Expanding Research: Preventing and Treating Alzheimer's Disease

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Disclosures

- In the past 12 months I have been a consultant/advisor to the following companies on topics of trial design and data analysis
  - Medpace,
  - Sanofi-Aventis,
  - Takeda,
  - Genentech,
  - Targaset,
  - Hoffman-LaRoche
  - Neurcog trials.

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Today's Topics

- How far we have come
  - Diagnosis
  - Treatment
- What we know about lifestyle
  - Treating your co-morbidities, diet, supplements
  - Activity: physical, mental, social
- Research: Taking the next step

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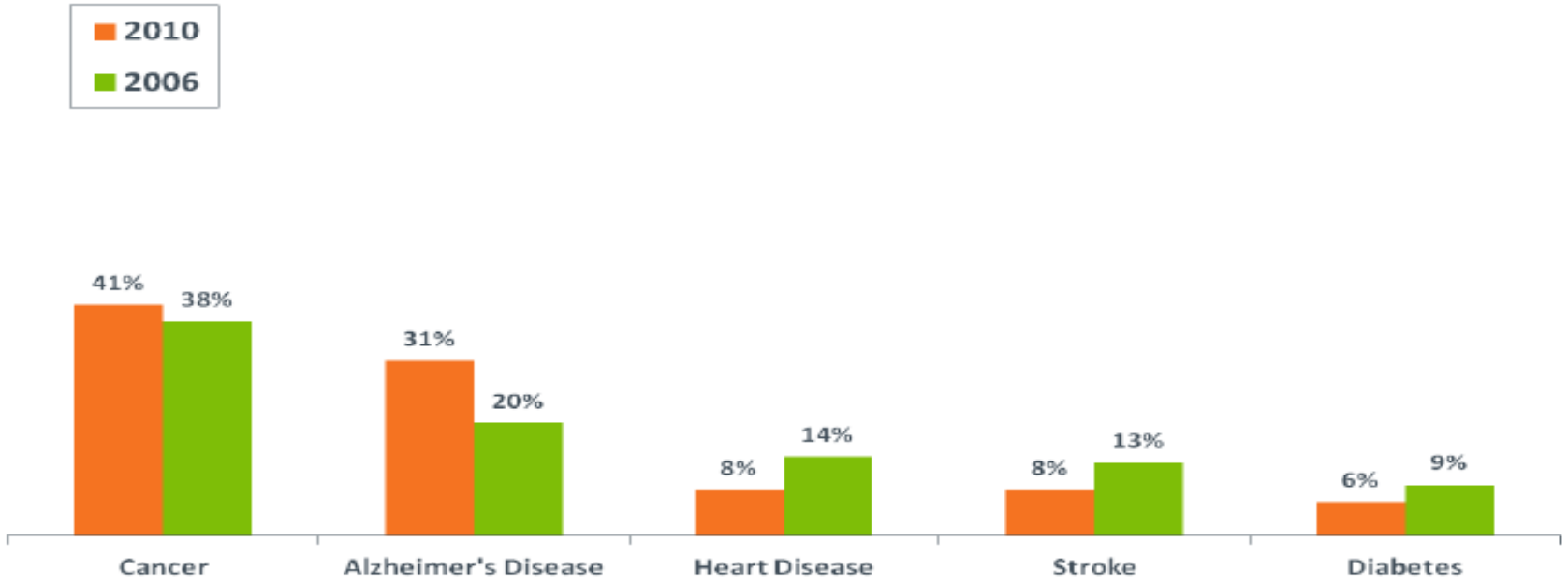
Fear of Alzheimer's Disease



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

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What we know about Diagnosing and Treating Alzheimer's Disease

- Improved confidence in diagnosis by clinical evaluation, imaging and biomarkers
- Known genetic risk of Apoliprotein ε4
- Approved treatments for treating AD exist with robust though modest effects
- Functional benefit with Vitamin E demonstrated in mild and moderate disease

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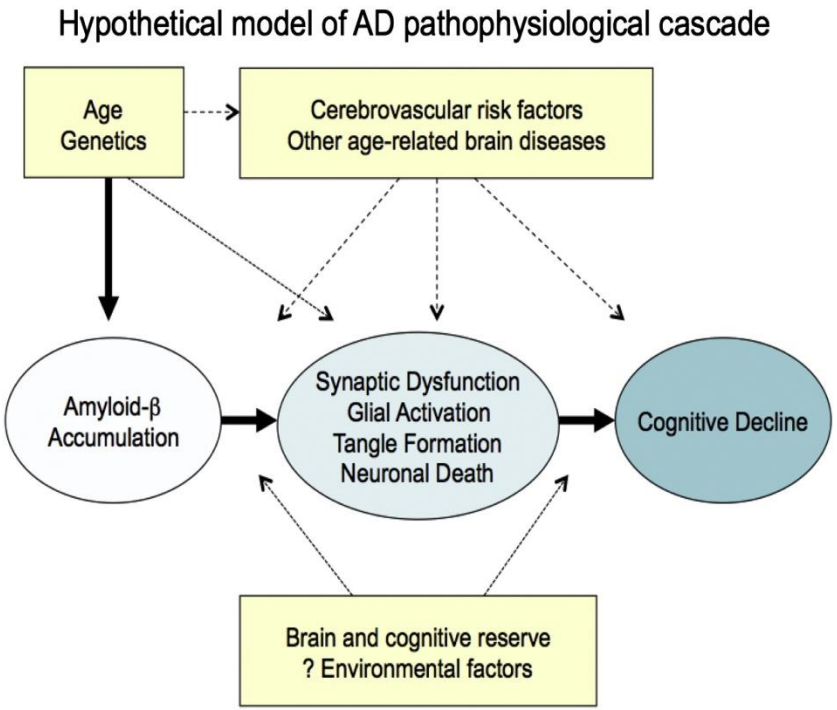
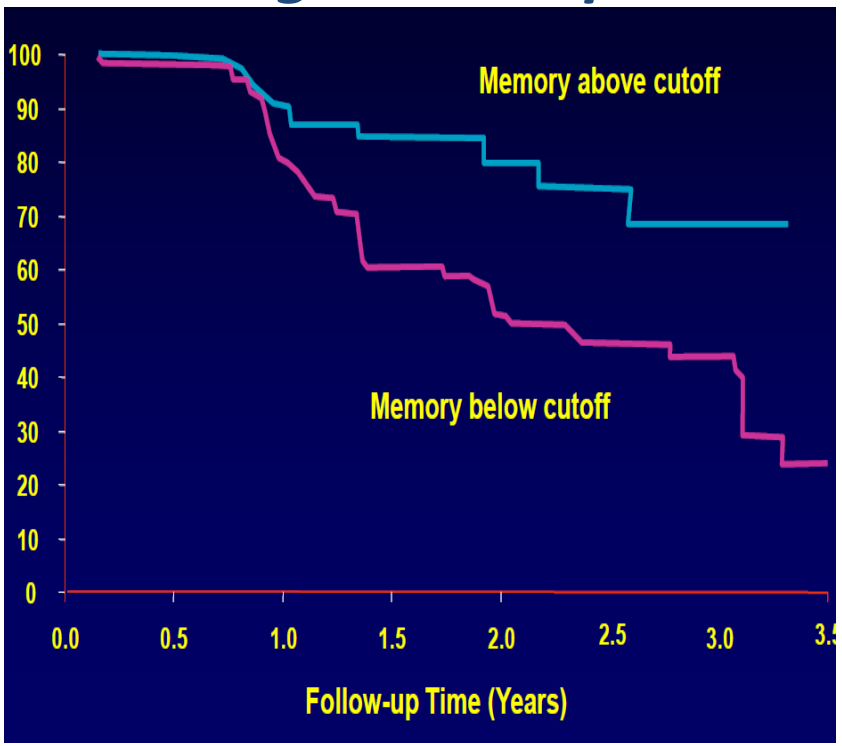
Cognitive Decline Precedes Dementia



Mild Cognitive Impairment



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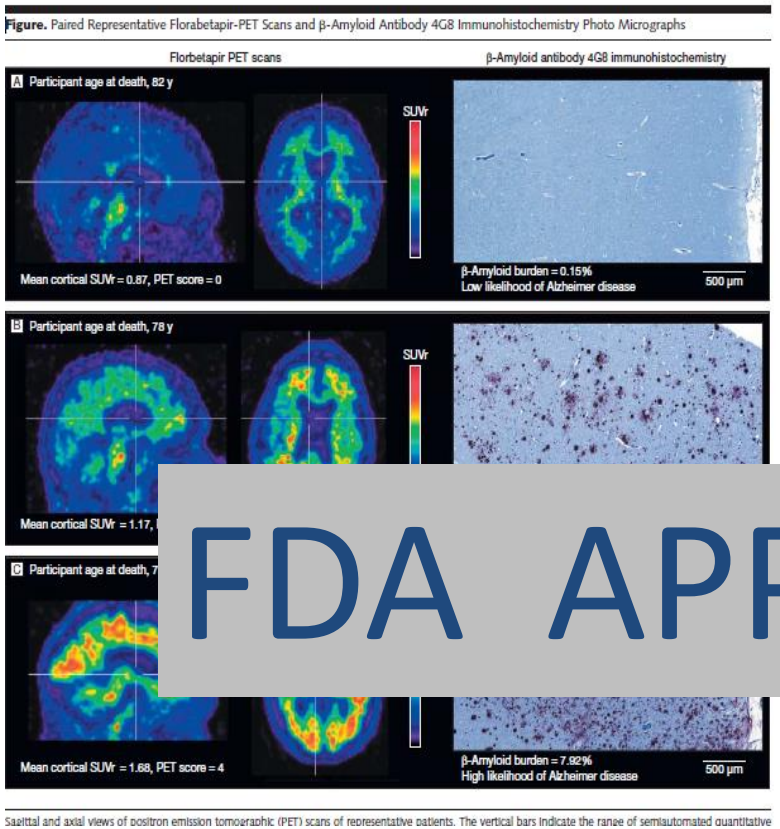
Use of Florbetapir-PET for Imaging - Amyloid Pathology

PET images were mixed in random analysis.

poral, parietal, anterior cingulate, pos-



High correlation between imaging and neuropathology

Does not rule out other

FDA APPROVED

ogy and

proximity to ligand

manufacturer

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Biomarkers in the Cerebrospinal Fluid (CSF)

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

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Apolipoprotein ε 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

Neuropsychiatric Disease and Treatment

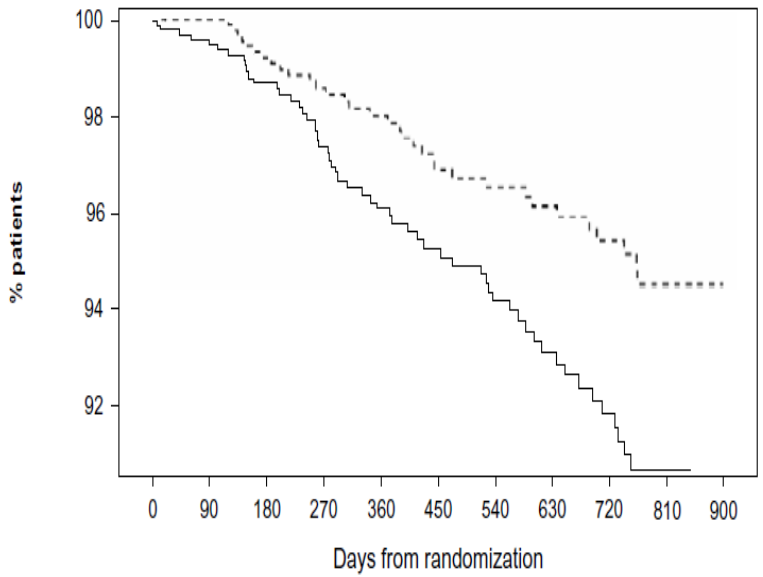
Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease

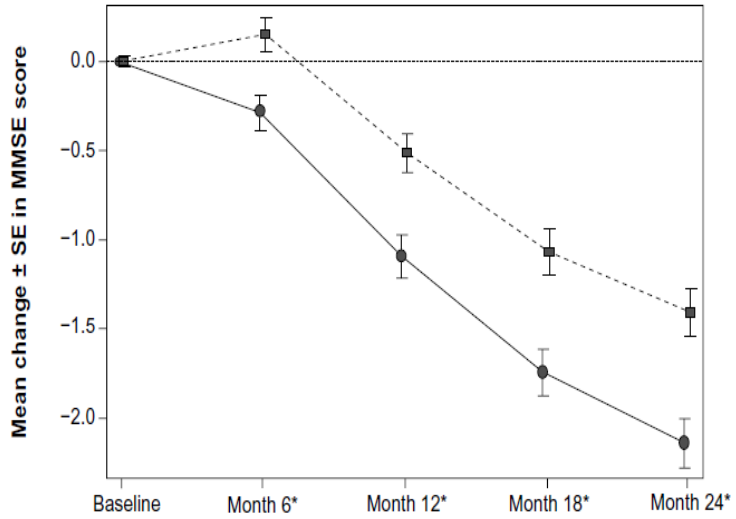
Survival Benefit



Patients at risk											
Placebo	1,021	947	816	699	633	552	492	411	332	3	0
Galantamine	1,024	943	811	715	639	571	512	432	356	7	0

Placebo ------ Galantamine

Cognitive Benefit



Number of patients				
Placebo 906	888	891	891	891
Galantamine 905	873	874	874	874

Placebo ---■--- Galantamine

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Treatment benefits persist even for patients with moderate and severe disease

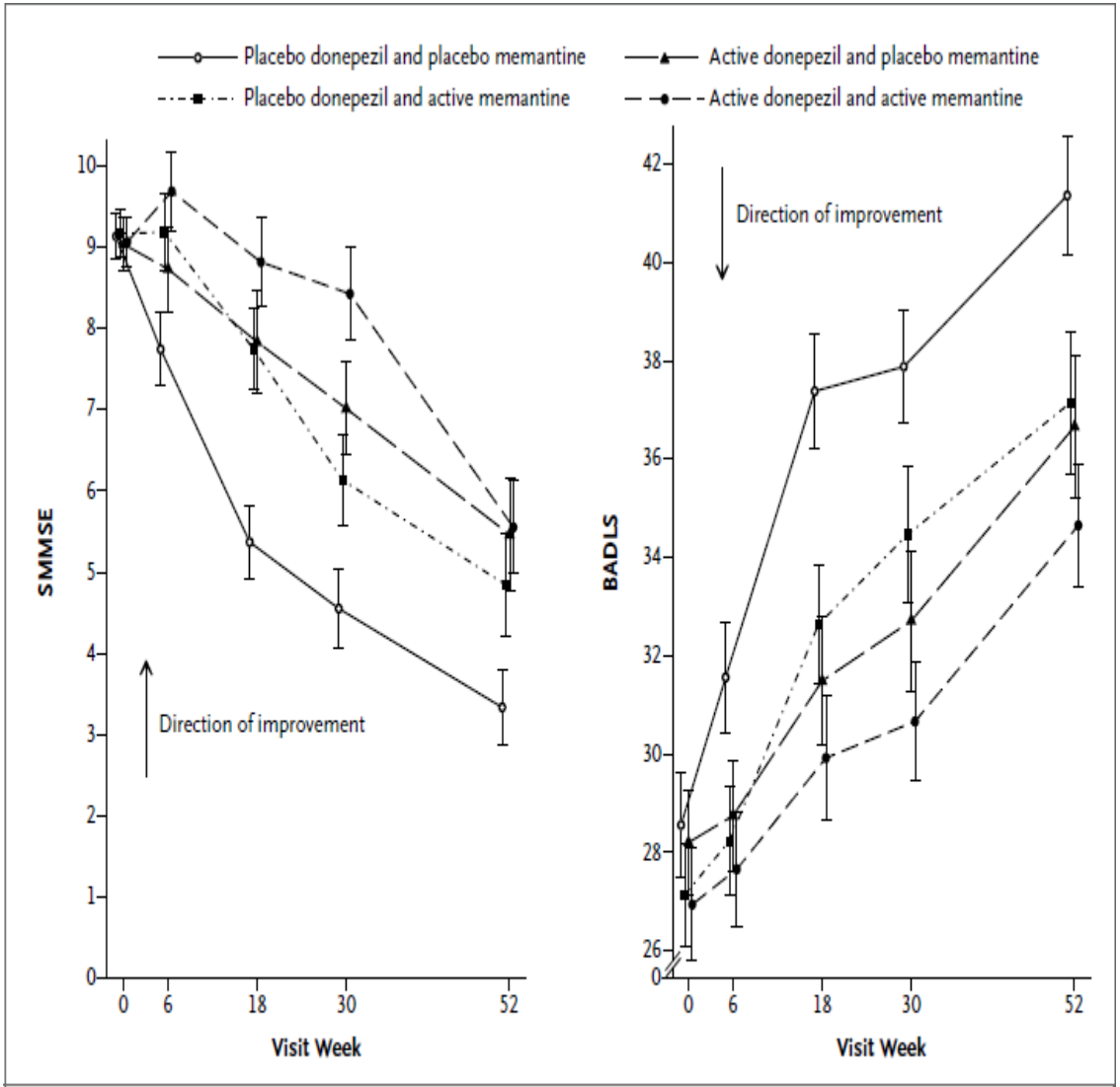

Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. I bars denote the standard error.

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From: **Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease: The TEAM-AD VA Cooperative Randomized Trial**

JAMA. 2014;311(1):33-44. doi:10.1001/jama.2013.282834

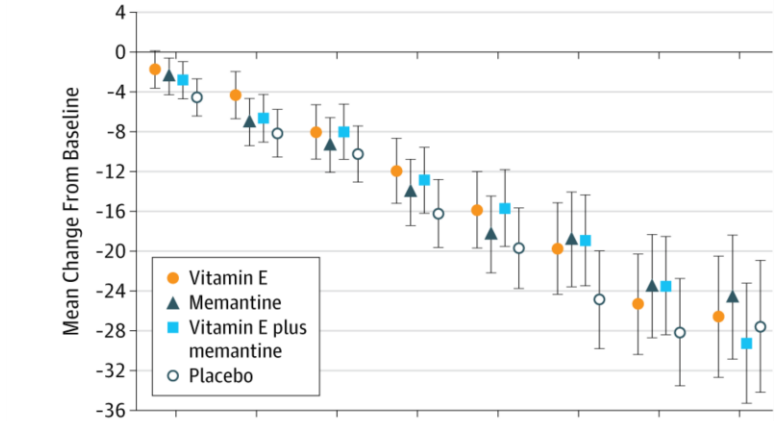

Figure Legend:

Changes in Primary Outcome (ADCS-ADL Inventory Score) During the 4-Year Study Period, Compared With BaselineIn this between-group comparison, lower scores indicate worse functioning. Data are least squares means at each time point. Values have been adjusted for baseline scores as a fixed effect and the study site as a random effect. ADCS-ADL indicates Alzheimer's Disease Cooperative Study/Activities of Daily Living; error bars, 95% CIs.

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)

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What Do we know about Lifestyle & Modifiable Risks

- Diet
- Sedentary lifestyle
- Stress
- Head injury
- Diabetes
- Hypertension
- Hypercholesterolemia
- Stroke
- Depression

- Epidemiological connection
- No clinical trial evidence
- Maybe an indirect path
- Maybe not independent risk factors

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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 to3 million cases worldwide**
- **184 000–492 000 cases in the USA**
- **Very little evidence that reducing these risks will benefit cognition**

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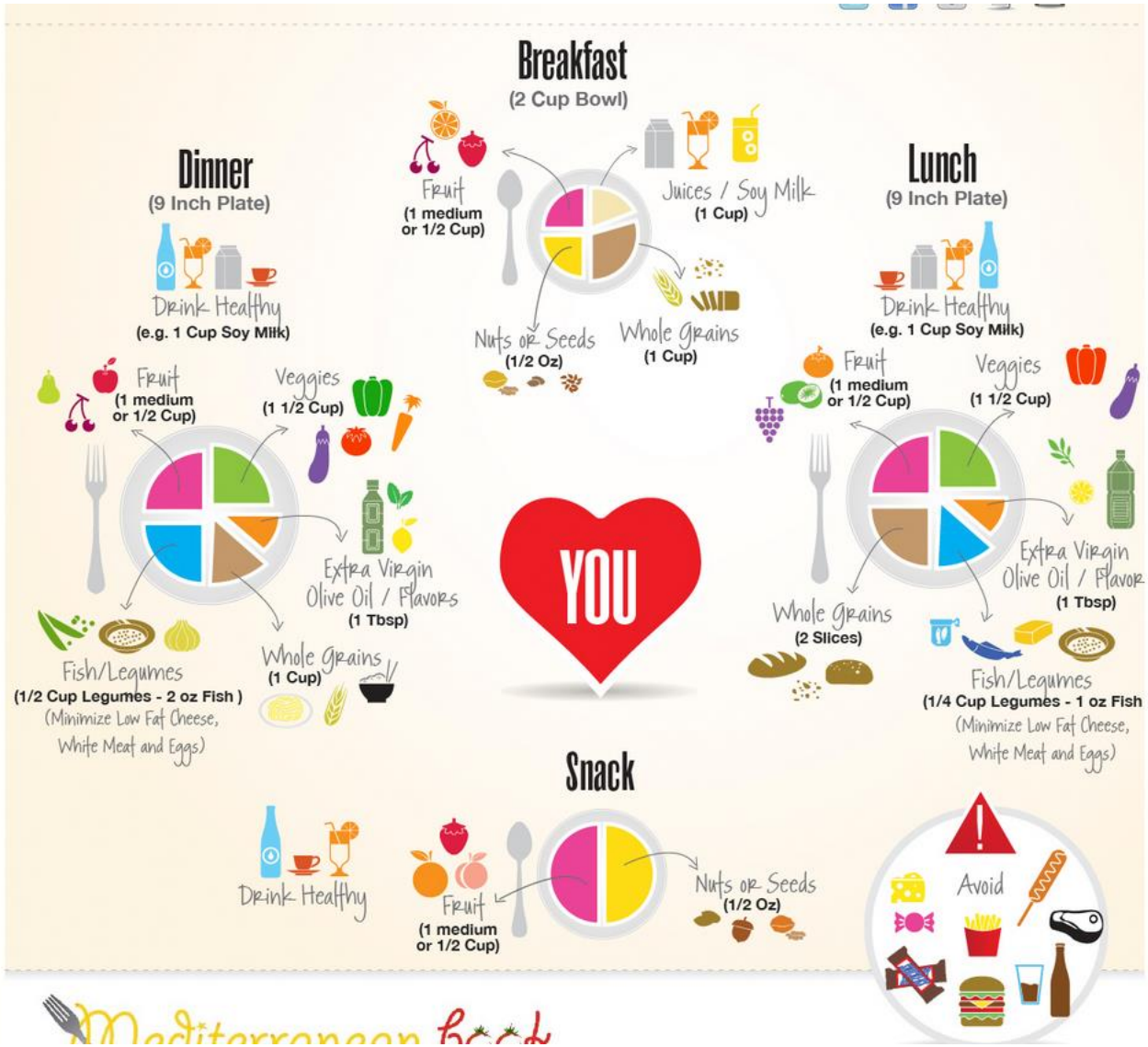
Mediterranean Diet and Dementia



Diet Affecting Cardiovascular Outcomes

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

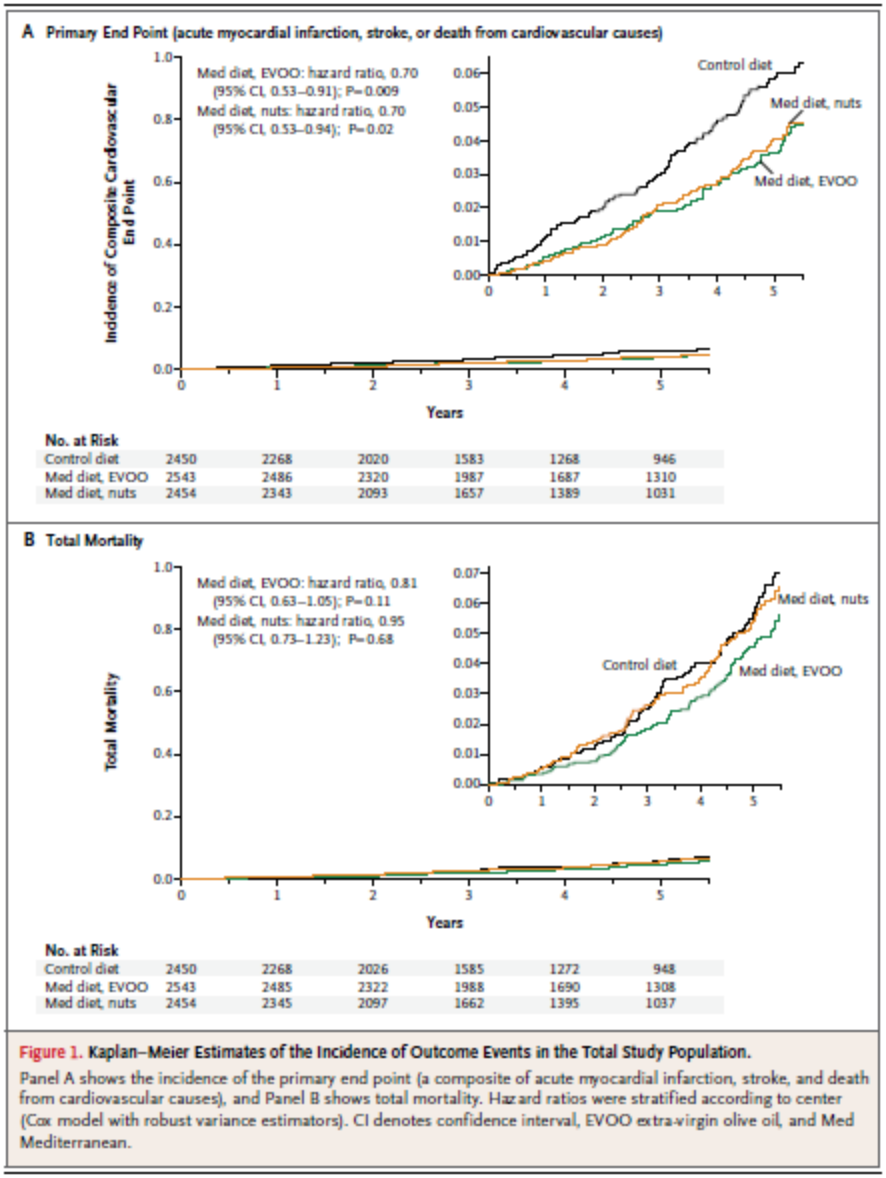


Figure 1. Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.
Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

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RESEARCH PAPER

Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

Elena H Martínez-Lapiscina,[1,2] Pedro Clavero,[3] Estefania Toledo,[1,4] Ramon Estruch,[4,5] Jordi Salas-Salvadó,[4,6] Beatriz San Julián,[1] Ana Sanchez-Tainta,[1] Emilio Ros,[4,7] Cinta Valls-Pedret,[4,7] Miguel Á Martinez-Gonzalez[1]

Table 4 Multivariable-adjusted means after a 6½-year follow-up and differences versus control (95% CIs) in each intervention group

	MedDiet+EVOO (n=224)		MedDiet+Nuts (n=166)		Control (low-fat diet) (n=132)
	Mean (95% CI)	p Value (vs control)	Mean (95% CI)	p Value (vs control)	Mean (95% CI)
MMSE	27.73 (27.27 to 28.19)		27.68 (27.20 to 28.16)		27.11 (26.61 to 27.61)
Adjusted diff. versus control (95% CI)	+0.62 (+0.18 to +1.05)	0.005	+0.57 (+0.11 to +1.03)	0.015	0 (reference)
CDT	5.31 (4.98–5.64)		5.13 (4.78–5.47)		4.80 (4.44–5.16)
Adjusted diff. versus control (95% CI)	+0.51 (+0.20 to +0.82)	0.001	+0.33 (+0.003 to +0.67)	0.048	0 (reference)

Small but significant benefit in overall cognition

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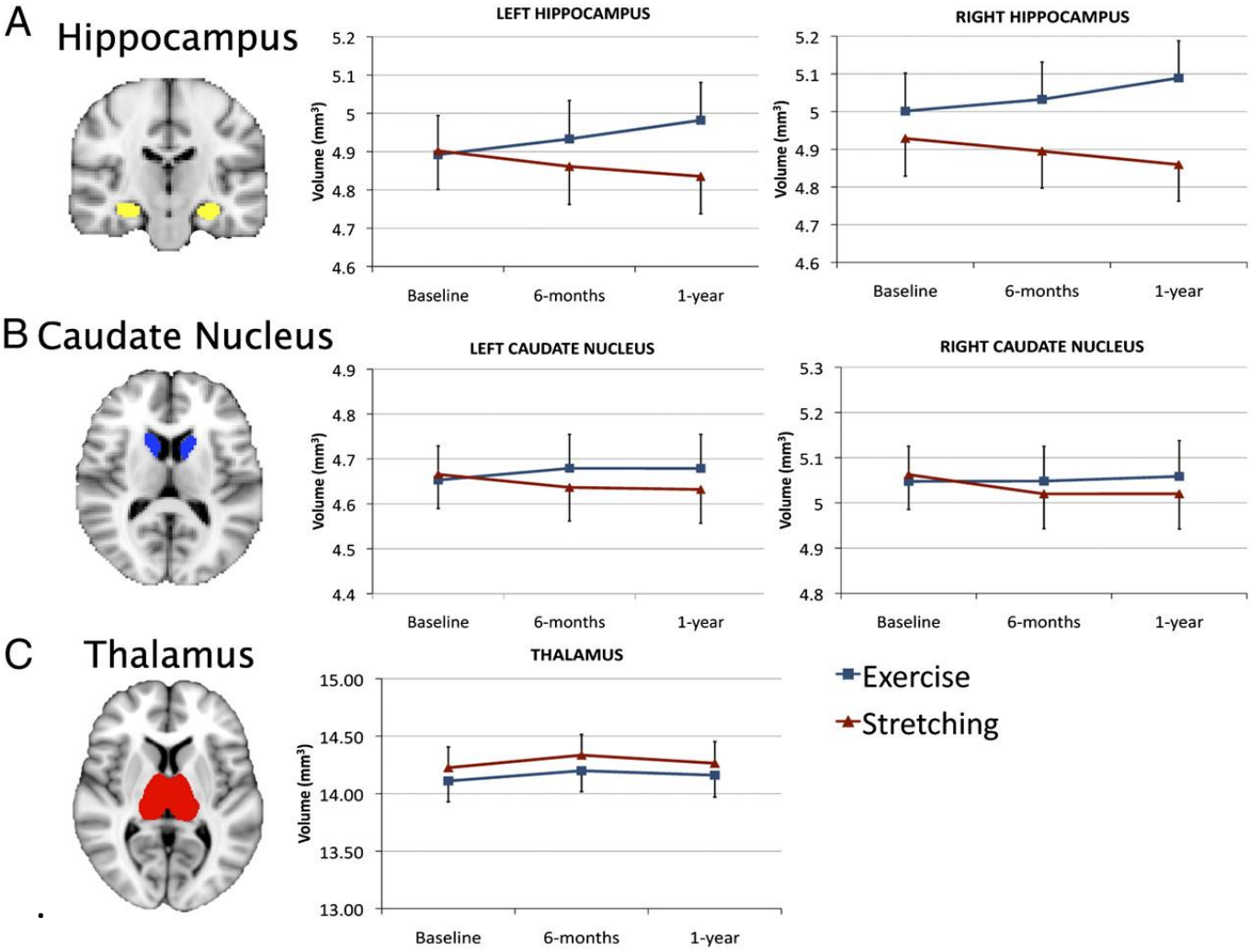
What about Physical activity to benefit cognition in healthy elders?

- 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.

Increase in hippocampus volume in aerobic exercise group
Improved spatial memory in both groups



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

The women of the Vakhegula Vakhegula soccer team, ranging in age from 49 to 84, warmed up before a game last month near Tzaneen, South Africa.

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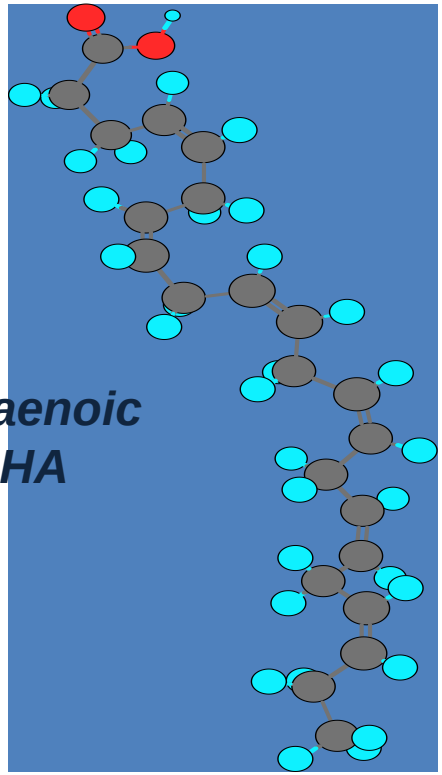
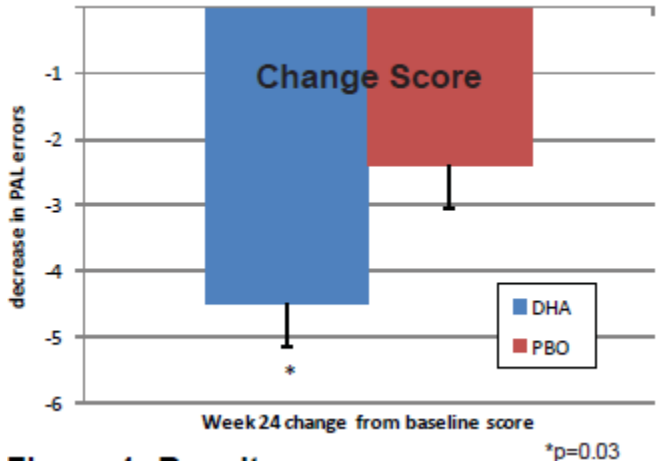
Supplement Benefit?
Only in those with low intake?

- MIDAS study
  - AAMI
  - Low omega 3 diet
  - Treated with DHA
  - Benefit in learning



Docosahexaenoic Acid – DHA



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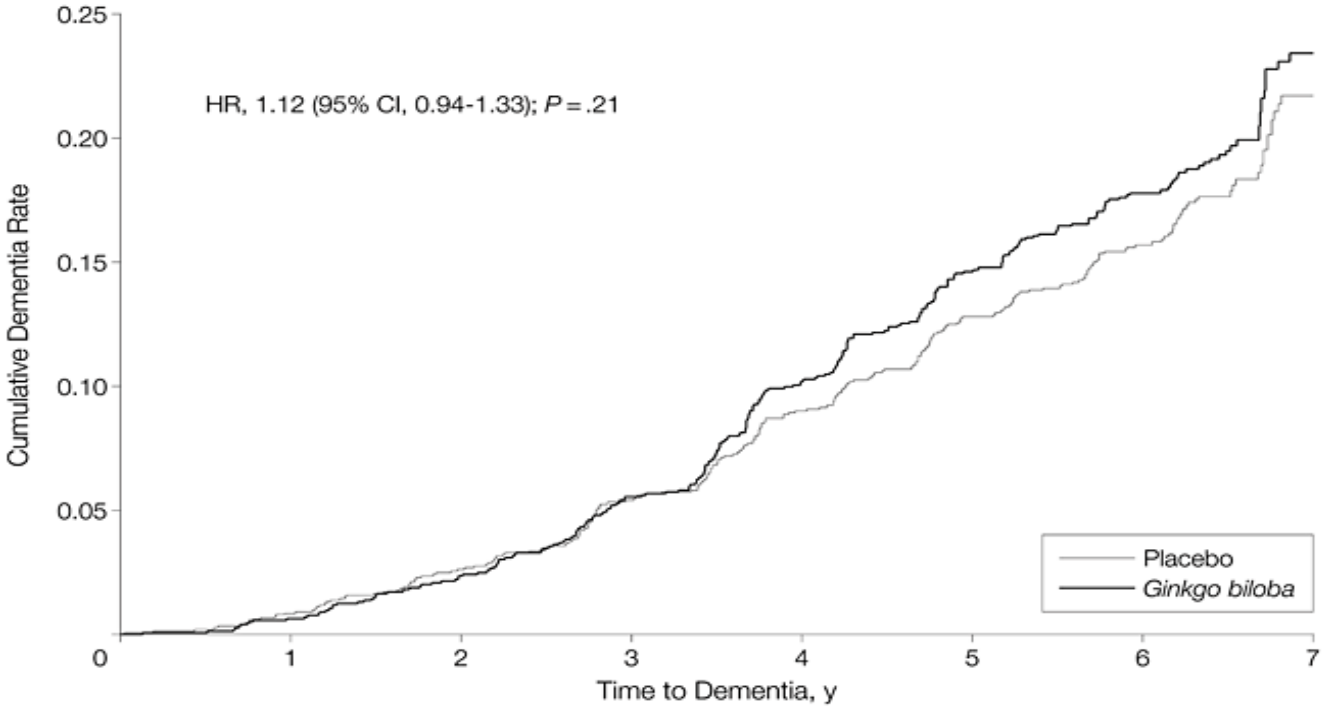
Dementia Prevention Trial Ginkgo Biloba vs. Placebo



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

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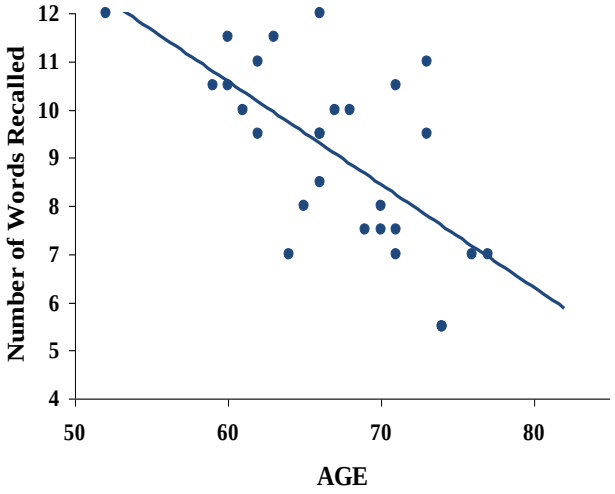
DeKosky, S. T. et al. JAMA 2008;300:2253-2262.

JAMA

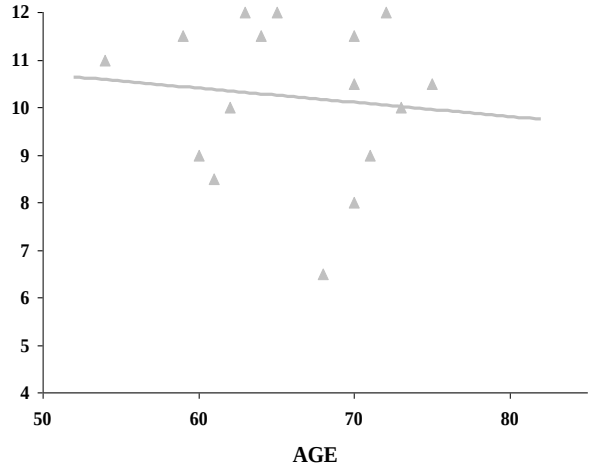
Stress, Age and Word Recall

R=-0.68



PTSD+

R=-0.03



PTSD-

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Golier, Yehuda , Lupien et al.
Am J Psychiatry, 2002

Cut down on distractions

- **Focus on one thing at a time**
- **Give the item you want to learn or remember your full attention**
- **Remember that multi-tasking is for the young – not the young-at-heart**

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What is the A4 Study?

- A4 = Anti-Amyloid Treatment in Asymptomatic Alzheimer's
- First-ever trial designed to prevent memory loss in people at a higher risk for AD but who have no symptoms
- Testing whether a new investigational treatment, called an anti-amyloid antibody, can prevent memory loss associated with AD

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The Goal of the A4 Study

To determine whether we can prevent memory loss in people who may be at a higher risk for developing Alzheimer's disease (AD) before they show symptoms

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A4study.org

A4 Fast Facts

100% voluntary

100% confidential

No cost to participants

Monetary compensation /transportation reimbursement* provided

Lasts for 3.5 years/requires monthly visits

Investigational medication or placebo delivered through monthly IV

Can withdraw any time

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Anti-Amyoid treatment in Asymptomatic AD – The A4 Trial

- Older individuals (ages 65-85)
- Normal thinking and memory function
- Presence of amyloid on imaging
- May be at risk for developing Memory Loss
- Treatment with Solanezumab or placebo to reduce the rate of memory decline

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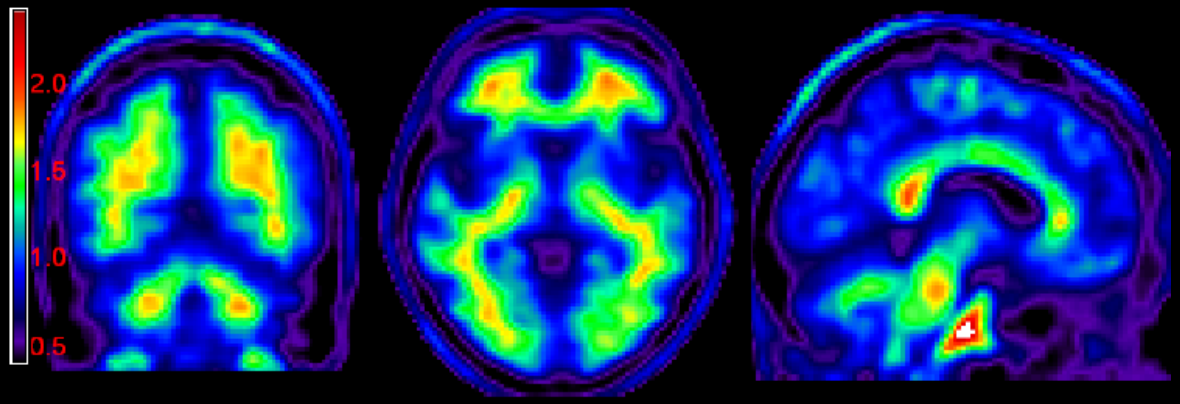
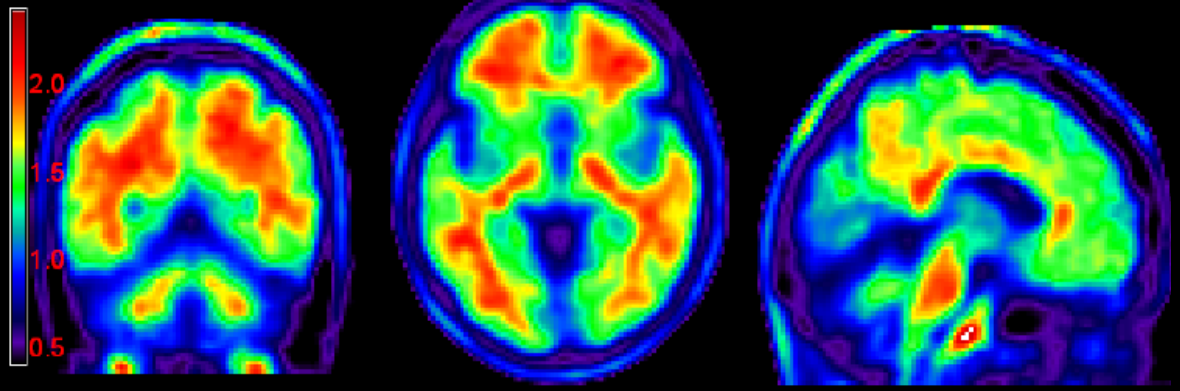
^{18}F-AV-45 Representative Images: Healthy Controls

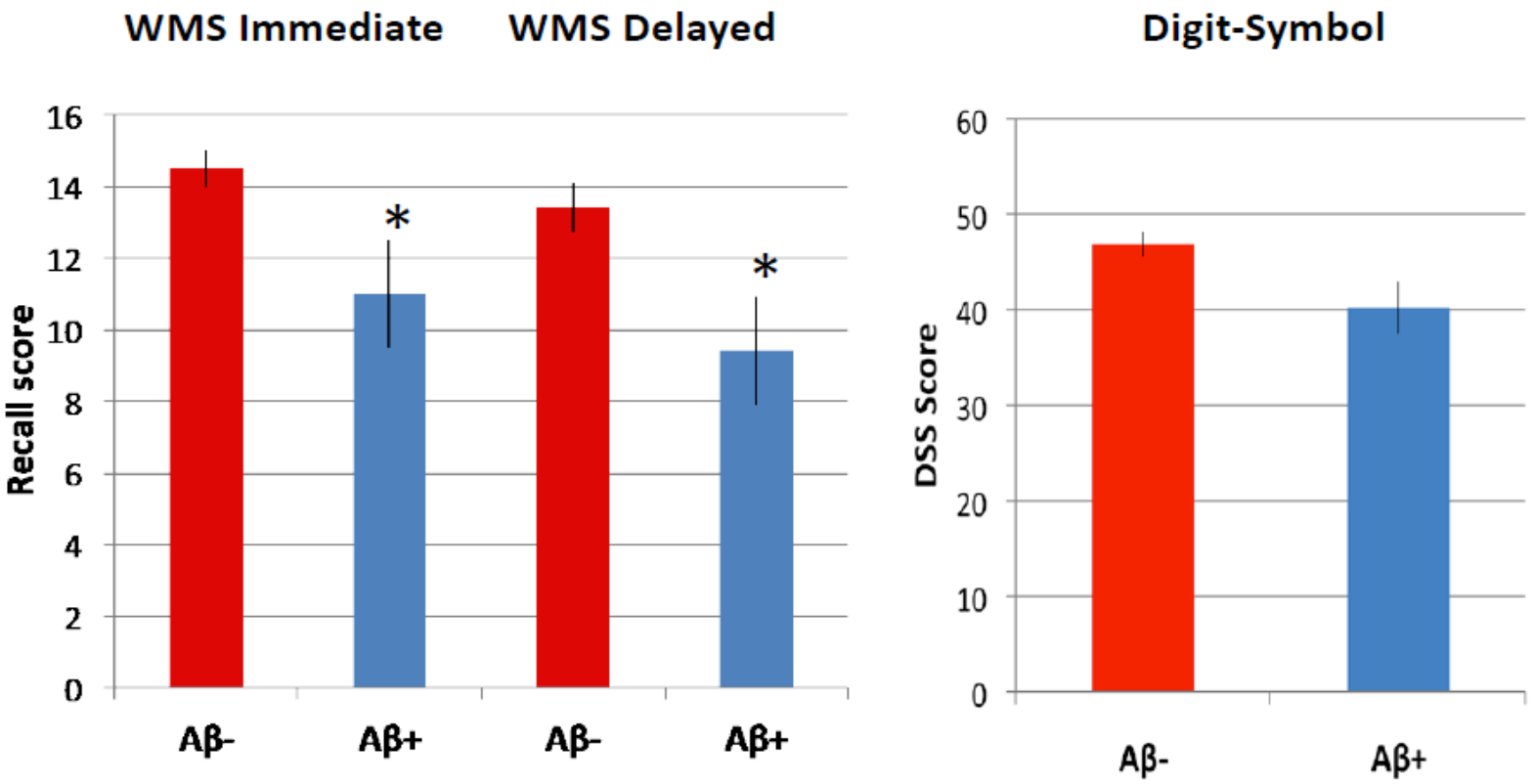
Amyloid Negative HC



Amyloid Positive HC



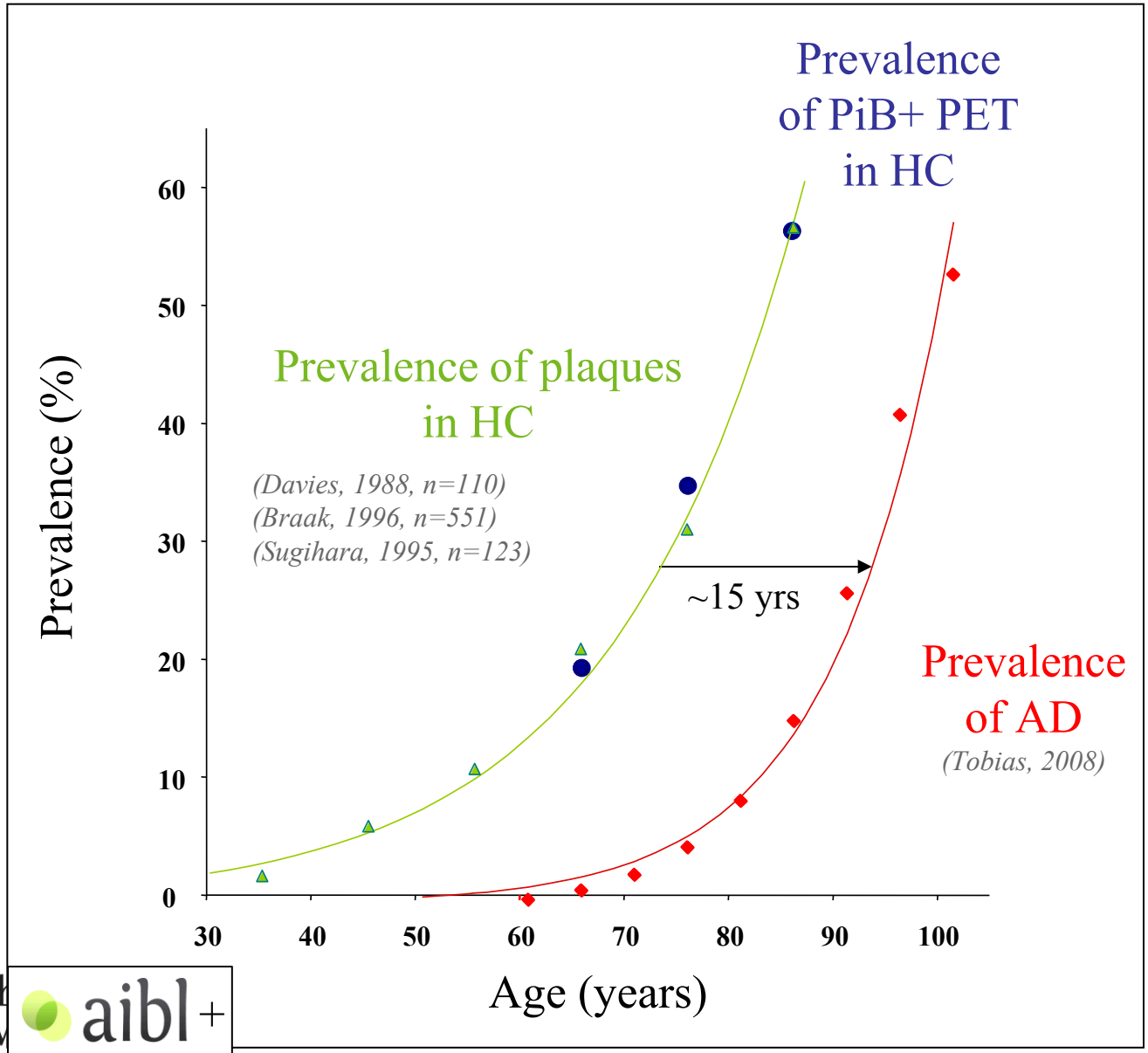
Cognition in Aβ Pos vs. Neg in HC > 70 years old



Florbetapir (^{18}F AV-45) Phase II Study

Sperling R et al *Neurobiology of Aging* 2012

Preclinical Alzheimer's Disease?



Rowe C et al *Neurobiology of Aging* 2010

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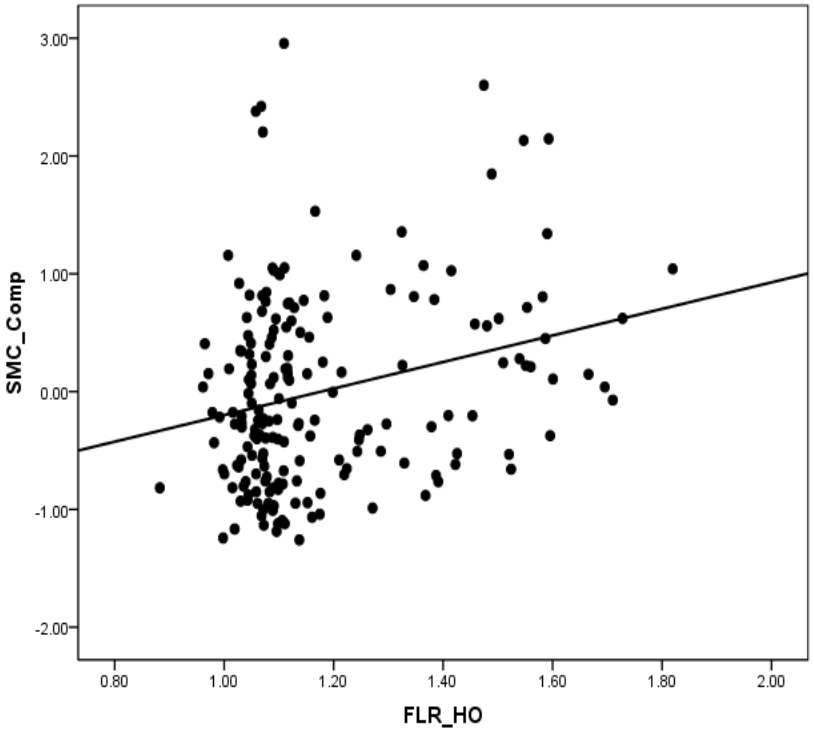
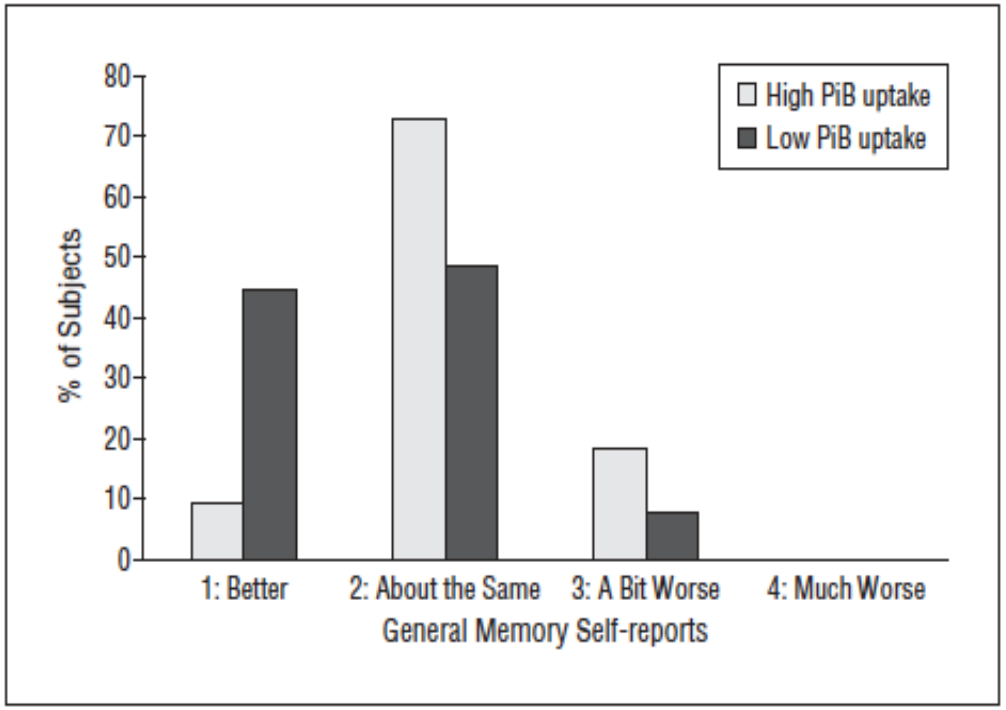
aibl

Subjective memory concerns associated with amyloid burden among “normal” elderly





Perrotin A et al *Arch Neurology* 2012

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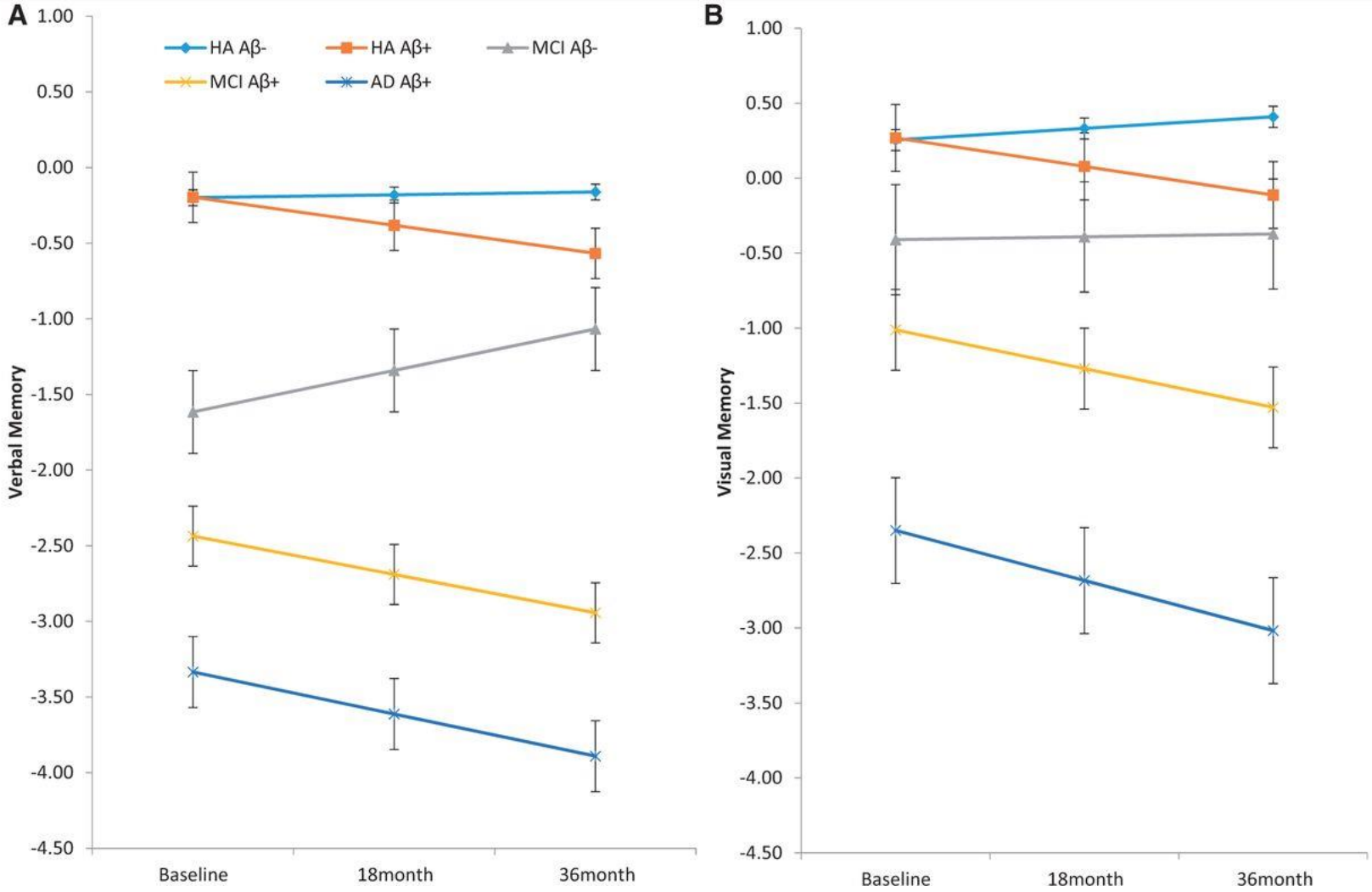
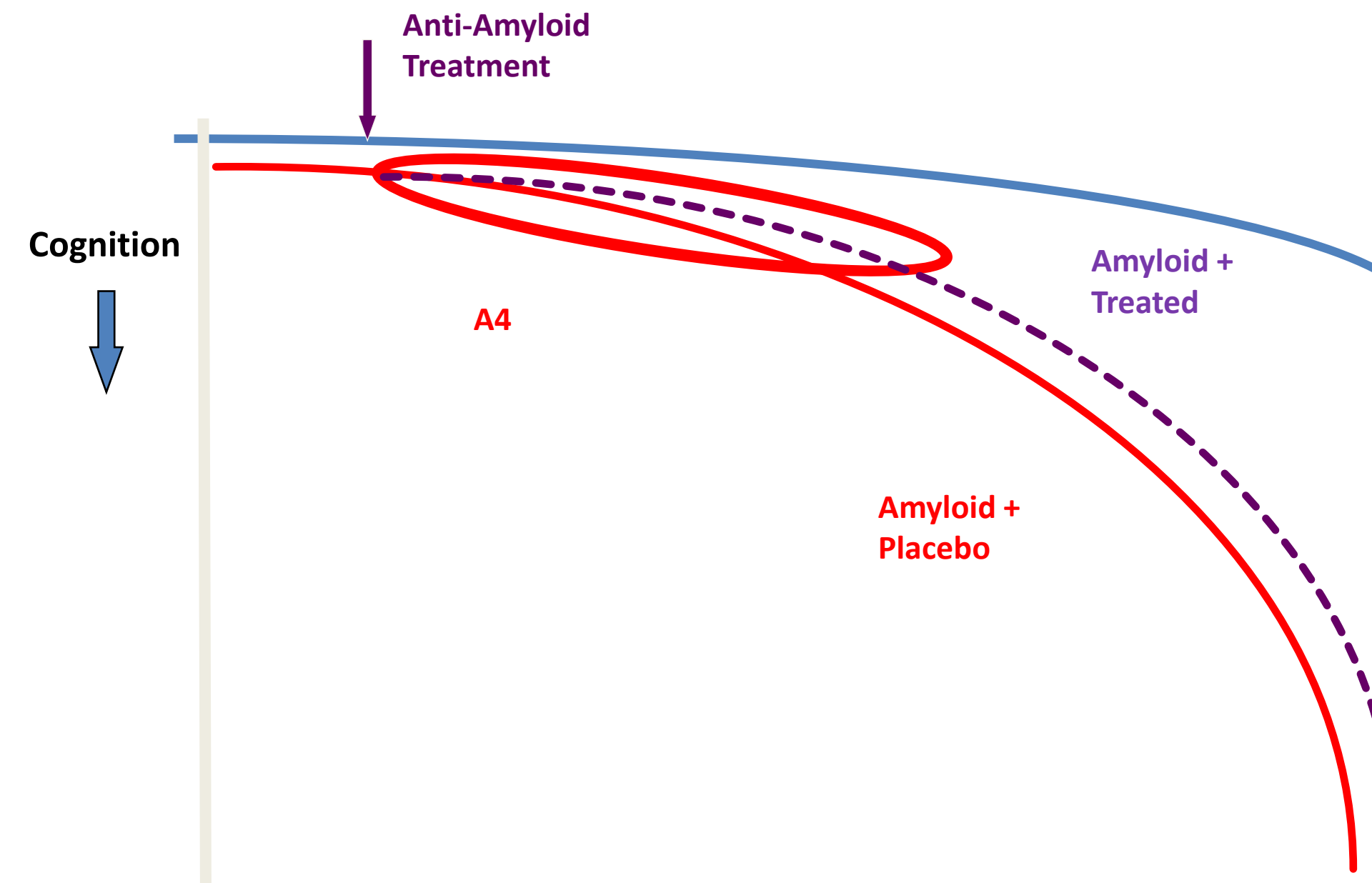
Effect of amyloid on memory decline from preclinical to clinical Alzheimer's disease



AIBL data

Lim Y et al *Brain* 2014

The A4 Study


Anti-Amyloid
Treatment
Cognition
A4
Amyloid +
Treated
Amyloid +
Placebo

Solanuzamab

- Monoclonal antibody, binds to amyloid-β peptides; “ineffective” at plaque formation
- Minimally effective in AD
- Clinical trials moving to “milder AD” & asymptomatic individuals

Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.

Table 3. Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	−1.3 (−2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	−1.6 (−3.1 to 0.1)	0.04
ADCS-ADL score†	−10.9 (−12.7 to −9.1)	−9.3 (−11.2 to −7.5)	1.6 (−0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	−0.3 (−0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	−0.2 (−1.8 to 1.5)	0.85
MMSE score	−2.8 (−3.6 to −2.0)	−2.1 (−2.8 to −1.3)	0.8 (0.2 to 1.4)	0.01
Free $A\beta_{40}$ in CSF — pg/ml	−649.0 (−2139.5 to 841.5)	−1258.1 (−2695.8 to 179.7)	−609.1 (−1228.4 to 10.2)	0.05
Free $A\beta_{42}$ in CSF — pg/ml	−35.1 (−129.5 to 59.3)	1.0 (−94.1 to 96.2)	36.1 (−1.0 to 73.3)	0.06
Total $A\beta_{40}$ in CSF — pg/ml	−876.4 (−4342.5 to 2589.8)	2156.8 (−1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total $A\beta_{42}$ in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

* The methods used to analyze between-group differences in outcomes from baseline to week 80 were the same as those used in EXPEDITION 1. Measurements of Aβ in the CSF were available at baseline and follow-up for 32 patients in the placebo group and 44 patients in the solanezumab group.

† The original primary outcomes were the changes from baseline to week 80 in scores on the ADAS-cog11 and the ADCS-ADL scale. After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the ADAS-cog14 in patients with mild Alzheimer's disease.

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Doody RS et al. N Engl J Med 2014;370:311-321.

Mild Alzheimer's Disease vs. Moderate Alzheimer's Disease EXPEDITION 2, Intention-to-Treat Population.

Table 4. Outcomes in Patients with Mild Alzheimer's Disease and in Those with Moderate Alzheimer's Disease at Enrollment in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mild Alzheimer's Disease				Moderate Alzheimer's Disease				Test for Heterogeneity
	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	P Value‡
	placebo	*solanezumab*			*placebo*	*solanezumab*			
ADAS-cog11 score	5.1	3.6	−1.5 (−3.0 to 0.0)	0.05	10.9	10.0	−0.9 (−3.1 to 1.3)	0.43	0.65
ADAS-cog14 score	5.8	4.1	−1.7 (−3.5 to 0.1)	0.06	12.7	11.3	−1.5 (−4.1 to 1.1)	0.26	0.88
ADCS-ADL score	−8.9	−6.6	2.3 (0.2 to 4.4)	0.04	−16.3	−15.8	0.5 (−2.6 to 3.5)	0.77	0.34
CDR-SB score	1.6	1.3	−0.3 (−0.8 to 0.2)	0.22	3.4	3.2	−0.3 (−0.9 to 0.4)	0.44	0.95
NPI score	1.5	1.0	−0.5 (−2.4 to 1.3)	0.58	8.0	8.4	0.4 (−2.5 to 3.4)	0.78	0.60
MMSE score	−2.4	−1.8	0.7 (−0.1 to 1.4)	0.10	−5.8	−4.8	1.0 (0.0 to 1.9)	0.04	0.60

* Methods used to analyze between-group differences (solanezumab group minus placebo group) from baseline to week 80 were the same as those used for the primary analysis. In the placebo group, 325 patients had mild Alzheimer's disease and 194 had moderate Alzheimer's disease; in the solanezumab group, 322 patients had mild Alzheimer's disease and 199 had moderate Alzheimer's disease.
† The P value is for the comparison between the solanezumab group and the placebo group.
‡ The P value is for the comparison between patients with mild Alzheimer's disease and those with moderate Alzheimer's disease.

Mild Alzheimer's disease (MMSE score of 20 to 26 at visit 1)

Moderate Alzheimer's disease (MMSE score of 16 to 19 at visit 1)

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Doody RS et al. N Engl J Med 2014;370:311-321.

A4 Study Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β pathology on PET imaging
- Randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 168 weeks
- Trial N=1000+ (N=500+ per treatment arm)
- Observational cohort of amyloid negative "screen fails" – LEARN study
- Ethics component – Disclosure of amyloid status

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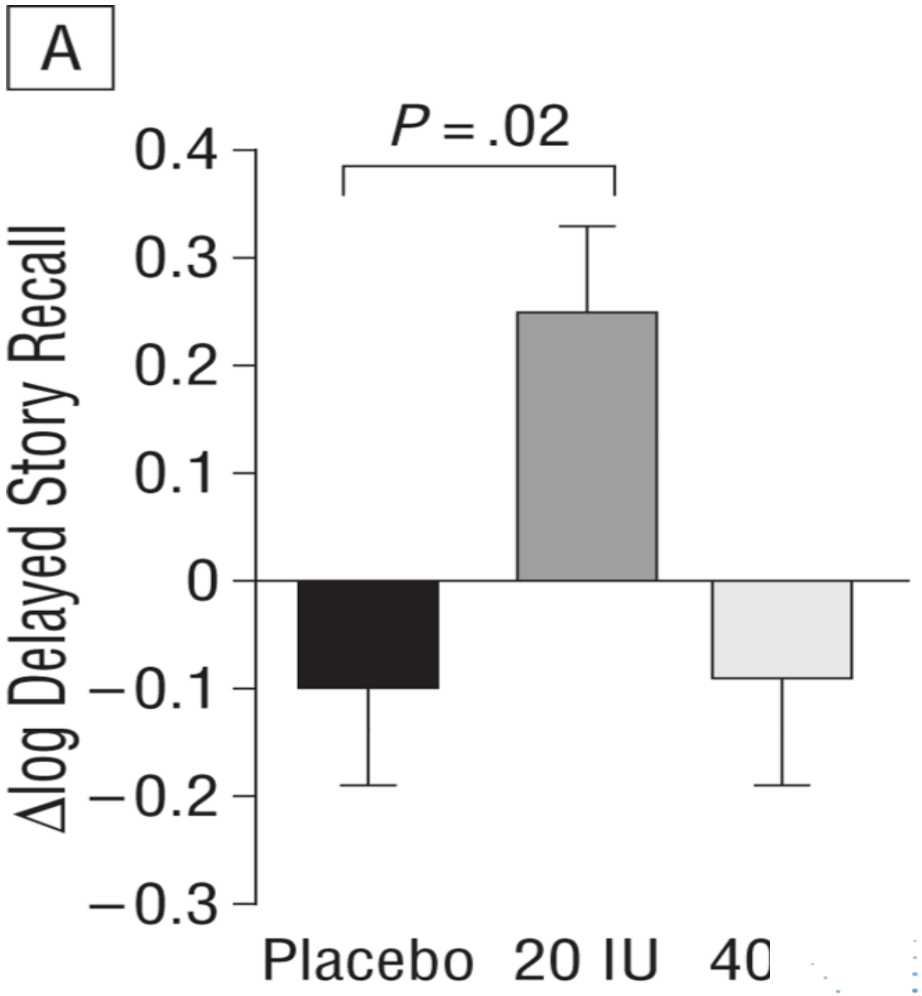
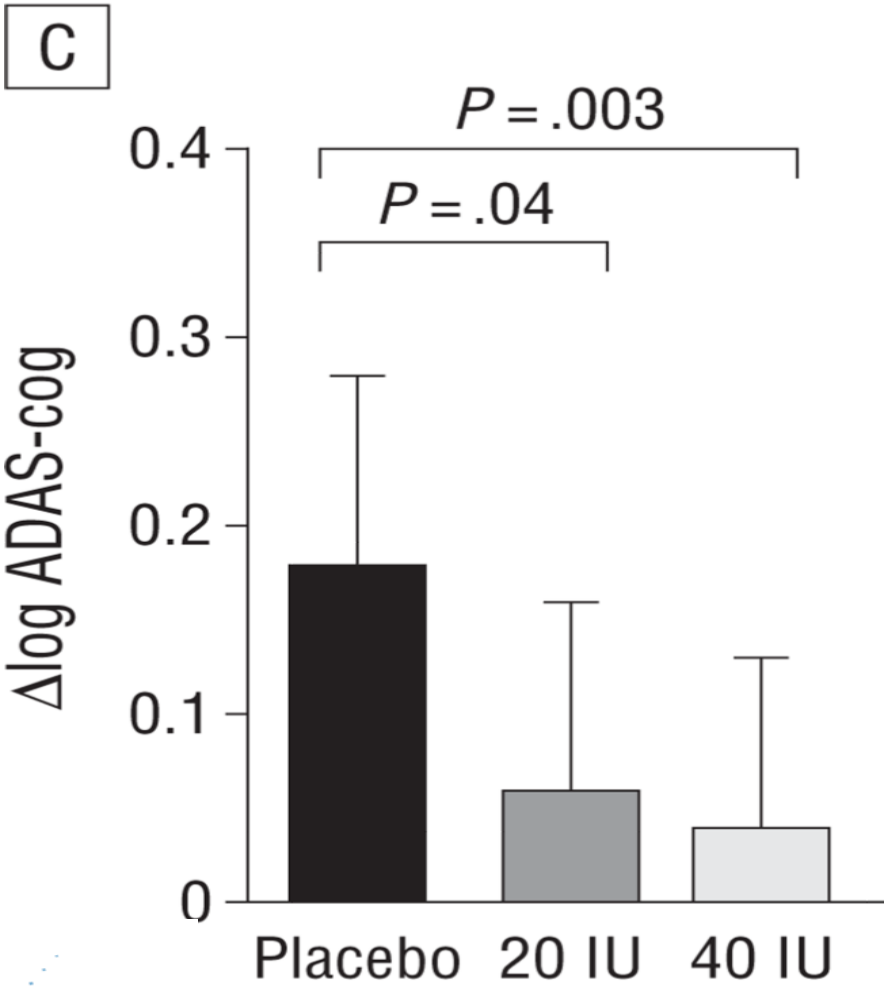
Intranasal Insulin Therapy for Alzheimer Disease and Amnestic MCI





SNIFF

STUDY OF NASAL INSULIN TO FIGHT FORGETFULNESS

SNIFF

- 12 months for 250 participants
- Mild Cognitive Impairment

or mild AD

- 55-85 years of age
- No use of diabetic medications

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What Can I Do To Minimize Cognitive Impairment?

- **Treat your treatable conditions**
  - High cholesterol Hypertension
  - Diabetes Depression
- **Protect your brain**
  - Seat belts Helmet
  - Ladders Falls
- **Support Research**
  - Participate Be a study partner
  - Encourage funding

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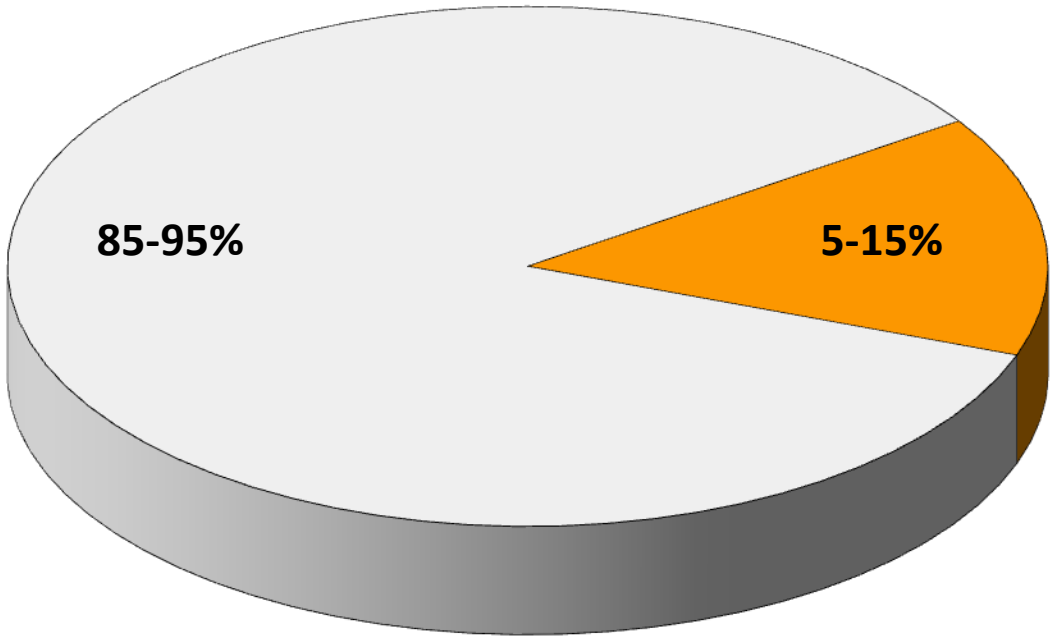
Low Subject Recruitment Hinders Research Progress

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



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

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

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Information on AD Research

- Our 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

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ClinicalTrials.gov

A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

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ClinicalTrials.gov currently lists 168,848 studies with locations in all 50 states and in 187 countries.

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Example: "Heart attack" AND "Los Angeles"

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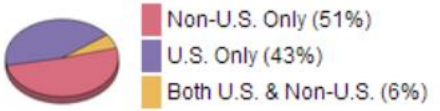
Advanced Search | See Studies by Topic

See Studies on a Map

Search Help

- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies



Total N = 33,126 studies
Data as of June 12, 2014

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4 studies found for: Alzheimer's Disease AND Maine | Open Studies

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Status	Study
Recruiting	**Progress of Mild Alzheimer's Disease in Participants on Solanezumab Versus Placebo** **Condition:** Alzheimer's Disease **Interventions:** Drug: Solanezumab; Drug: Placebo
Recruiting	**Study of the Safety and Effectiveness of Two Doses of Investigational Study Drug EVP-6124 in Subjects With Alzheimer's Disease** **Conditions:** Alzheimer's Disease; Dementia **Interventions:** Drug: Drug: EVP-6124; Drug: Placebo
Recruiting	**Efficacy and Safety Study of ELND005 as a Treatment for Agitation and Aggression in Alzheimer's Disease** **Condition:** Alzheimer's Disease **Interventions:** Drug: ELND005; Drug: Placebo
Recruiting	**Study of Lu AE58054 in Patients With Mild - Moderate Alzheimer's Disease Treated With Donepezil** **Condition:** Alzheimer's Disease **Interventions:** Drug: Placebo; Drug: Lu AE58054

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