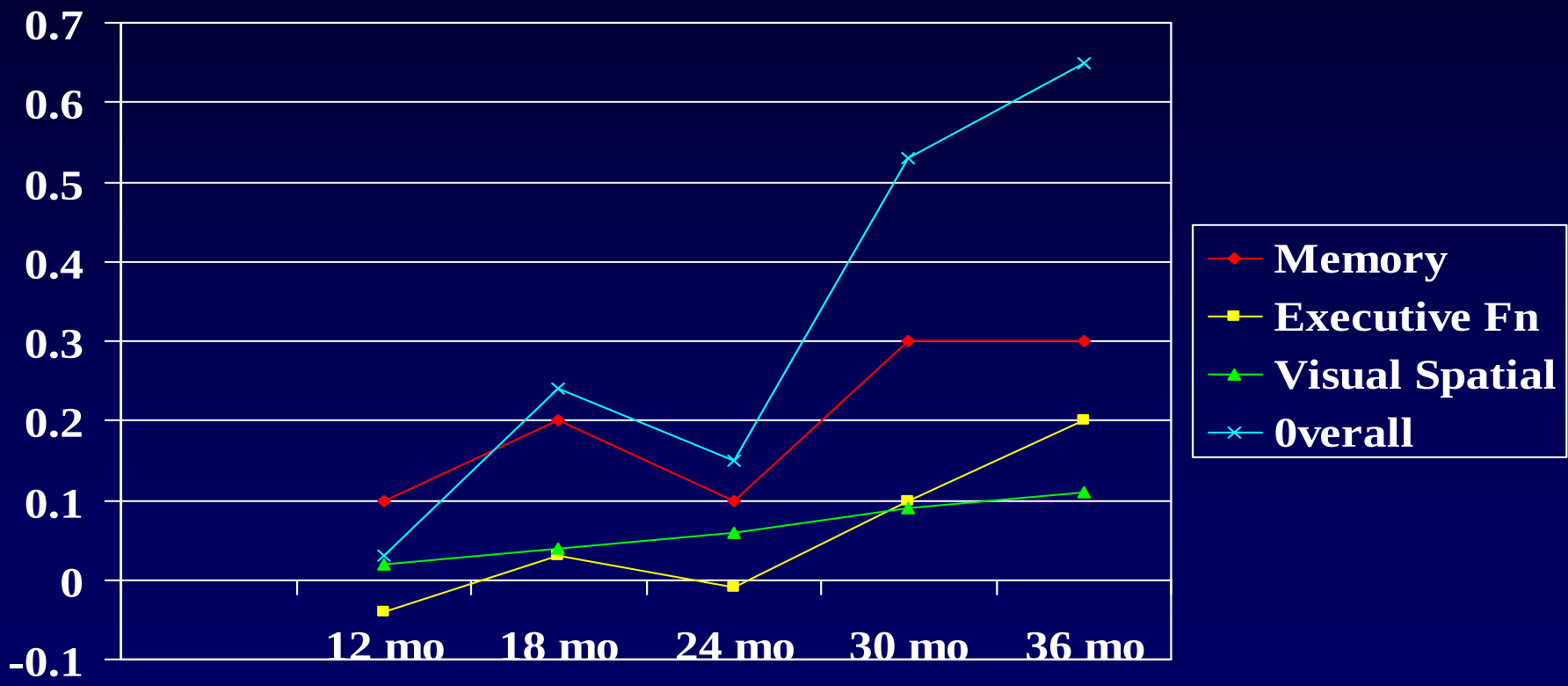


# Progression of Cognitive Decline in MCI

## *Placebo Group*

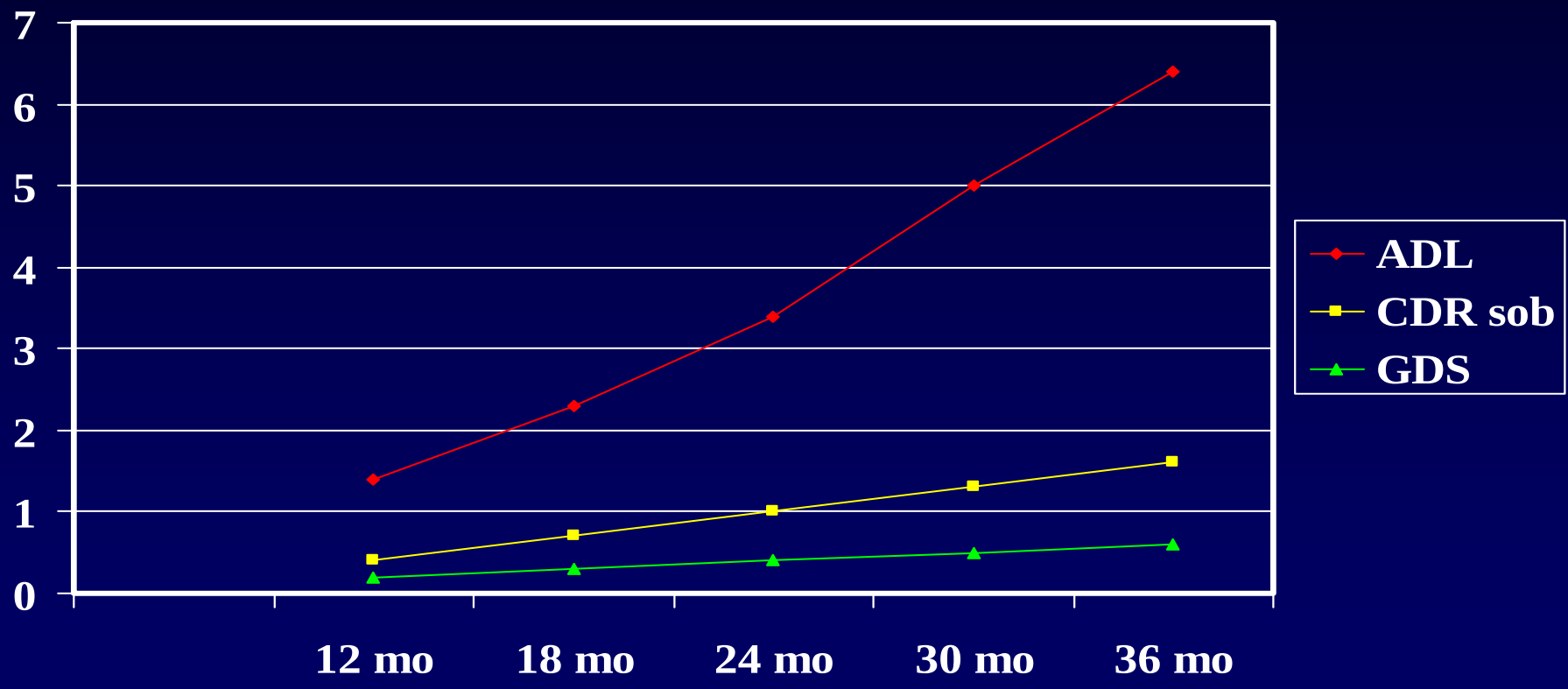


# Progression of Cognitive Decline in MCI
## *Placebo Group*



# Progression of Functional Decline in MCI

## *Placebo group*

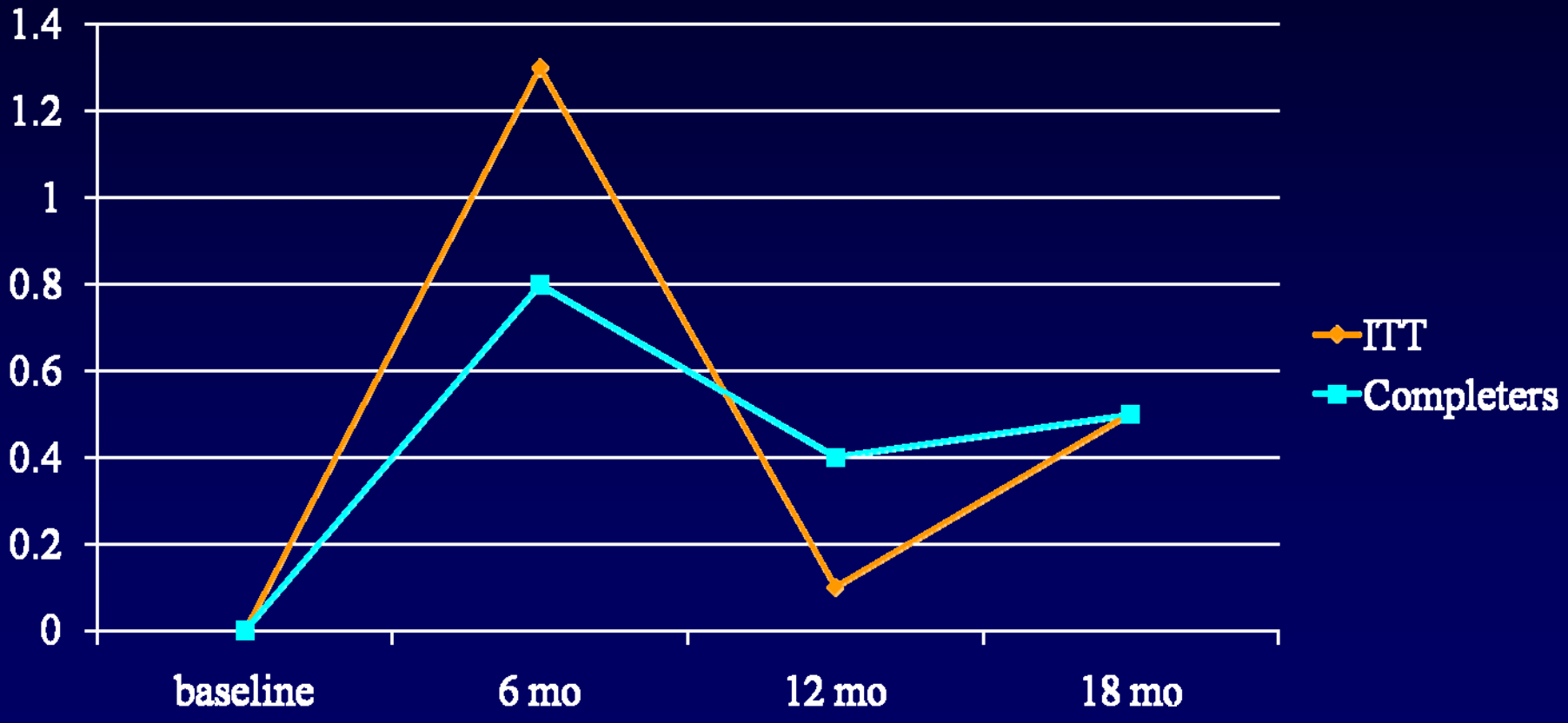



***From Petersen et al 2005***

# Measuring Cognition in the non-demented

- Methods for observing the transition from normal to early impairment will be critical for making use of the “Prodromal” or “ Preclinical” diagnoses.
- Understanding what will progress first will permit detection and provide an outcome at the population level.
- Difficult to identify a specific pattern to predict a certain disease and practice may obscure decline.

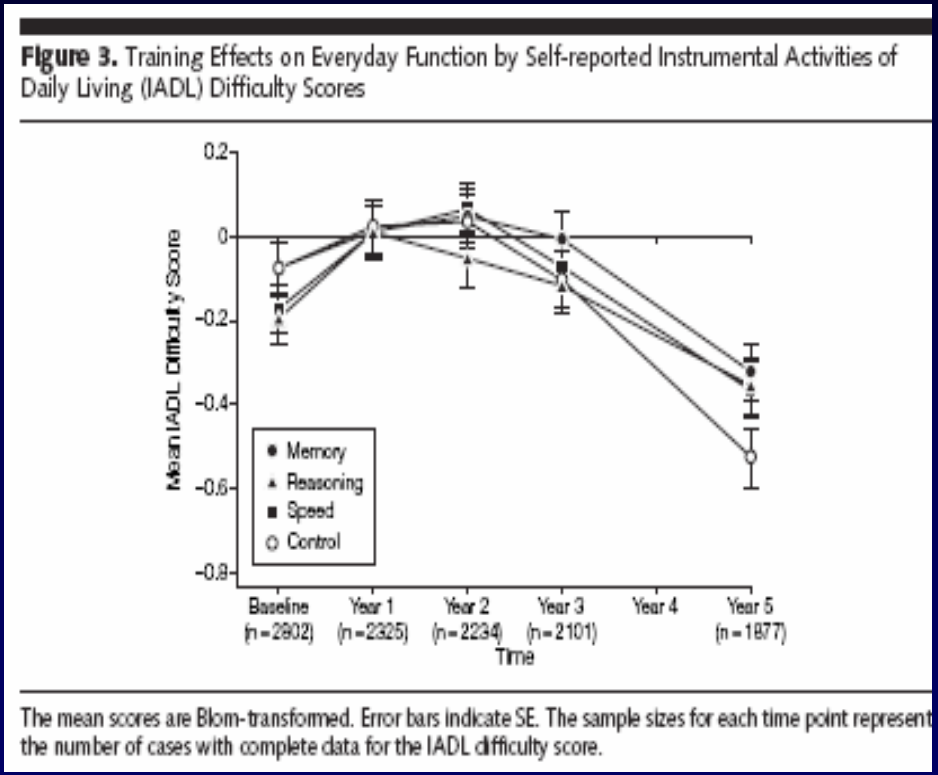
# Progression of ADAScog Decline in non-demented Elders




*Lautenschlage et al JAMA 2008*

# Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults

- Elders: ≥ 65yr community dwelling, non-demented
- 10 session Training & Booster
  - Memory, Reasoning
  - Processing Speed, Control
- 5 year follow-up
- Retained learning
- No Self reported IADL except in Reasoning group




*JAMA 2006 296; 2805-2814*

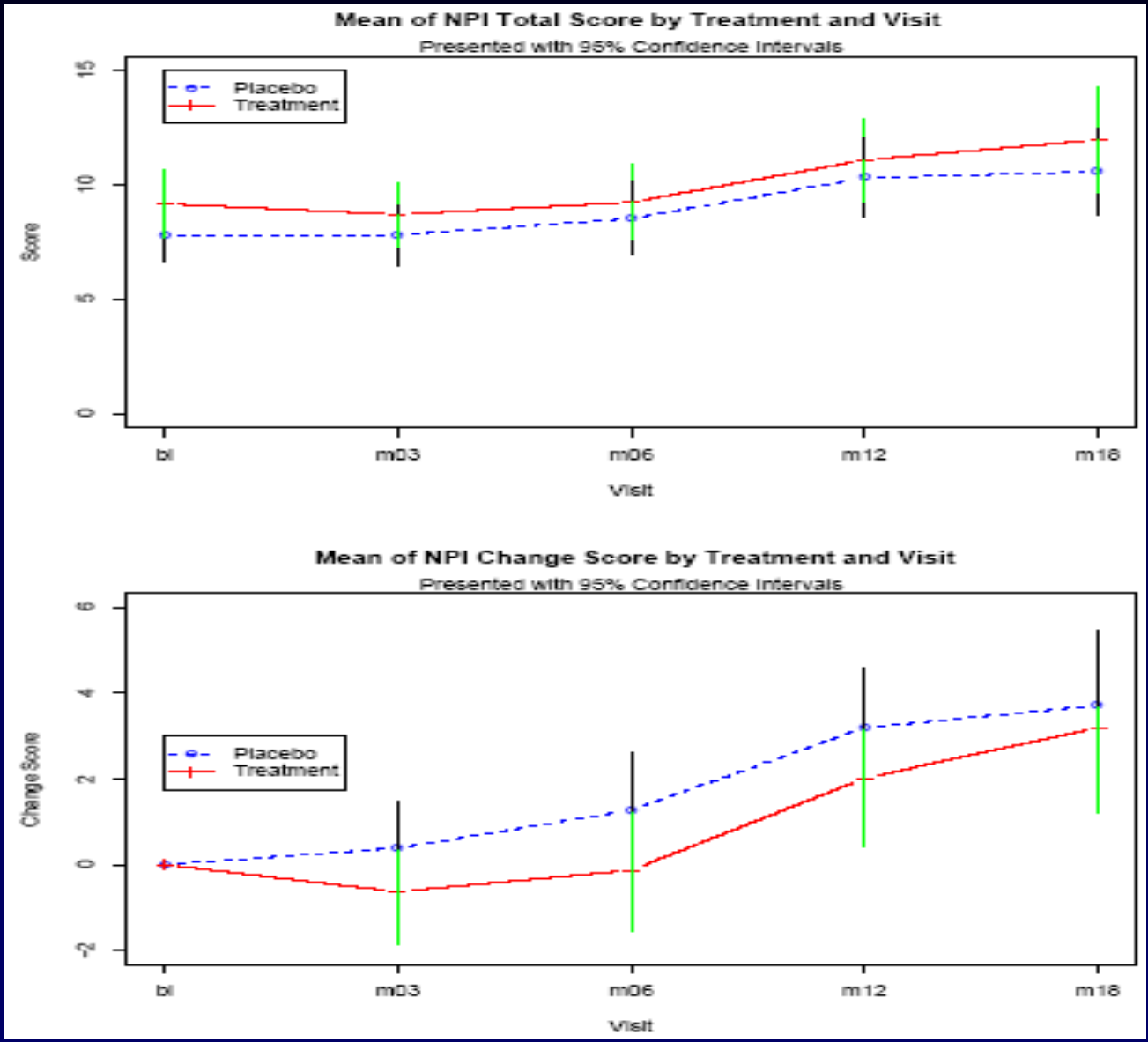
# Behavior

- Behavioral changes in AD well documented
- Represent significant disability, loss of QOL and increased expense of care and management
- Behavioral changes apparent in MCI
- Less is known about behavioral changes with age related cognitive deficits
- Behavioral symptoms are NOT currently part of the diagnosis

# Measuring Progression with Behavioral Measures

- Challenge: The nature of the behavioral disturbances change and some may decrease as others increase
- Novel approaches include:
  - Measuring new incidence of specific behaviors
  - Cumulative episodes
  - Multiplicity of presence and disruption

# CLASP: NPI


Mean of NPI Total Score by Treatment and Visit
Presented with 95% Confidence Intervals
Placebo
Treatment
Score
0
5
10
15
bl
m03
m06
m12
m18
Visit
Mean of NPI Change Score by Treatment and Visit
Presented with 95% Confidence Intervals
Placebo
Treatment
Change Score
-2
0
2
4
6
bl
m03
m06
m12
m18
Visit

# Conclusions

- Cognitive and functional instruments are able to measure clinical progression across a wide spectrum of disease severity in AD
- Progression of disease can be assessed both in terms of rate of change with continuous variables as well risk of progression or time to progress with discreet outcomes.
- These same principles of measuring progression are possible in MCI and in aging at-risk populations.