Preventing and Treating Alzheimer's Disease: Recruiting Patients for Clinical Trials

Mary Sano, PhD

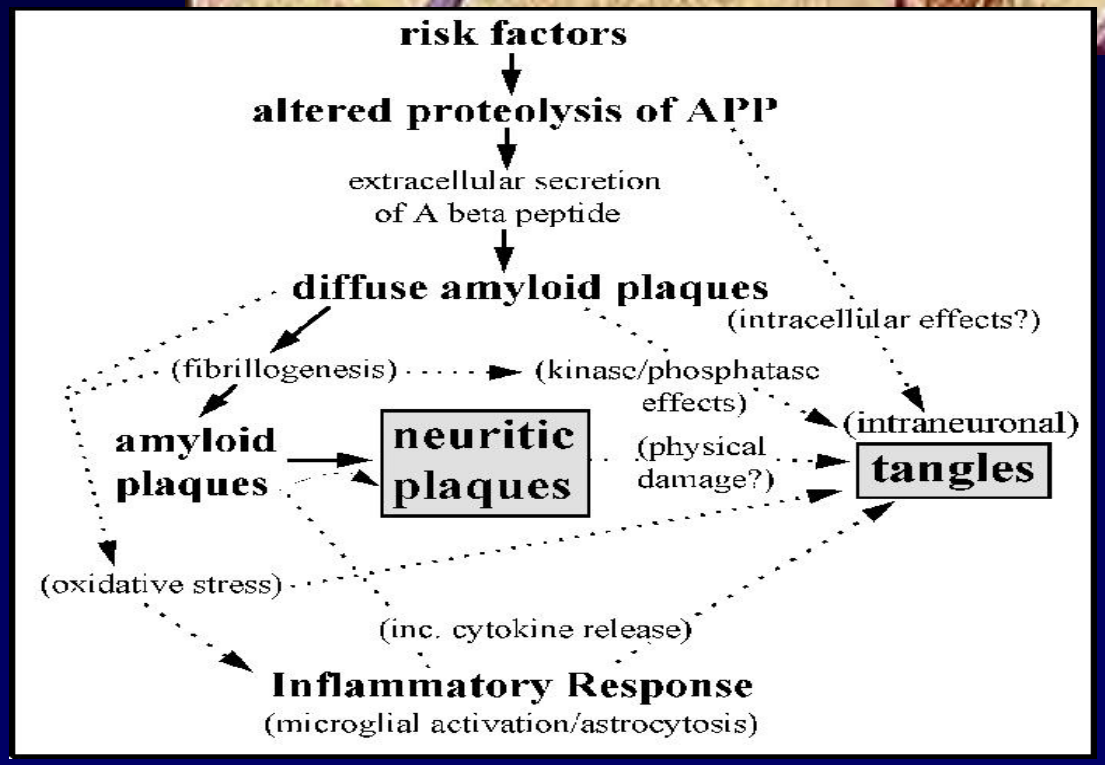
Mount Sinai School of Medicine

James J Peters Veterans Affairs Hospital

June 15, 2013

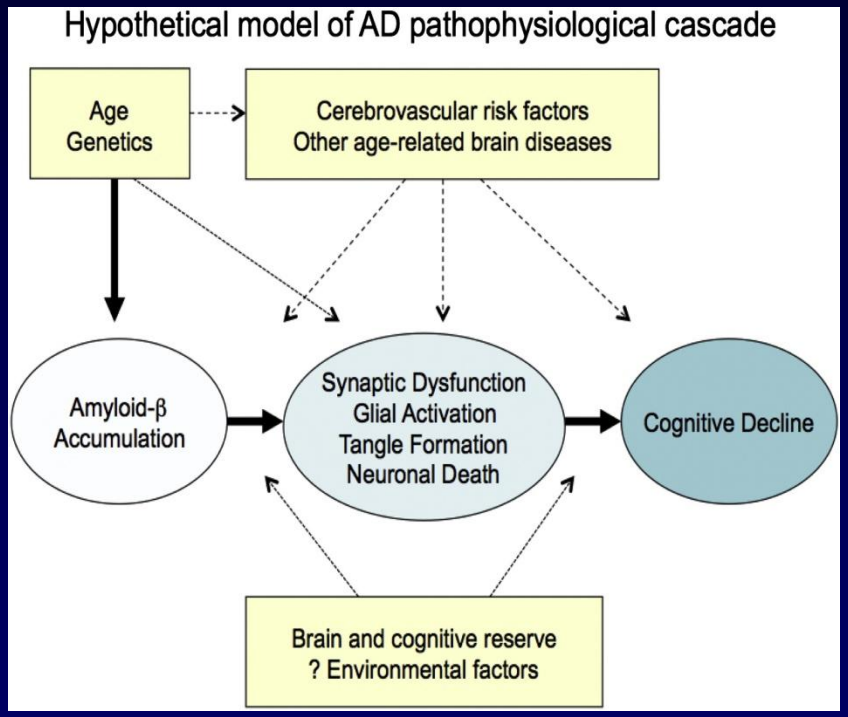
Goals and Learning Objectives.

- Current thinking about the biology of Alzheimer's Disease that can be targeted for treatment and prevention;
- Trial designs and demands in Alzheimer disease studies;
- Methods for referring patients to clinical research

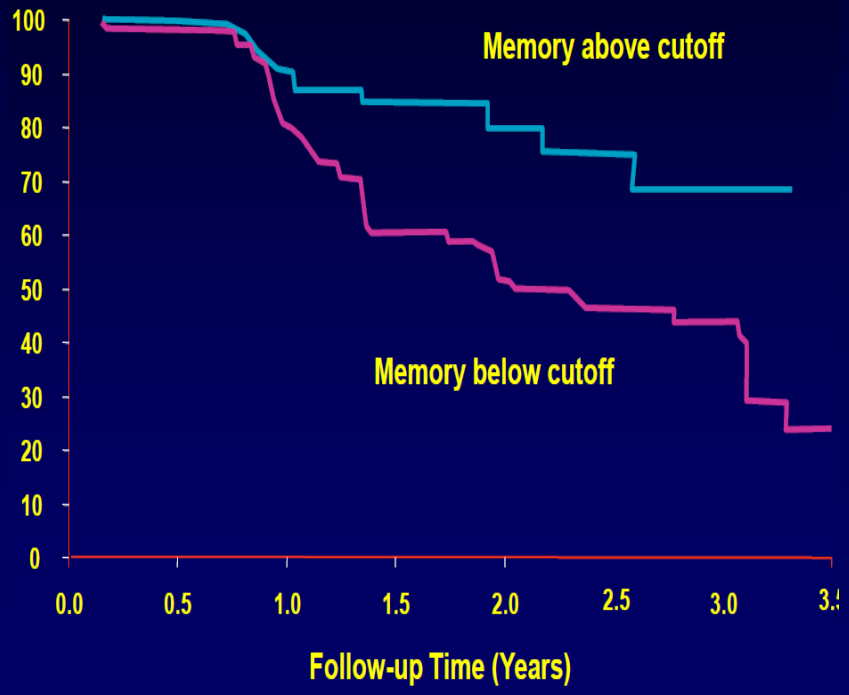


Hypotheses about Plaques & Tangles

What is Cognitive Decline



Mild Cognitive Impairment



The Good News

- Evidence of reduced incidence of dementia and cognitive decline
  - Better education
  - Higher standard of living
  - Better detection in prevalence studies

Education and Dementia

	Education Expenditure*	Incidence**		
		2005	2020	2050
Indonesia	8.1	191	314	932
Thailand	20	71.4	137	377
Malaysia	27	20	39	139
*** % of 2002 National Budget;**cases/1000**				

http://www.ei-ie.org/asiapacific/en/newsshow.php?id=98&theme=educationforall&country=indonesia

The Controversy

7 Risks for 50% of AD

- **Diabetes,**
- **Midlife hypertension,**
- **Midlife obesity,**
- **Smoking,**
- **Depression,**
- **Cognitive inactivity/ low educational attainment**
- **Physical inactivity..**

Can we really reduce risk?

- **10–25% reduction in all risk factors could potentially prevent as many as 1·1–3·0 million cases worldwide**
- **184 000–492 000 cases in the USA**

NIH Conference

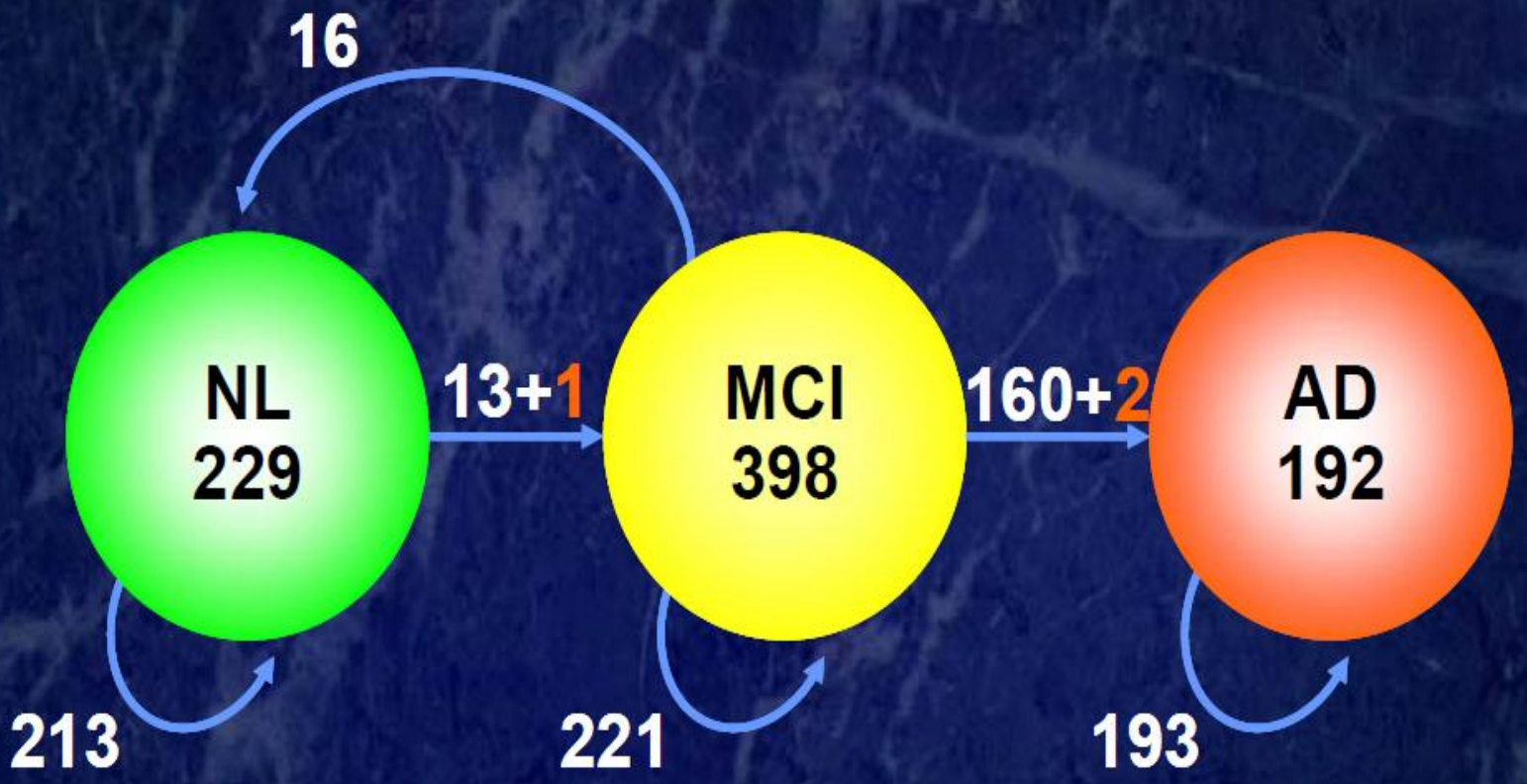
Annals of Internal Medicine

National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer Disease* and Cognitive Decline

Martha L. Daviglus, MD, PhD, MPH; Carl C. Bell, MD; Wade Berrettini, MD, PhD; Phyllis E. Bowen, PhD; E. Sander Connolly Jr., MD; Nancy Jean Cox, PhD; Jacqueline M. Dunbar-Jacob, PhD, RN; Evelyn C. Granieri, MD, MPH, MSEd; Gail Hunt, BA; Kathleen McGarry, PhD; Dinesh Patel, MD; Arnold L. Potosky, PhD; Elaine Sanders-Bush, PhD; Donald Silberberg, MD; and Maurizio Trevisan, MD, MS†

- Insufficient evidence to support… use of pharmaceutical or dietary supplements to prevent cognitive decline or AD
- Promising research is under way
  (e.g. antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement)

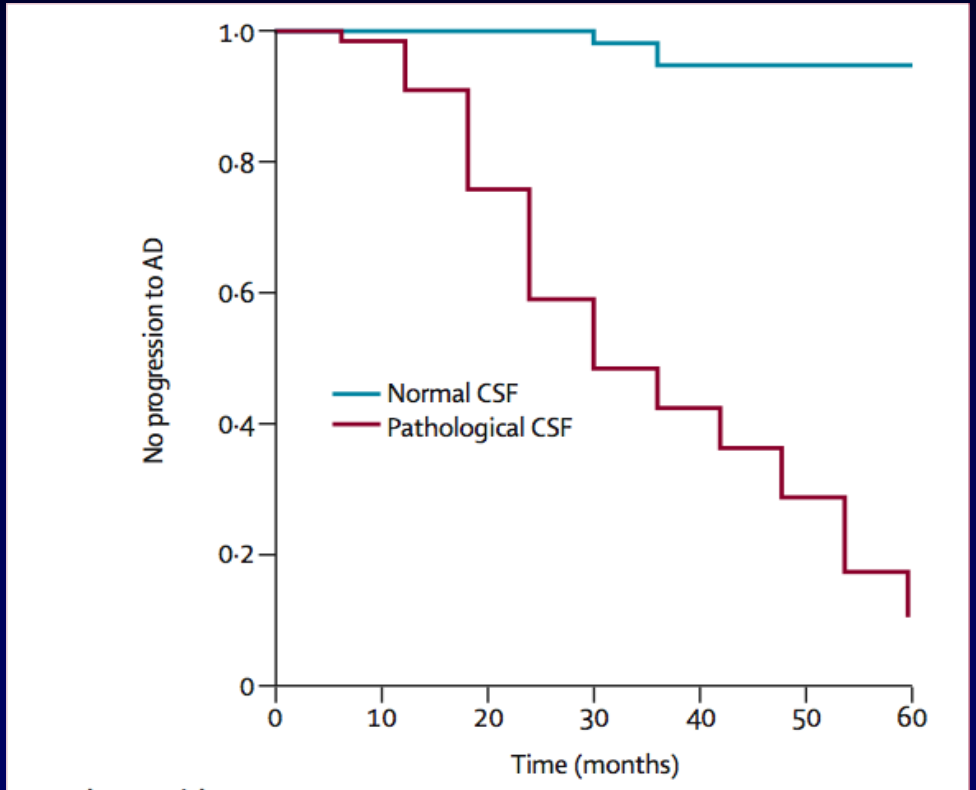
ADNI Conversion Rates



Year	Normal → MCI	MCI → AD
0-1	1.4% (0.0-3.2)	16.0% (11.3-20.4)
1-2	2.4% (0.0- 4.7)	23.9% (19.0-29.5)
2-3	0.0% (0.0-3.4)	9.5% (5.8-13.5)

CSF Levels Predict Progression from MCI to AD

- Pathological CSF:
  - $A\beta_{42}$: <530 ng/L
  - T-tau: >350 ng/L
- Sensitivity: 95%
- Specificity: 83%
- MCI population:
  - Peterson criteria
  - Memory complaint
  - Excluded causes of impairment but not white matter changes or depression



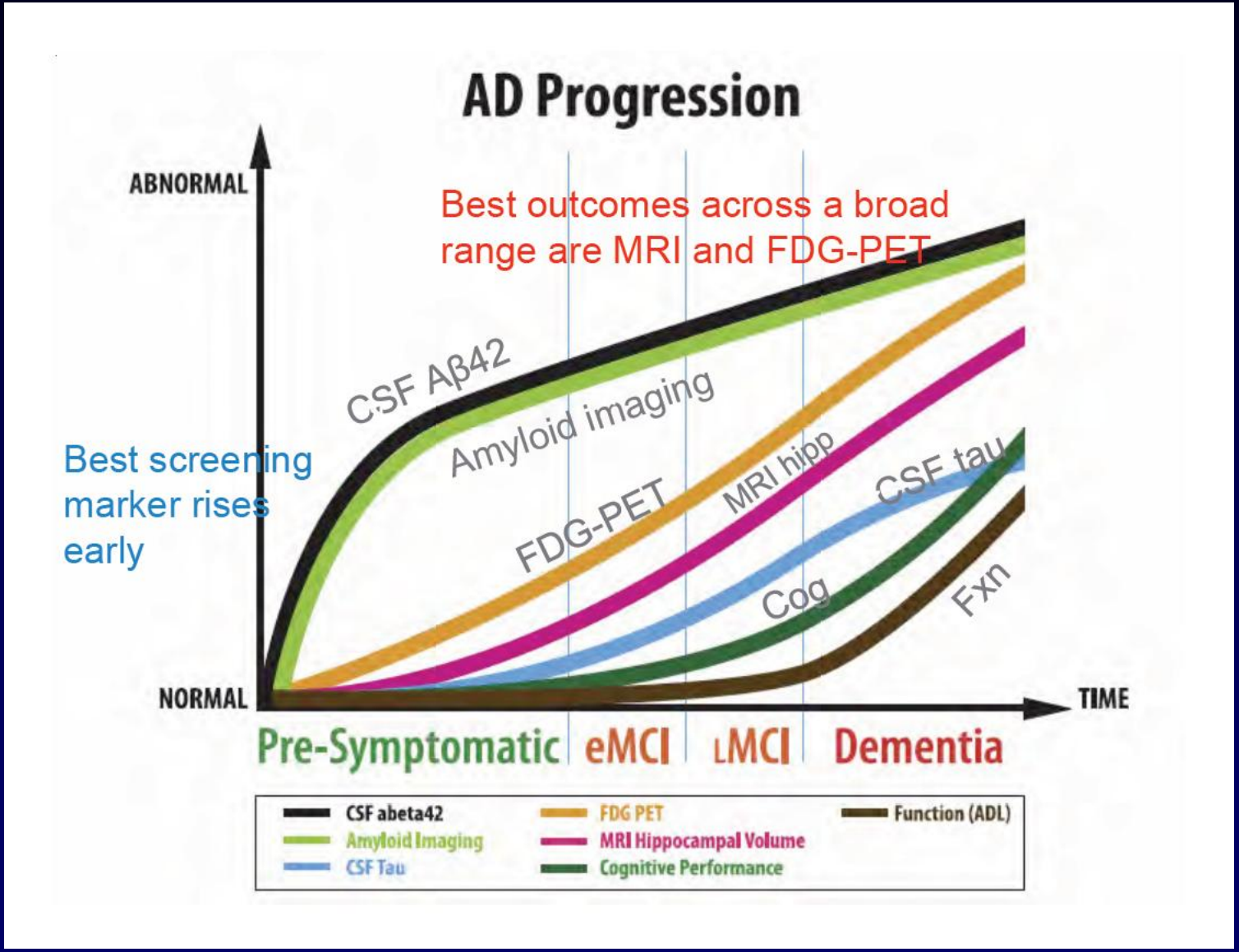
Hansson O, et al. Lancet Neurol. 2006;5:228-234. Peters RC, et al. Arch Neurol. 1999;56:303-308.

Table 2. Association Between CSF Aβ1-42/ CSF P-Tau$_{181P}$ Mixture Model Classification and Diagnostic Follow-up Broken Down by Diagnosis at Baseline

Diagnosis at Baseline	Mixture Model Classification	Latest Follow-up Diagnosis, No. (%)			*P* Value for Association[a]
		Normal	MCI	AD	
Normal	AD	37 (91)	3 (8)	0	.13
	Healthy	71 (99)	1 (1)	0	
MCI	AD	2 (1)	100 (73)	35 (26)	.04
	Healthy	3 (6)	42 (82)	6 (12)	
AD	AD	0	0	88 (100)	>.99
	Healthy	0	0	10 (100)	

100% accuracy if you have AD
35% of Normals were mislabeled AD
Only 26% of MCI labeled AD had progressed

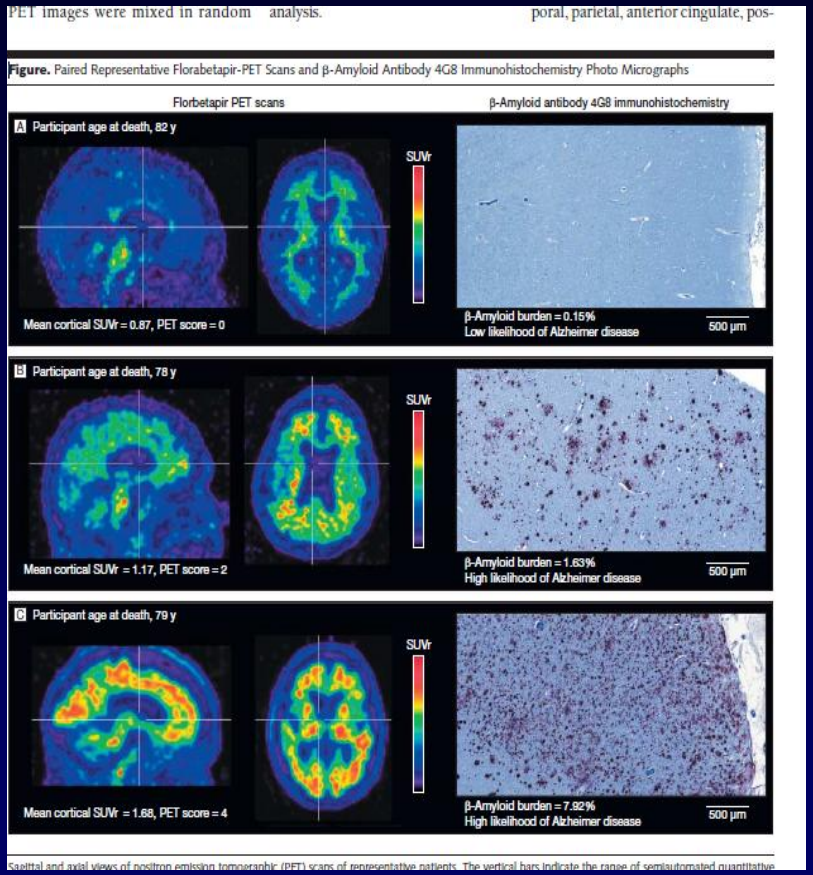
Finding the Best Measure to Predict Dise



Apolipoprotein E for AD Risk

- Risk of AD increased by presence of e4
  - OR=3.2 (95% CI, 2.9–3.5) 1 allele
  - OR=11.6 (95% CI, 8.9–15.4) 2 allele
- Recommendation for use:
  - Only as within clinical work up in symptomatic cases
    - » JAMA 1995
  - Reconsideration in prodromal or non-symptomatic?
    - » Alzheimer &Dementia 2011

Use of Florbetapir-PET for Imaging -Amyloid Pathology



PET images were mixed in random analysis. poral, parietal, anterior cingulate, pos-

Figure. Paired Representative Florabetapir-PET Scans and β-Amyloid Antibody 4G8 Immunohistochemistry Photo Micrographs

Sagittal and axial views of positron emission tomographic (PET) scans of representative patients. The vertical bars indicate the range of semiautomated quantitative

High correlation between imaging
and neuropathology

Does not rule out other pathology

Requires PET technology and proximity to ligand manufacturer

Caveat

- All prognostic markers of dementia depend on neuropsychological deficit
- To date no evidence that biomarkers in the presence of intact cognition predict dementia
  - Predict worsening, but not dementia
- *Stay tuned: as drug discovery moves forward using new criteria, this will matter*

Limitations of Biomarker studies

- All done in pristine populations
- >95% are Caucasian, college educated, at tertiary medical centers
- Little is known about prediction in the presence of co-morbidity and in the hands og general practice providers

Translational Medicine:
How we know what to test

- Observational and epidemiological studies provide hints to risk factors, protective factors and potential treatments.
- The laboratory discovers the mechanisms of pathology and models for intervention.
- Clinical Trials provide the ultimate test of efficacy and safety.

Translating to Treatments not so straight forward

Cocktail lounge, Norway:

LADIES ARE REQUESTED NOT TO HAVE CHILDREN IN THE BAR.

Instructions for using a hotel air conditioner, Japan:

IF YOU WANT TO BE COOL IN YOUR ROOM, PLEASE CONTROL YOURSELF.

Hotel lobby, Bucharest:

THE LIFT IS BEING REPAIRED FOR THE NEXT DAY. DURING THAT TIME WE REGRET THAT YOU WILL BE UNBEARABLE.

On the front desk of a hotel, Colombia:

IF THIS IS YOUR FIRST VISIT TO OUR COUNTRY, YOU ARE WELCOME TO IT.

- **Epidemiological data**
- **Laboratory Results**
- **Animal Models**
- **Biomarkers**
- **Testomonial**

Why we need to do the Trials

Observation Hint	Treatment Trials	Secondary Prevention	Primary Prevention	Comment
Anti-inflammatory	No effect in AD	No effect of COX II	ADAPT	Safety issues
Estrogen	No effect in AD	?	No effect	Safety issues
Anti-oxidant	Mild effect in AD	No effect of vitamin E	No effect	Safety issues
Statins	Mild effect in AD	?	No effect	Need more studies

Clinical Trials in Dementia How many, How Long

Group	Outcome	Sample Size	Duration
AD Patients	Symptom change Slow Progression	200-300	6 months 1-2 years
MCI	Dementia	700-1000	3-4 years
Healthy Elders	Dementia	2000-4000	5-7 years
2011		15,000	7-10 yrs

Diet Affecting Cardiovascular Outcomes

- Unpredicted result
- Favoring higher fat intake
- Simple design
- Few exclusions
- 7500 enrolled
- Consider other outcomes

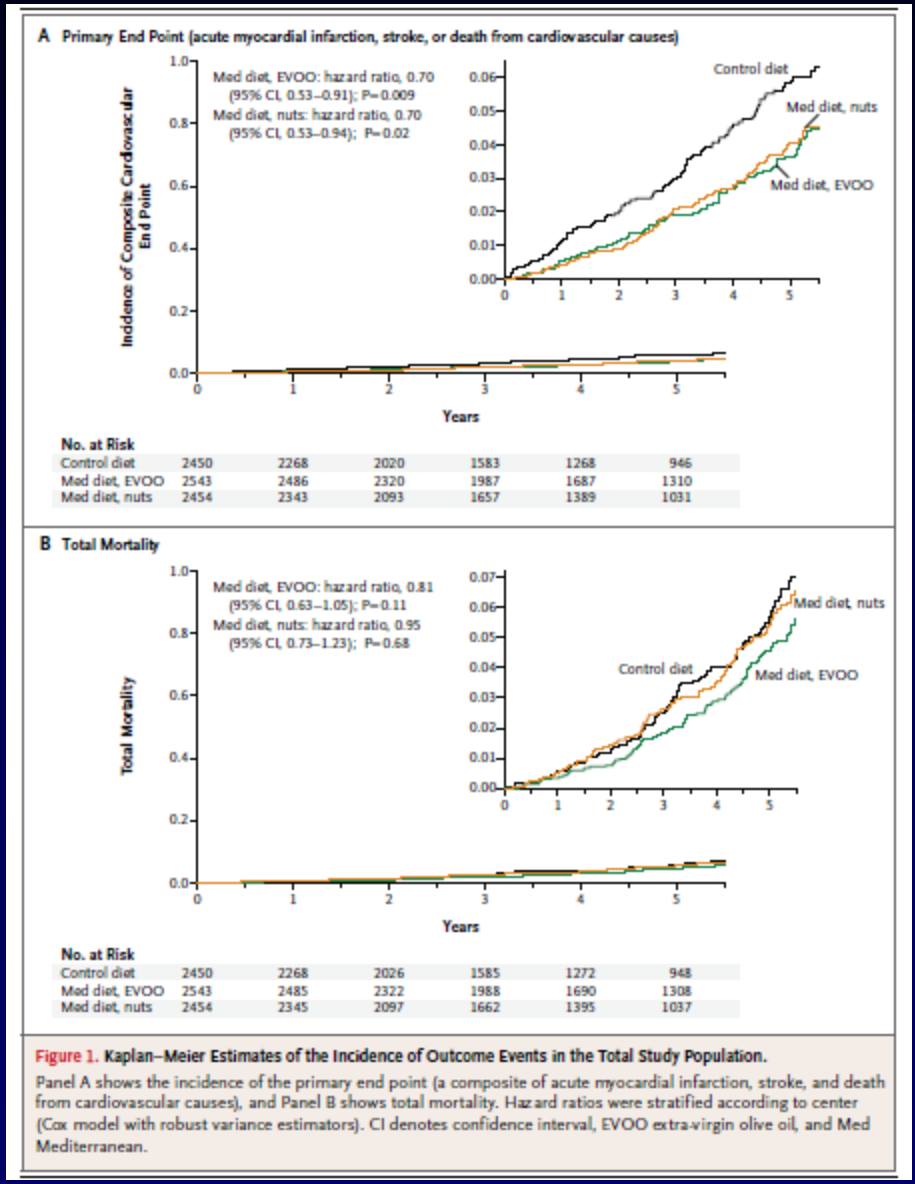
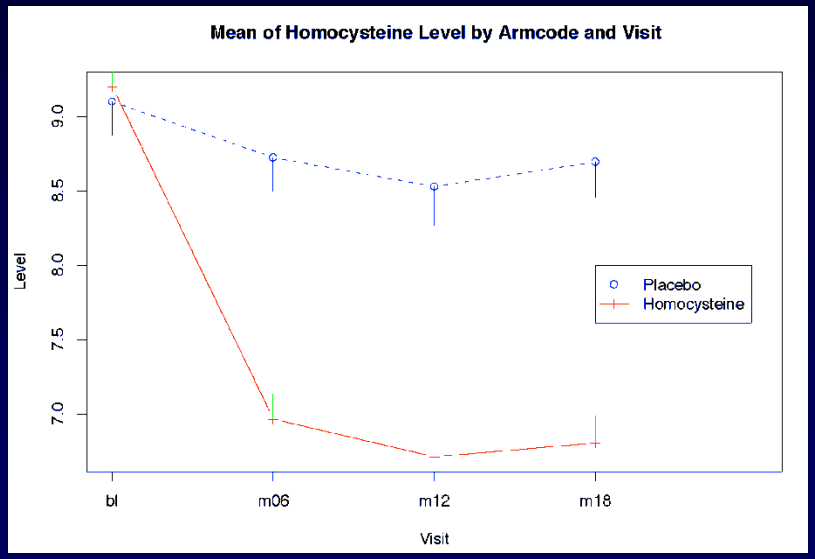


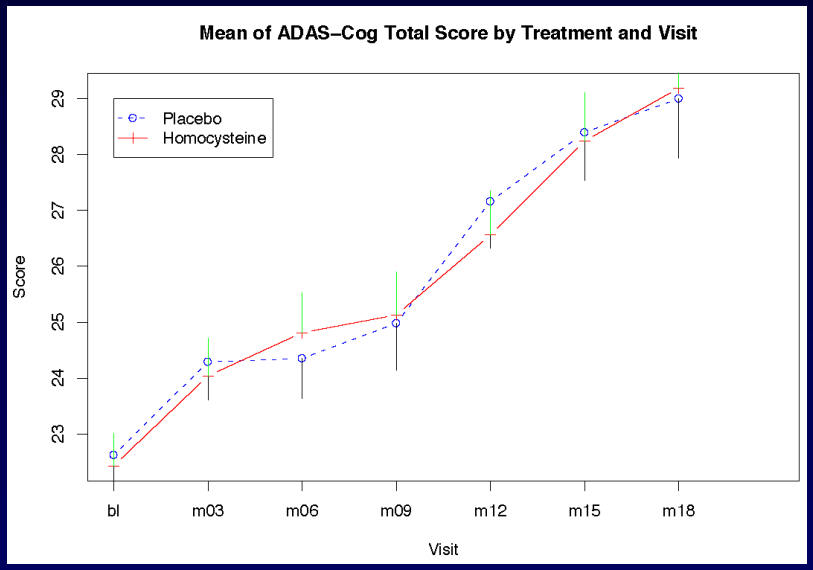
Figure 1. Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.

Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

Homocysteine Lowering in AD with Folate and B vitamins

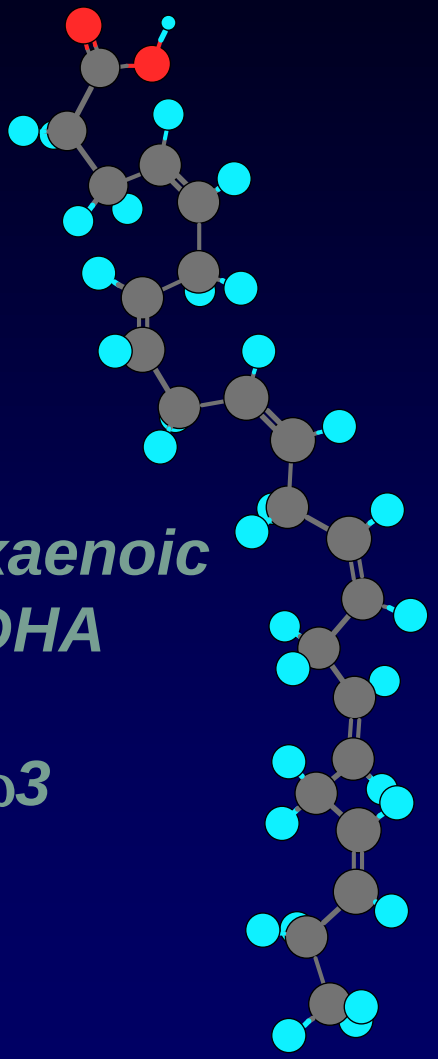
5 mg Folate 1 mg B12, 25 mg B6





- Some increase in depression
- Perhaps nutritional patterns provide maximum effect
  - Folate in grain and Use of multi-vitamins

Docosahexaenoic acid (DHA)

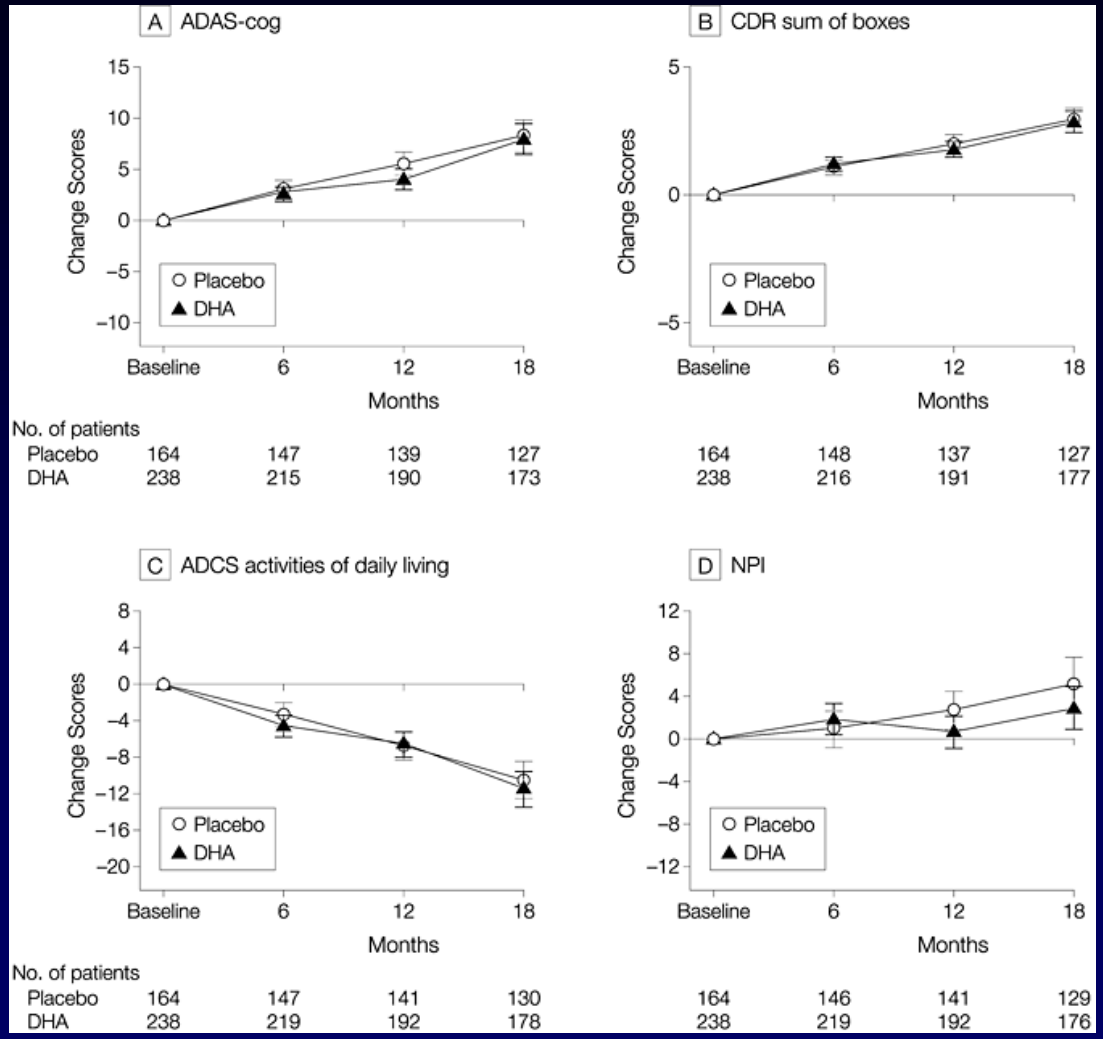


Docosahexaenoic Acid - DHA

22:6 ω3

- Omega-3 fatty acid
- Important component of cell membranes
- ***Found in all tissues***; most abundant in *neural*, *retinal* and *CV conducting tissue*
- Important in infant development and cardiovascular health

Change in Primary and Secondary Outcome Measures in the Alzheimer's Disease Cooperative Study (ADCS) DocosahDexaenoic Acid (DHA) Supplementation Trial



Quinn, J. F. et al. JAMA 2010;304:1903-1911

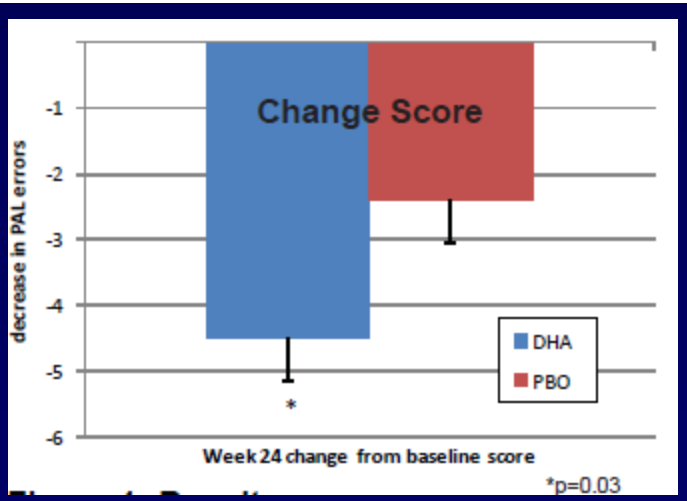
MIDAS Study

Goal

- Evaluate the effects of algal DHA on cognitive outcomes in healthy elderly (≥55 yrs.) with a mild memory complaint

Trial Design

- Study Population: Age-related Cognitive Decline
- Multi-center (19 U.S. sites)
- Randomized, double-blind, placebo-controlled, parallel, stratified by age (55-69; >70)
- Oral Dose: 900 mg/day algal DHA or placebo (corn/soy)
- Study Treatment: 6 months
- Sample Size: 485 subjects
- Primary Endpoint: cognitive test of memory & learning as measured by the CANTAB™ Paired Associate Learning (PAL) test
- Secondary Endpoints: other cognitive tests, activity of daily living skills, plasma phospholipid fatty acid levels, safety and tolerability



CLINICAL TRIALS

SECTION EDITOR: IRA SHOULSON, MD

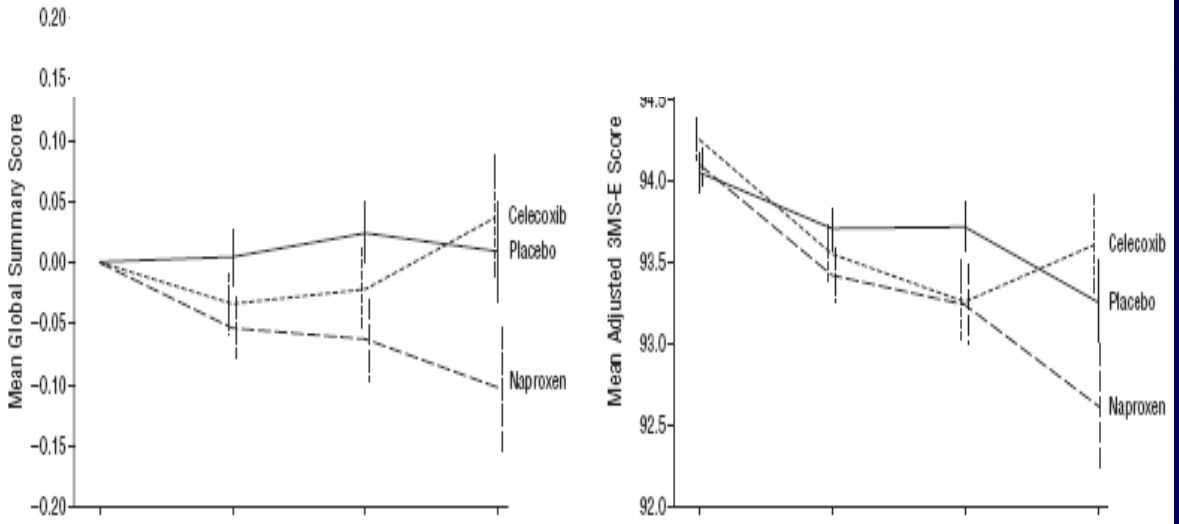
ARCHIVES EXPRESS

Cognitive Function Over Time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

NonSteroidal Trial

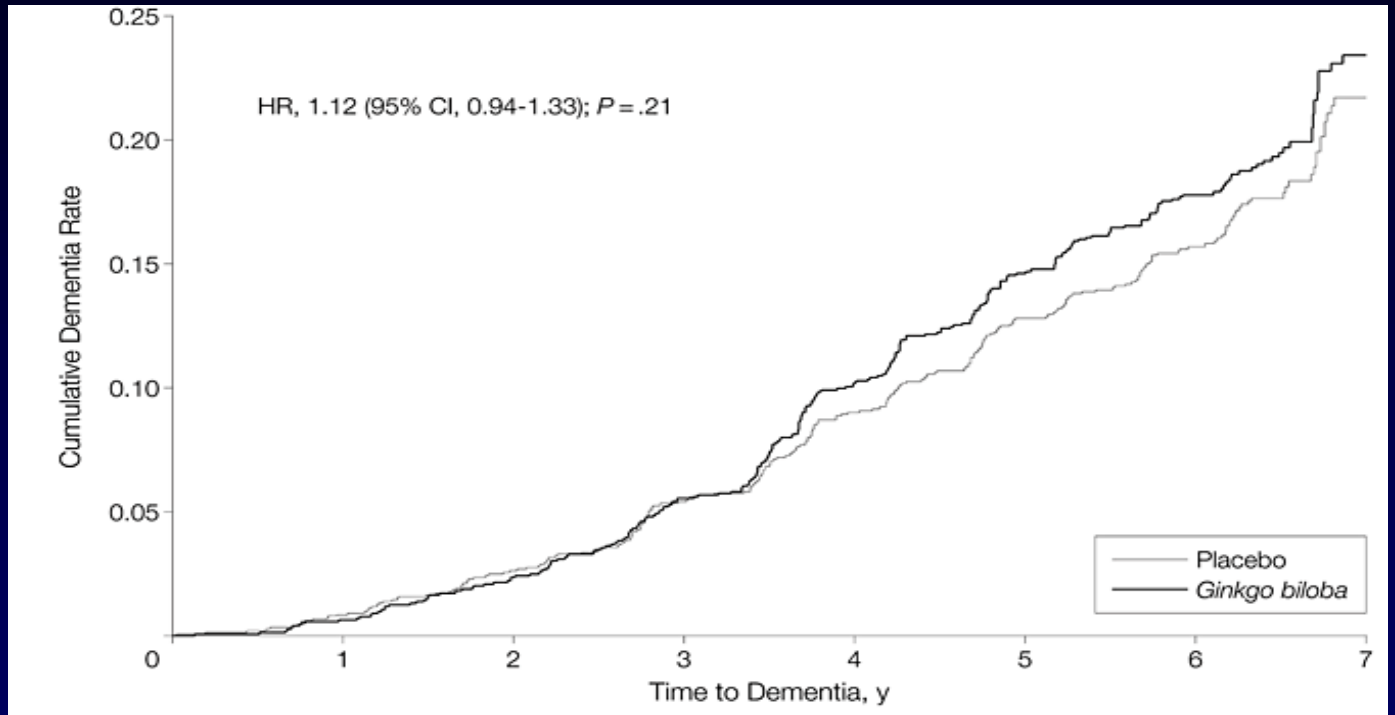
No benefit on protection of cognition

No reduction of dementia



Archives Neurol 2008

Dementia Prevention Trial Ginkgo Biloba vs. Placebo

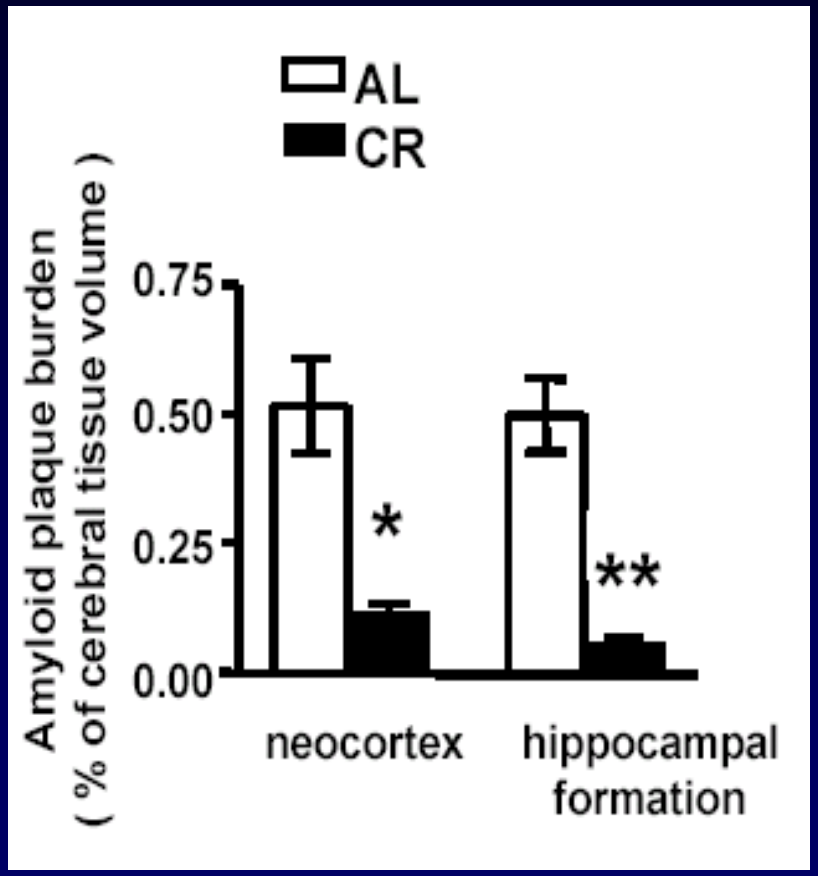


No. at risk								
Placebo	1524	1485	1423	1342	1243	1148	792	81
G biloba	1545	1521	1458	1369	1254	1129	775	97
No. with incident dementia								
Placebo	13	26	40	50	51	36	30	
G biloba	10	26	47	66	60	40	27	

DeKosky, S. T. et al. JAMA 2008;300:2253-2262.

JAMA

Understanding the Role of Lifestyle and Nutrition in AD

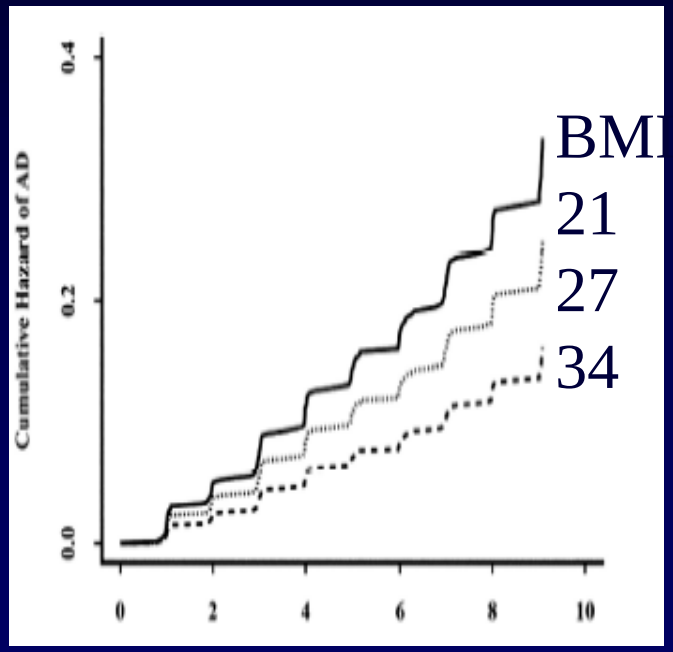


- Caloric Restriction in animals
  - Reduces amyloid
  - Increases longevity
  - Protects against motor slowing

Low BMI and Risk of dementia

- Religious Order Study
- 5.5 yrs of follow-up
- N=822
- Incident AD associated with Baseline BMI and with declining BMI
- Effect persists after adjustment for prevalent cases

Buchman et al 2005

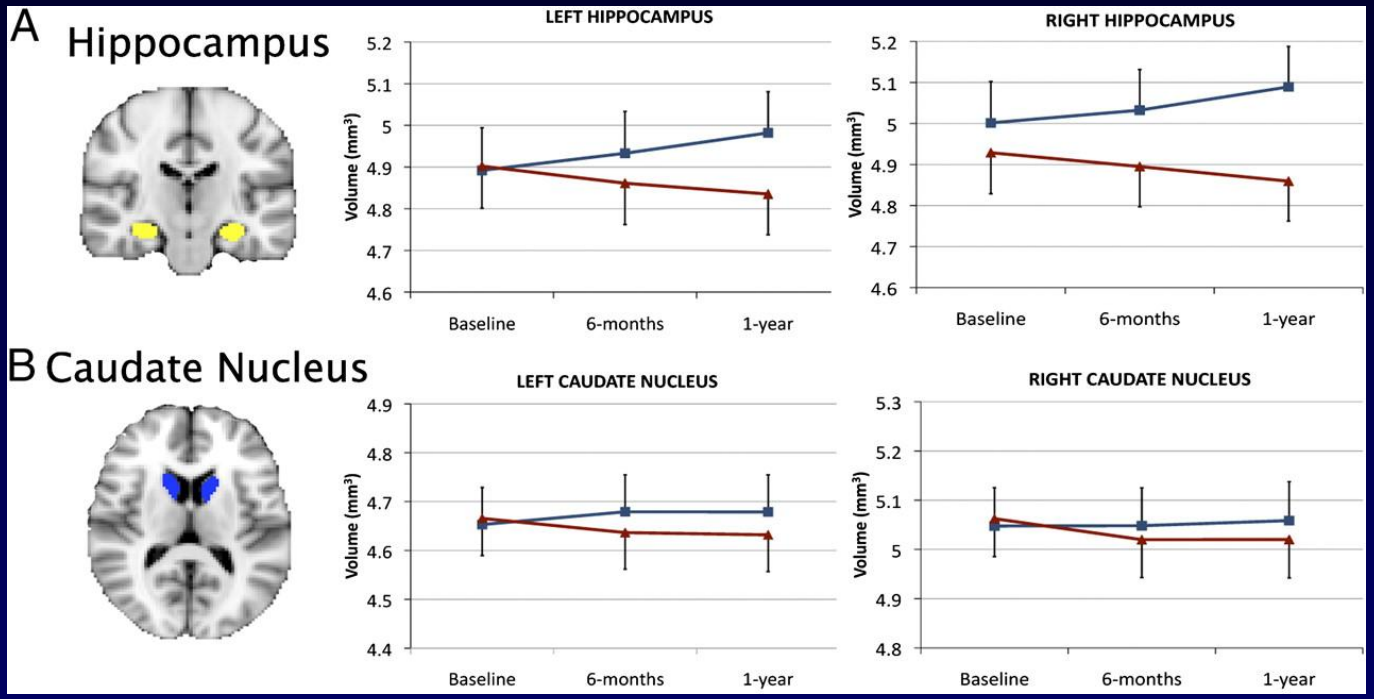


What about Physical activity to improve cognition in healthy elders

- Eleven studies of aerobic physical activity programs for healthy people (55+ yrs).
- Eight of these 11 studies
  - Aerobic exercise increased fitness of the trained group
  - Improved at least one aspect of cognitive function.
  - Cognitive speed, auditory and visual attention.
  - No consistent benefit on any domain
  - Majority of comparisons yielded no significant results.

Cochrane Collaboration

Stretching and Aerobic Exercise Improved Spatial Memory *Only Aerobic Exercise Increased Hippocampal Volume



Erickson K I et al. PNAS 2011;108:3017-3022

Leisure Activities

- **Board Games***
- **Reading***
- **Musical Instruments***
- **Crossword Puzzles***
- **Writing**
- **Group Discussions**
- **Dancing***

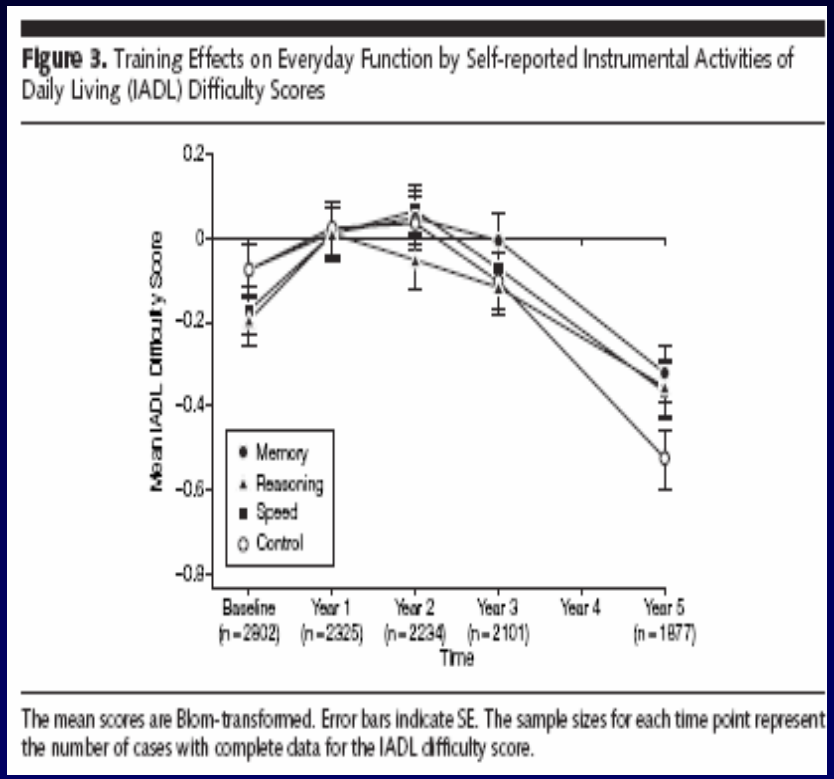
- Individual activities seem to have some benefit
- 1 cognitive activity /1day/ week= 7 % reduced risk
- 11 activities/day = 63% reduced risk
- ***Now we need the randomized trials***

Does Memory Training Help?

- Memory training may provide immediate help with specific material.
- Little evidence of generalizability.
- Tends to improve self esteem and reduce complaint in those without serious memory problems.
- In the presence of serious memory problems consider the risk of frustration.

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

Home Based Assessment: Background

- Develop efficient/effective methods for Primary Preventions Trials in dementia using new technologies
- Will Home Based Assessment (HBA) improve:
  - Recruitment of diverse elders?
  - Retention and reduce study costs?
  - Participation of those who find clinic-based assessment interferes with lifestyle?
- Aims:
  - Establish feasibility of HBA
  - Assess acceptability and efficiency of new methods of assessment

Proposed Technologies and Domains

- Mail In Administration & "tester administered" phone-based cognitive assessment **(MIP)**
- Telephone Assessment, automated presentation with vocal and key pad response **(IVR)**
- Computerized Assessment for presentation and response capture **(KIO)**

- Cognitive
- Functional
  - IADL
  - Performance-based Medication Compliance****
- Global
- Behavioral
- Quality of Life
- Pharmaco-economic

Dissatisfaction with Technologies

- **“so ugly”**
- **“takes up so much room”**
- **“glow disturbs sleep”**

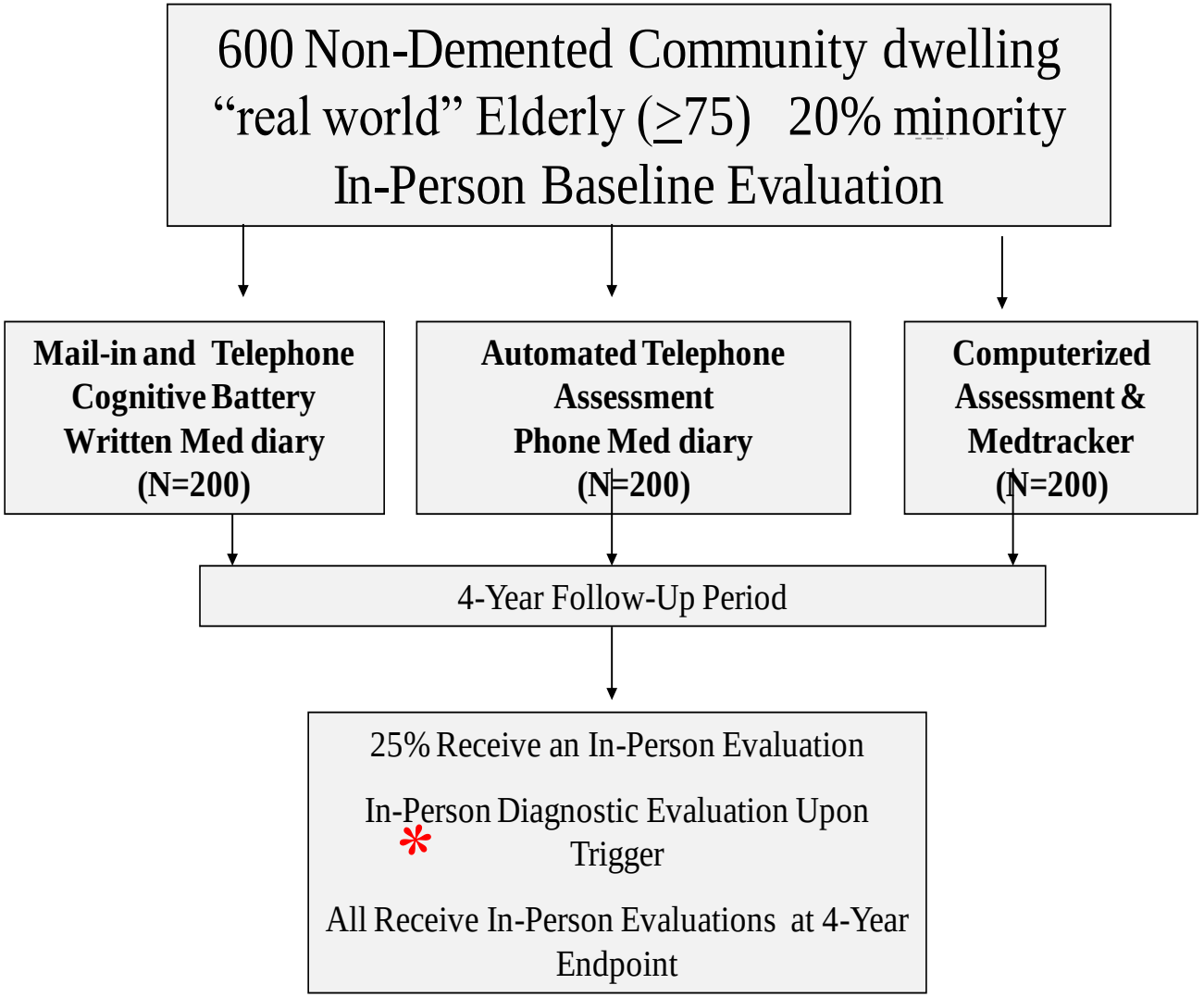
- **“interference of phone line”**
- **“static on line”**

Study Design

Subjects

Randomized to Home-Based Assessment Technologies

Procedures



Entry Criteria

Inclusion

- Age ≥ 75
- MMSE ≥26
- Independently living
- Study partner desirable but not required

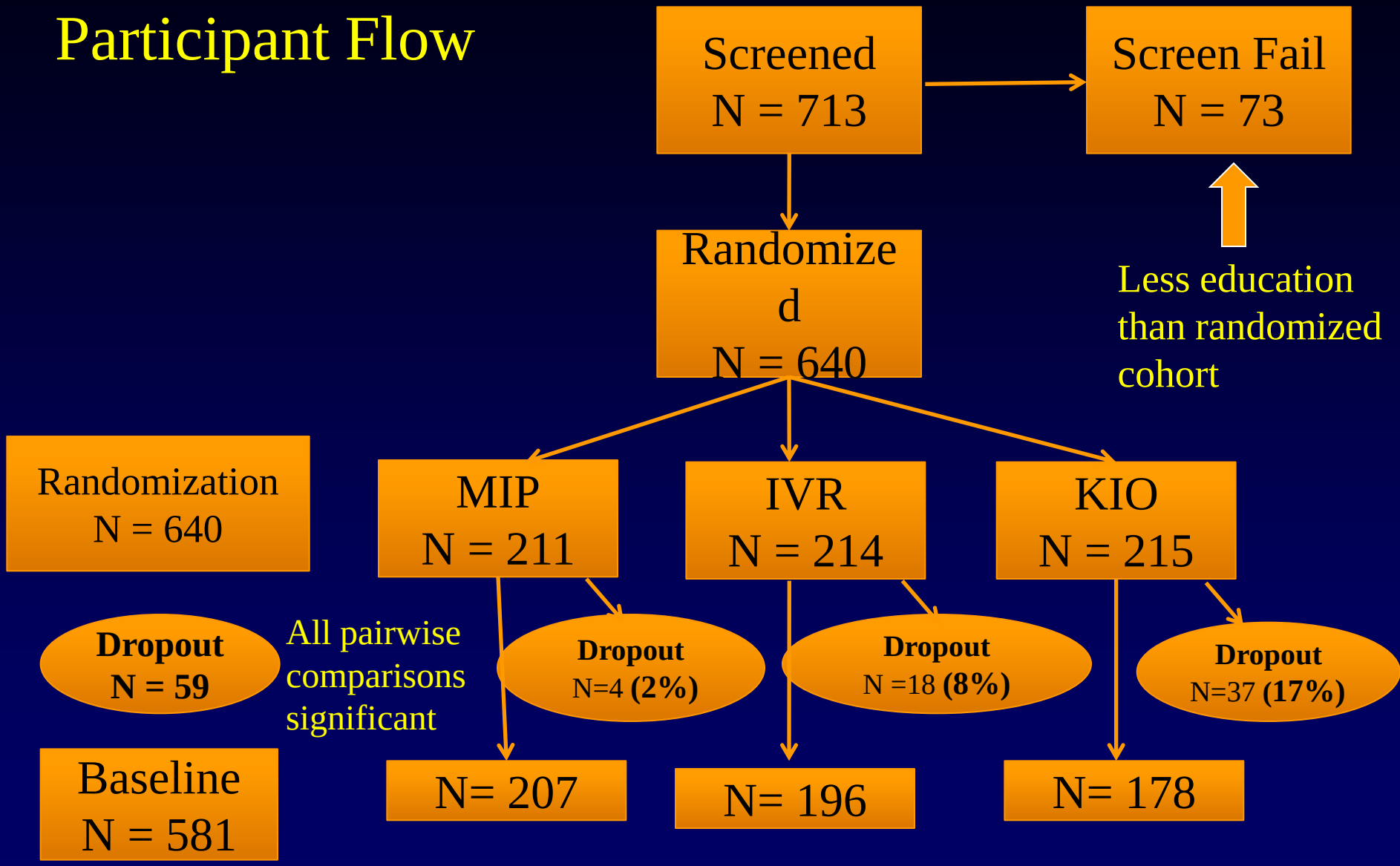
Exclusion

- Dementia
- Use of prescriptive cognitive-enhancing
- Use of non-study multi-vitamins
- Other conditions causing cognitive impairment
- Life expectancy < 5 years

1 in 5 enrollees were required to be "Minority"

All assessments were available in-home

Participant Flow



Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined

N	581	
Age *	80.9 (4.4)	Range = 75 – 98
Education	15.6 (2.9)	Range = 0 – 20
% Female	67	
% Racial/ethnic minority *	22	
% Married	42	
% History of hypertension	59	
% Cardiovascular disease	74	

No differences between baseline cohort and cohort that passed screening and discontinued after randomization

Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined (cont'd)

N	581
% Self-Report Current Memory Problem	28
% Self-Report Current Memory Problem is a Change from Before	21
% Self-Report Current Memory Problem worse than age peers	3
% MCI, by assessment	19
% APOE 4 (N = 471)	25
MMSE	28.8 (1.2)

Who Refused and Why?

Drop Out By Arm And Frequency		
MIP Annual	4 /105	4%
MIP Quarterly	0/106	0%
IVR Annual	7/107	6%
IVR Quarterly	11/107	10%
KIO Quarterly	16/109	15%
KIO Monthly	21/106	20%

Nature of complaints:

Inconvenience of the equipment

Too much time to participate

Efficiency

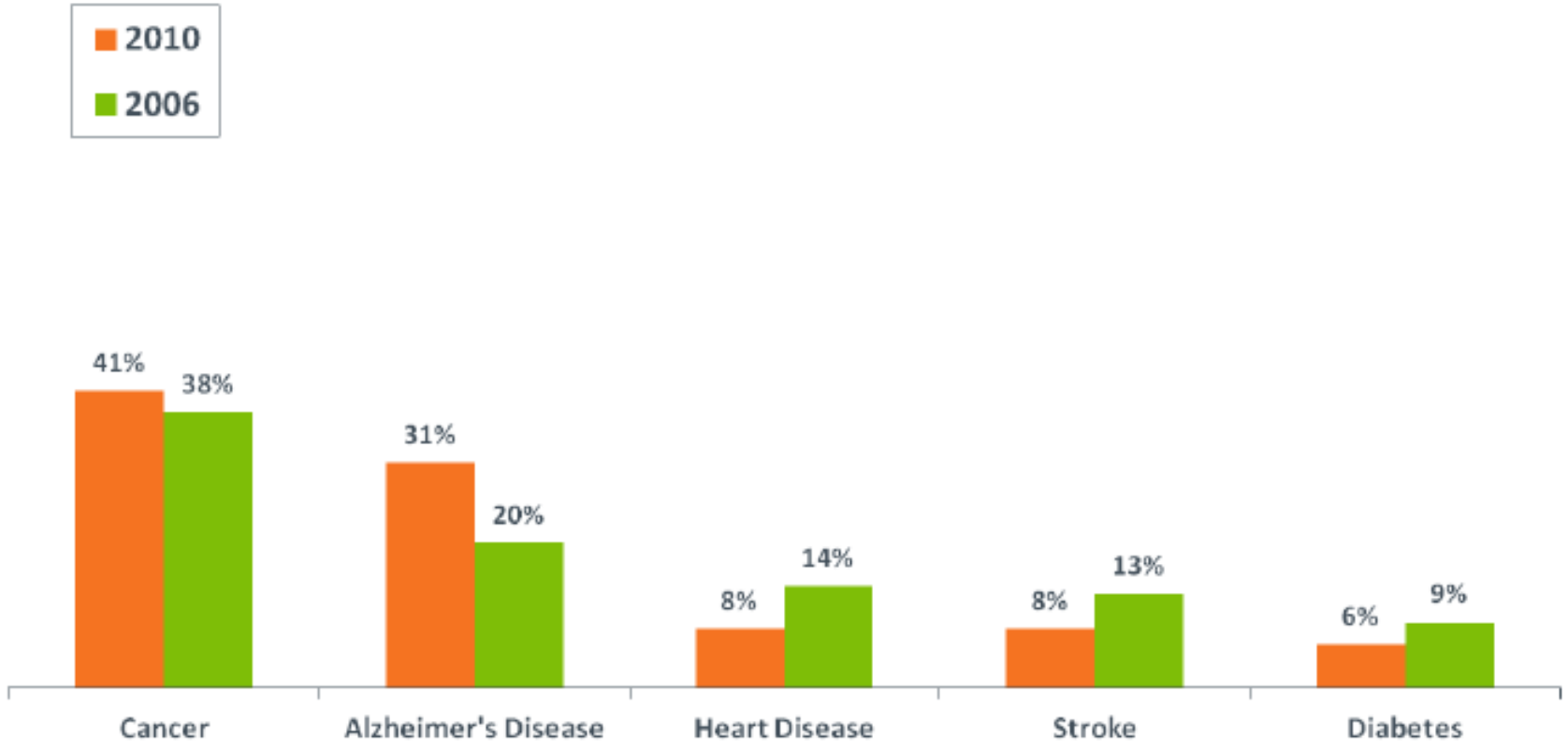
	IVR	KIO	MIP
Days to Baseline	39.2 (25.8)	55.7 (42.3)	33.5 (25.5)*
Training Time	39.1 (20.6)	76.7 (60.1)	25.6 (15.2)*
Preparation Time	24.0 (20.6)	141.4 (140.8)	18.6 (17.1)*
Time at Baseline w/o Testing	11.1 (16.8)	73.4 (235.6)	8.44 (23.77)*
Testing time	NA	NA	31.2 (12.8)
Total Time	72.0 (37.7)	280.4 (314.5)	79.1 (39.0)*
**P<0.001*			

Longer time from Screen to Baseline for KIO
Longer Training time for KIO and IVR
Longer Preparation Times for KIO

Summary/Considerations

- HBA trial enrolled a diverse, elderly cohort
- High technology assessment methods
  - Acceptability not affected by subject demographic and clinical characteristics
  - Require more time at study initiation
- Inconvenience of equipment and assessment frequency associated with non-participation
- Cognitive and functional assessments demonstrate adequate range to observe change over time

Fear of Alzheimer's Disease in the United States.



Since 2006, the percentage of those who fear getting Alzheimer's has increased more than the other illnesses.

What can you do to prevent cognitive loss and dementia

- Treat treatable conditions
- Protect the brain
- Maximize physical activity
- Maintain cognitive stimulation
- Insure social engagement
- Support research

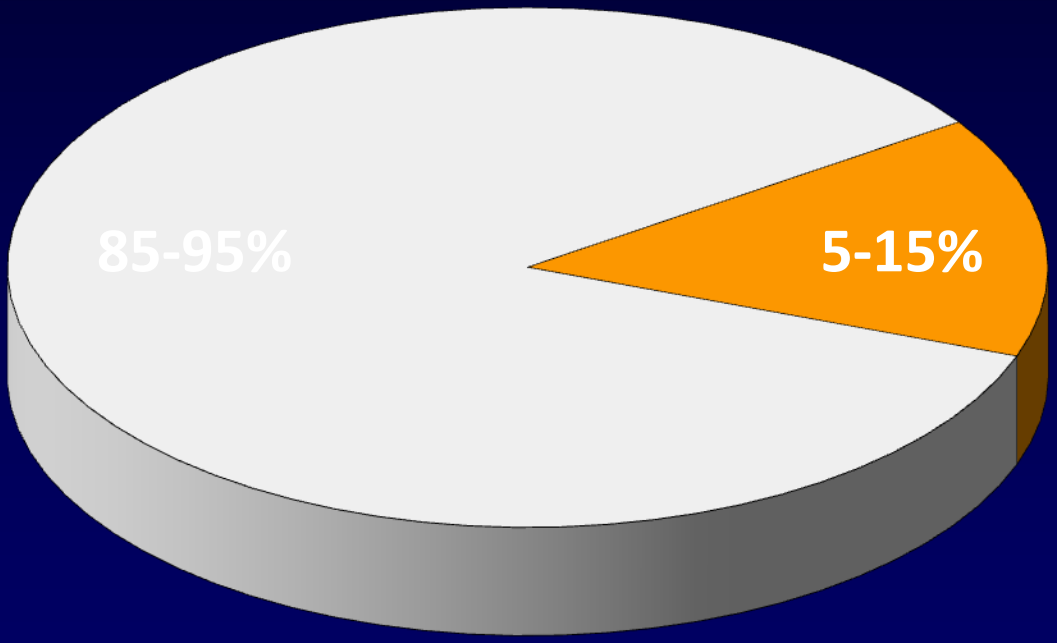
Whose job to support research

- Clinicians
  - Know how to refer to research,
- Volunteers (w or w/o disease)
  - Discuss with your family
  - Support the decision, be a study partner
- Everyone
  - Support public funding
  - Make your contribution

Low Subject Recruitment Hinders Research Progress

Reason for lost days [toward deadline for clinical trial completion]

Difficulty in recruiting patients

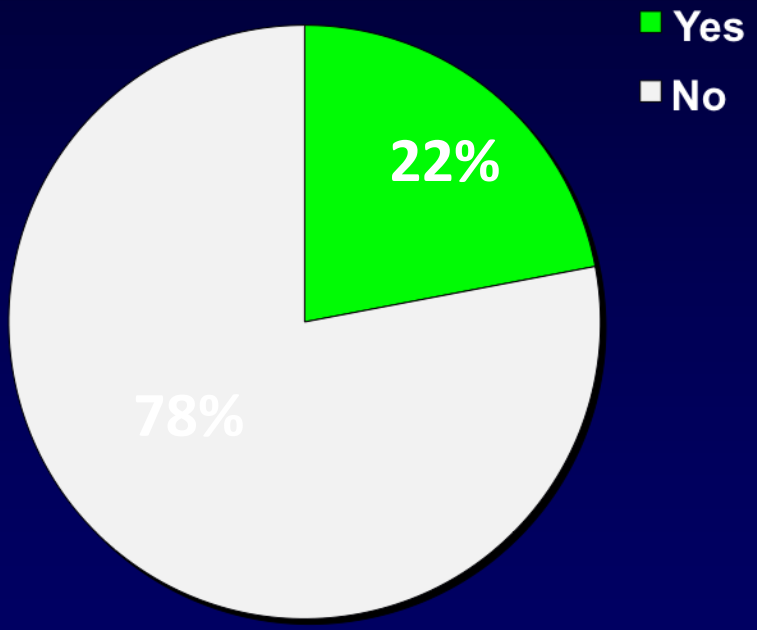


Other

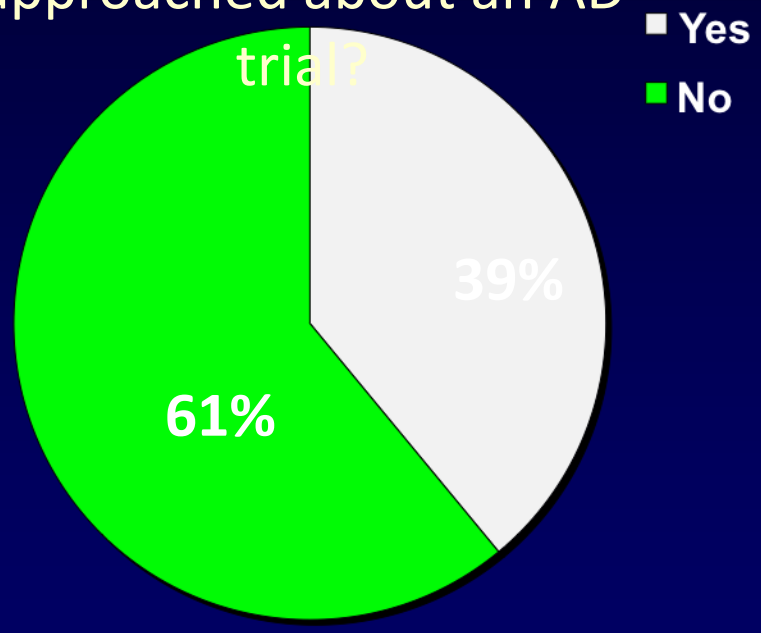
Cruz Rowe J, et a. The McKinsey Quarterly. 2002;2:134-141.

Trial Referral is an Underused Opportunity

Ever referred for an AD trial?



Have patients/caregivers approached about an AD trial?



Alzheimer's Association Physician Study. Final Report. February 2007.

Why Participate in Research

- Standardized evaluations even for the healthy
- Access to up-to-date research initiatives
- Potential for earliest access to new medications
- Support for family and friends
- Contribution from self to family, society***

Not all studies for all participants

- Inclusion criteria:
  - Insure safety
  - Limitations by age co-morbidities other medications
  - Insure the ability to measure efficacy
  - Hearing / visual difficulties make
- How to Choose:
  - Select by interest
  - Work with those you trust
  - Be honest about how much you can do
  - Ask questions

Remember, you can always change your mind

Information on AD Research

- My ADRC:
  - Mount Sinai: 212-241-8329
- Alzheimer's Association: National Site
  - 800-272-3900 (24 hr help line)
    - www.alz.org
- Alzheimer Disease Education and Referral Center
  - 800-438-4380

    www.alzheimers.org
- Clinical Trials
    - www.clinicaltrials.gov


ICAHN MEDICAL INSTITUTE
1425