

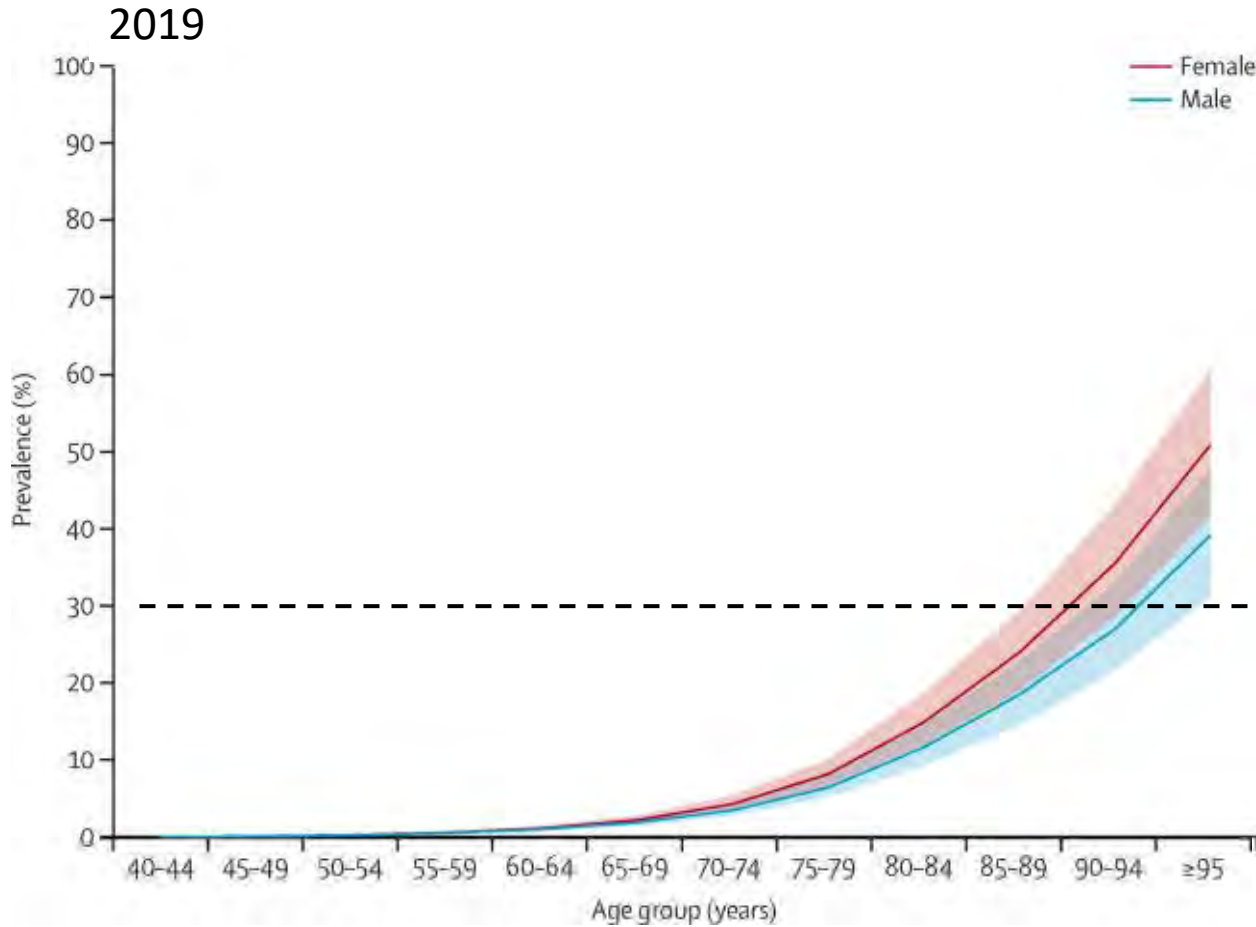
Maintaining Cognitive Health and Preventing Dementia

Los Altos Community Center
September 15, 2022

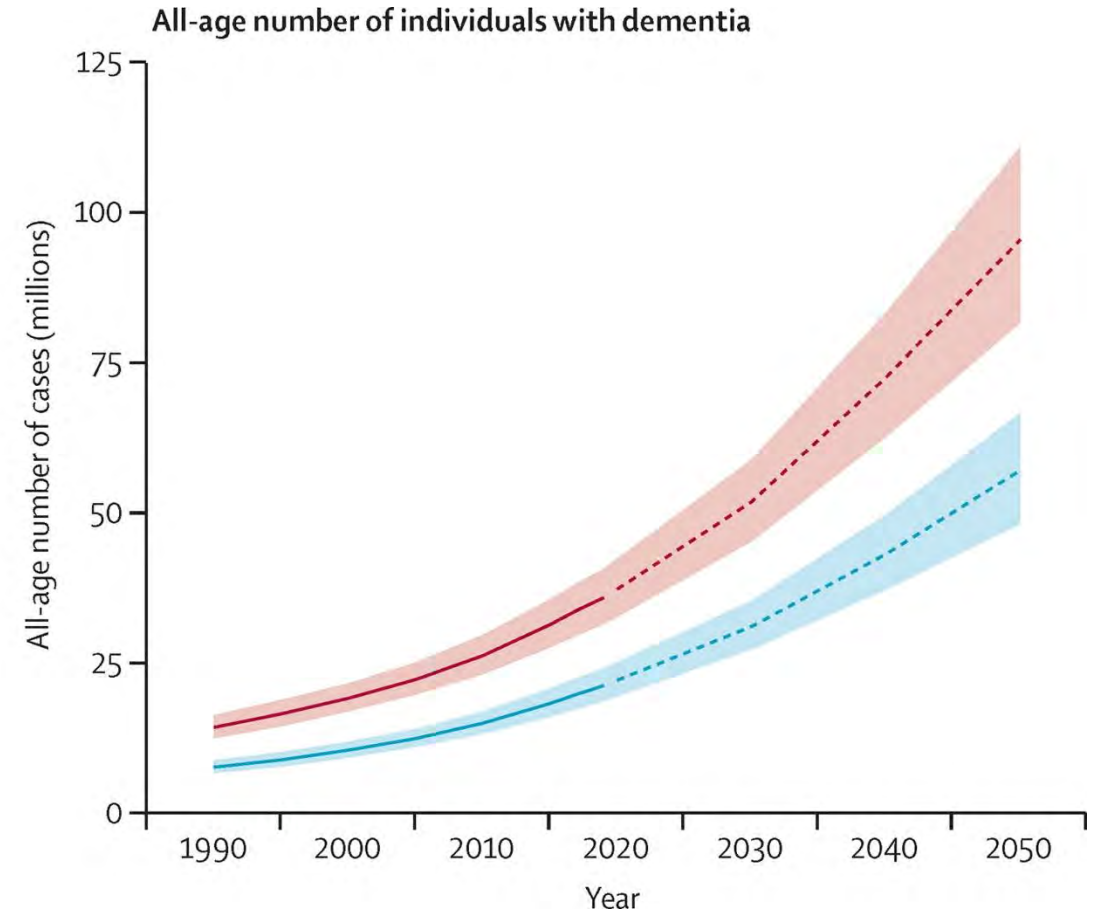
Frank M. Longo, MD, PhD
Professor and Chair
Department of Neurology and Neurological Sciences
Stanford University

Alzheimer's: age prevalence and global increase

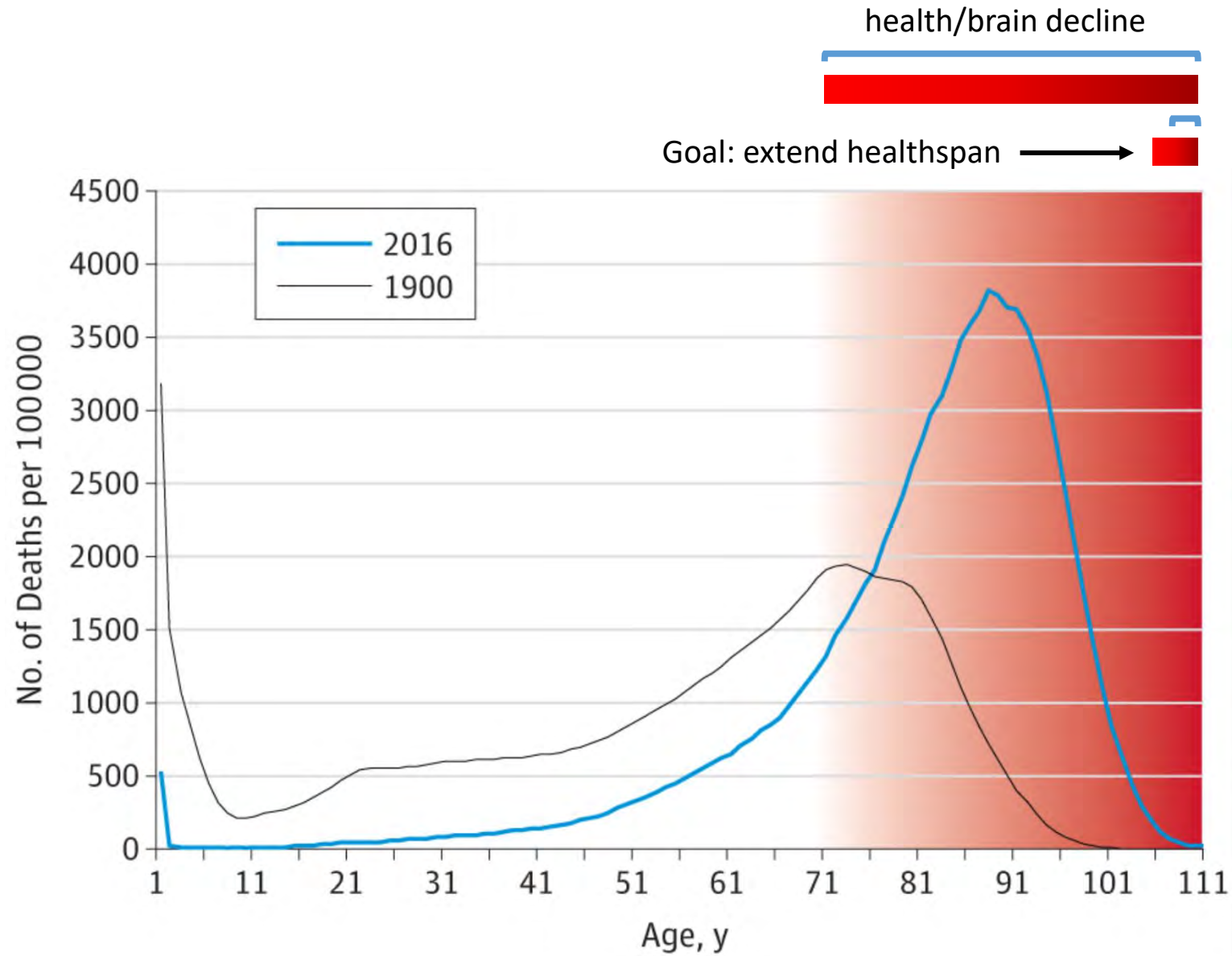
AD prevalence with age



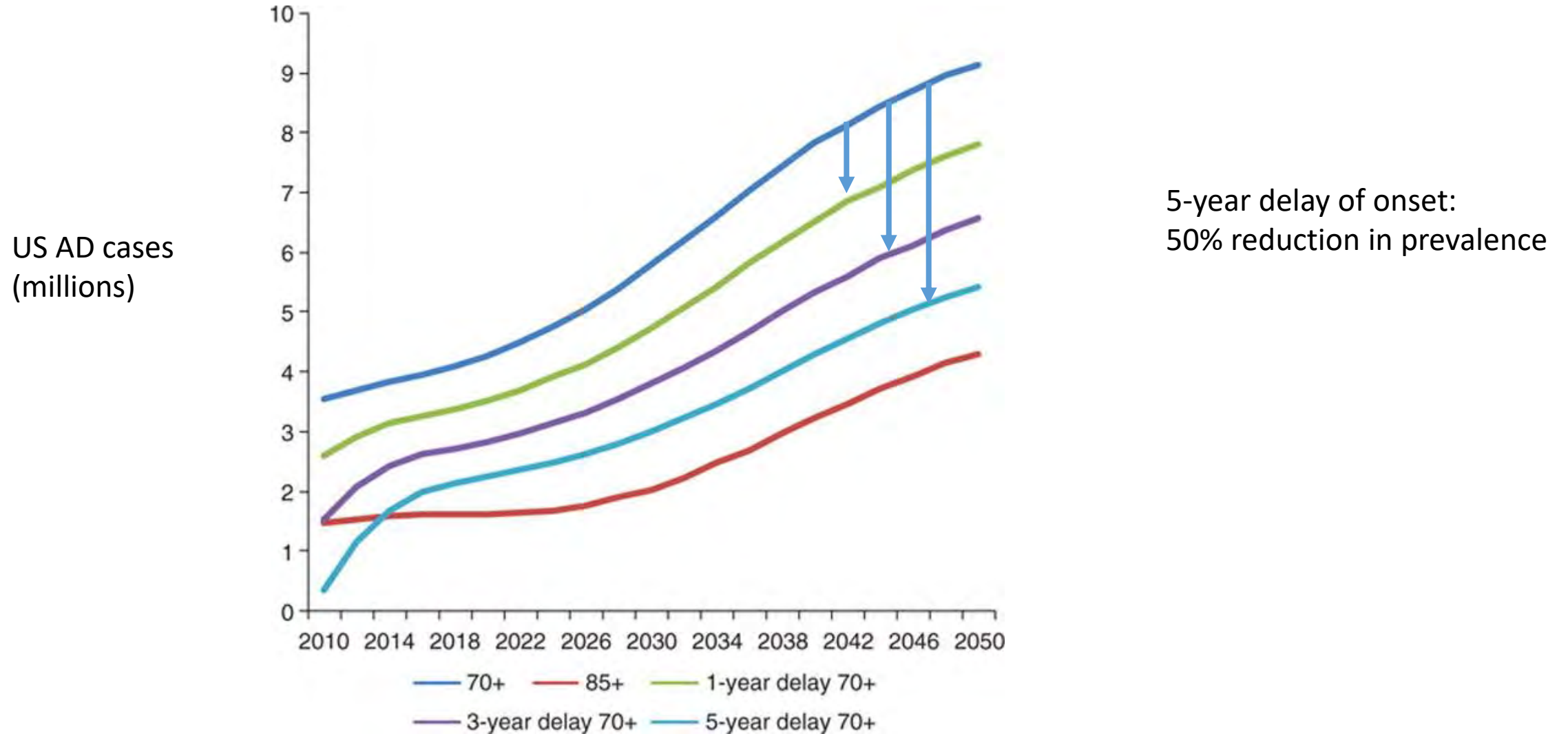
AD prevalence - global



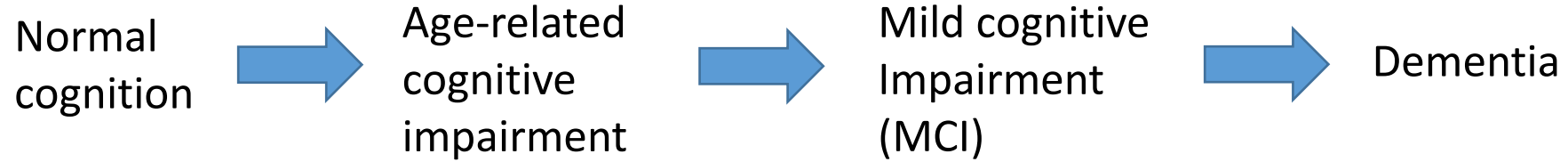
Lifespan vs Healthspan



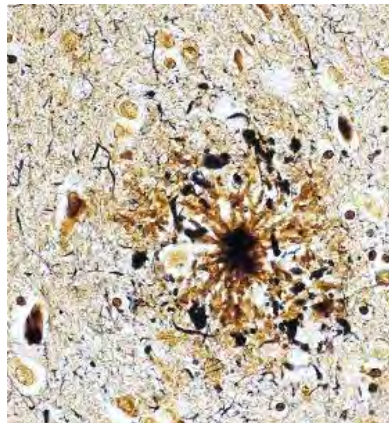
Value of delaying Alzheimer's disease onset



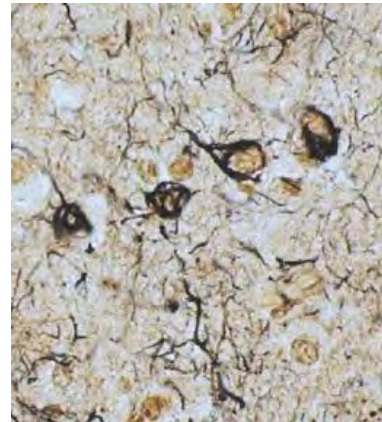
Cognitive healthspan



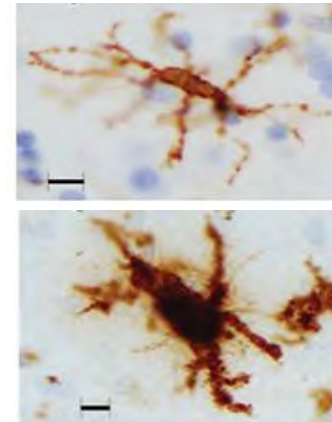
- Alzheimer's disease
- Vascular dementia
- Lewy body dementia
- Long-haul COVID (?)



Amyloid plaques



Tau tangles



Neuro-inflammation

Santiago Ramón y Cajal (1852-1934)

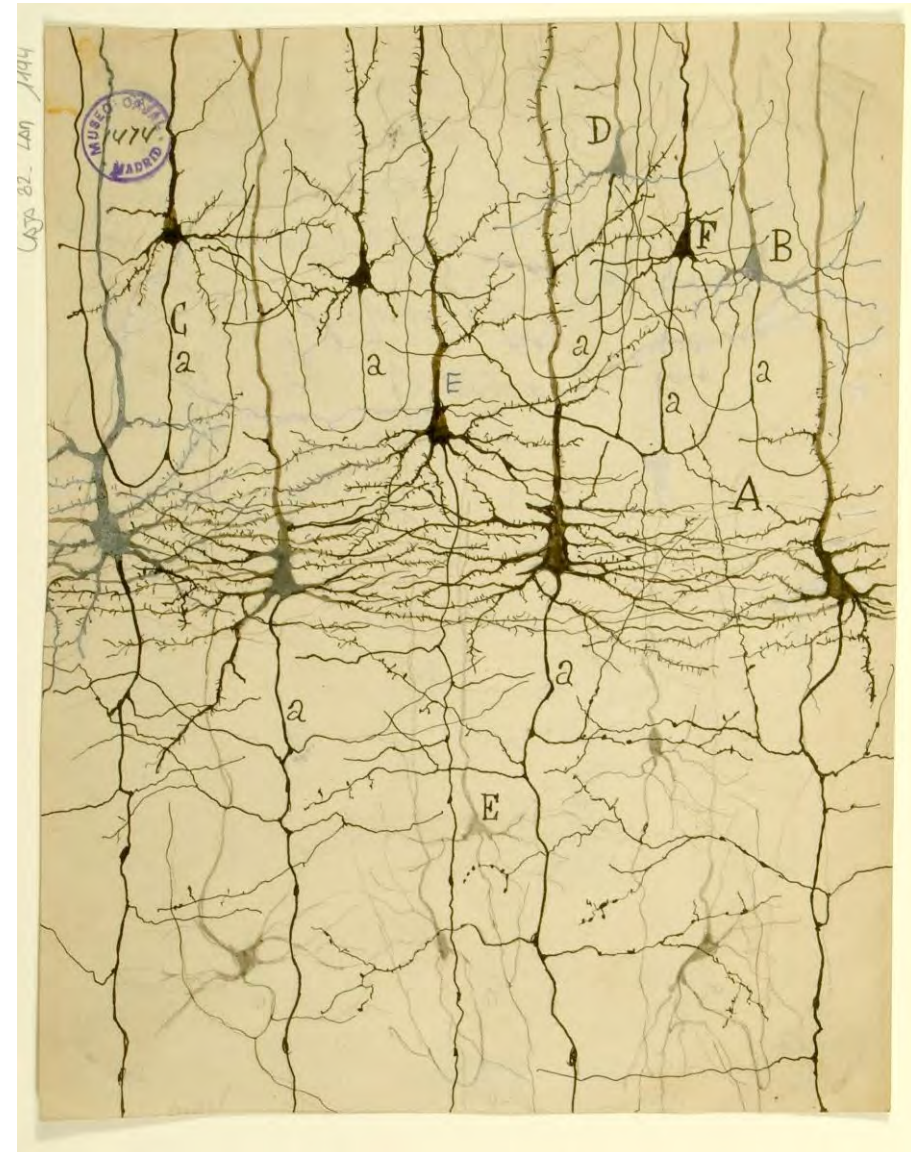
Nervous system:

Conventional perspective: continuous network

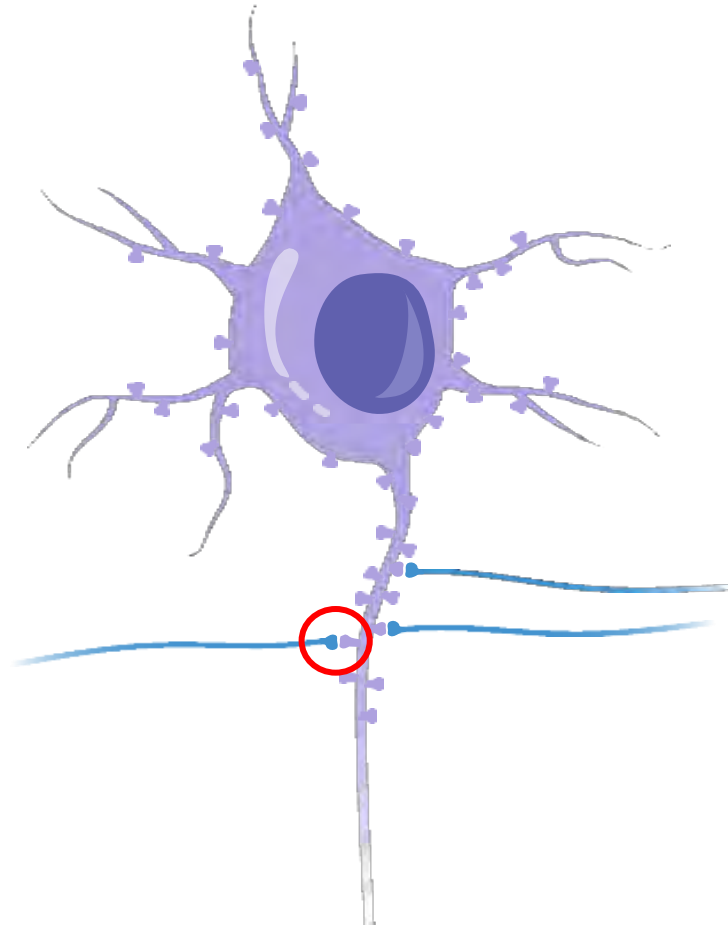
Cajal: individual neurons



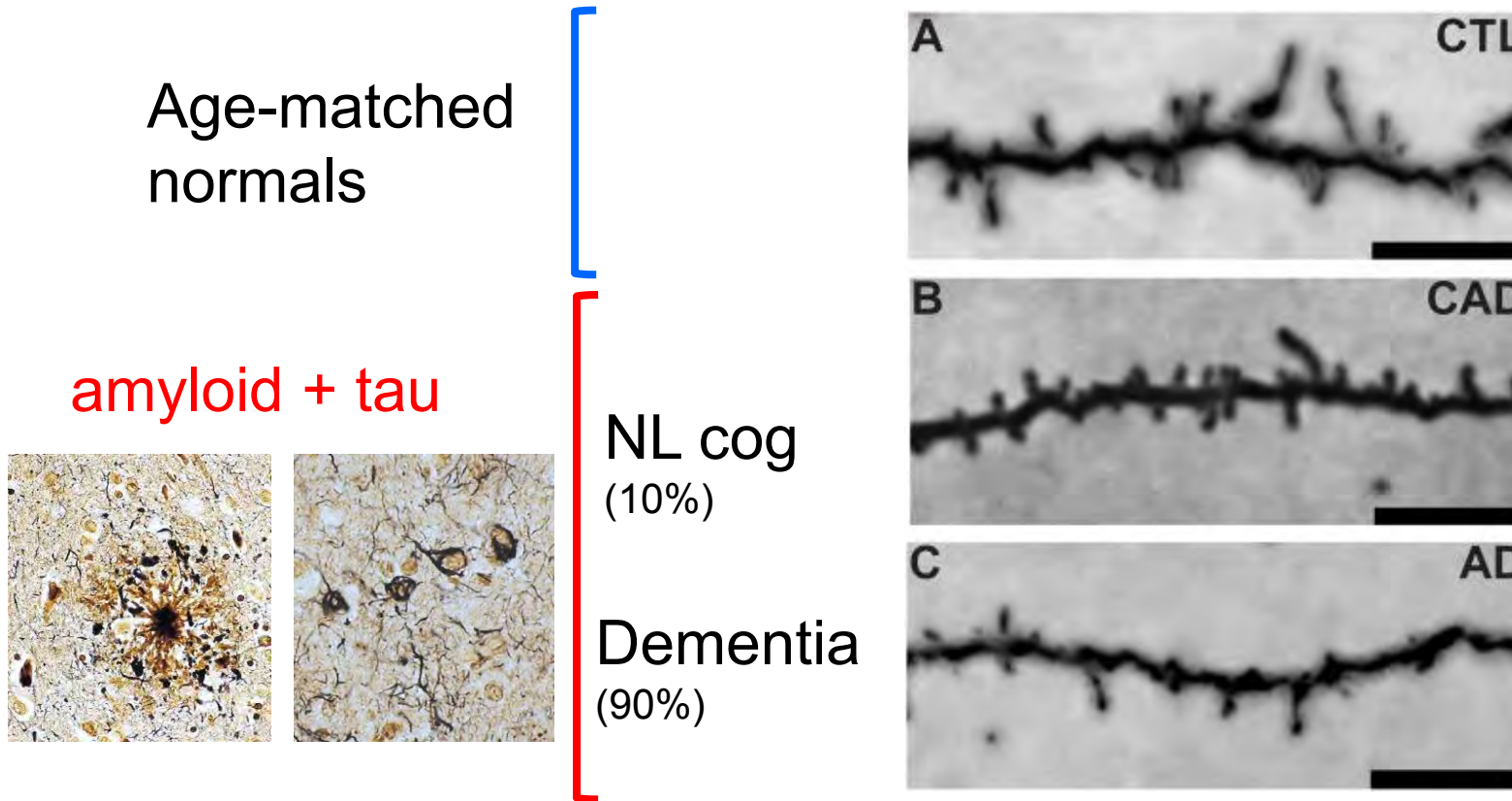
Nobel Prize 1906



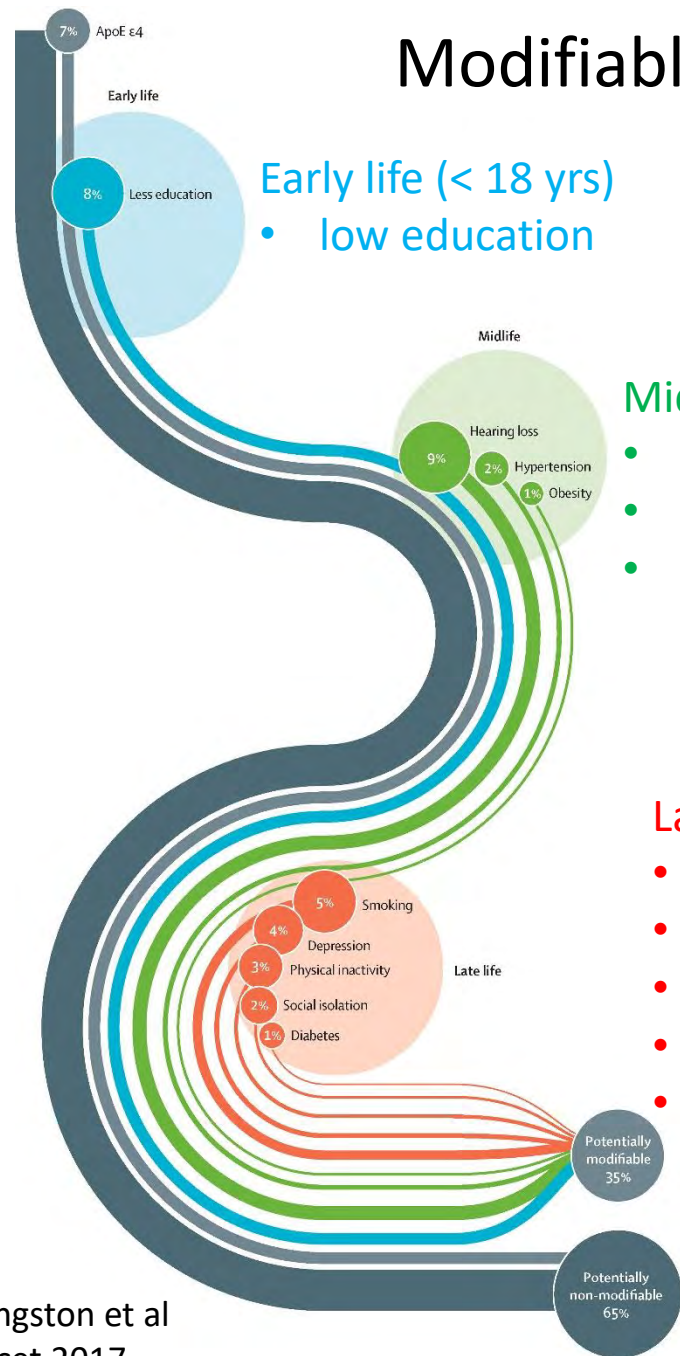
Synapses/spines – critical but vulnerable elements



In Alzheimer's disease: dendritic spine preservation associated with cognitive resilience



Modifiable dementia risk factors



Early life (< 18 yrs)

- low education

Midlife (45-65 yrs)

- hypertension
- obesity
- hearing loss

Later life (> 65 yrs)

- smoking
- depression
- physical inactivity
- social isolation
- diabetes

- 'Western' diet
- Anti-cholinergic medications
(Benadryl, Paxil, Elavil, Ditropan)

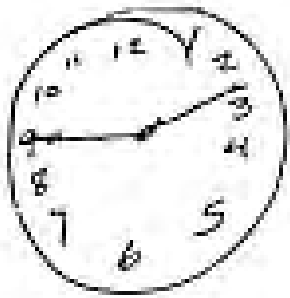
Montreal Cognitive Assessment (MOCA)

Normal: 27-30

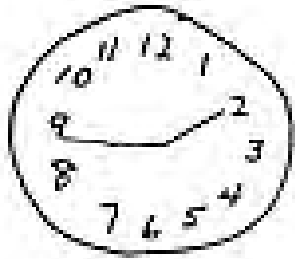
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME : _____
 Education : _____ Date of birth : _____
 Sex : _____ DATE : _____

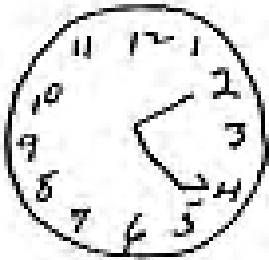
VISUOSPATIAL / EXECUTIVE		Copy cube	Draw CLOCK (Ten past eleven) (3 points)	POINTS			
		[]	[]	[]			
		[]	[]	[]			
		Contour	Numbers	Hands			
				___/5			
NAMING							
[]	[]	[]					
				___/3			
MEMORY							
Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
1st trial							
2nd trial							
ATTENTION							
Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order	[]	2	1	8	5	4
	Subject has to repeat them in the backward order	[]	7	4	2		
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[] FBACMNAAJKLBAFAKDEAAAJAMOF AAB					
Serial 7 subtraction starting at 100		[] 93	[] 86	[] 79	[] 72	[] 65	
		4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt					
				___/3			
LANGUAGE							
Repeat : I only know that John is the one to help today. []		The cat always hid under the couch when dogs were in the room. []					
				___/2			
Fluency / Name maximum number of words in one minute that begin with the letter F		[] _____ (N ≥ 11 words)					
				___/1			
ABSTRACTION							
Similarity between e.g. banana - orange = fruit		[]	train - bicycle		[]	watch - ruler	
				___/2			
DELAYED RECALL							
Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUEDE recall only	
	[]	[]	[]	[]	[]		
Optional	Category cue						
	Multiple choice cue						
				___/5			
ORIENTATION							
[]	Date	[]	Month	[]	Year	[]	Day
[]	Place	[]	City				
				___/6			
© Z.Nasreddine MD Version 7.0		www.mocatest.org		Normal ≥ 26 / 30		TOTAL	
Administered by: _____						___/30	
						Add 1 point if ≤ 12 yr edu	



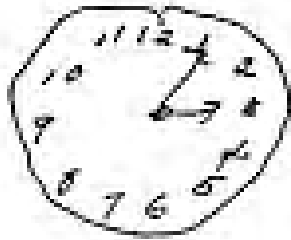
10



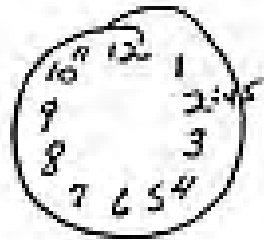
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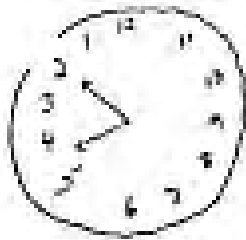
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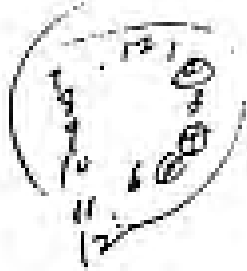
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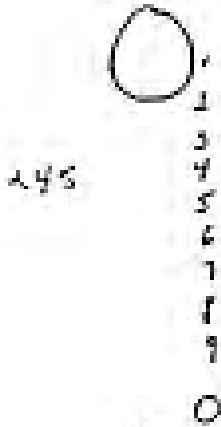
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5



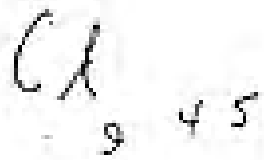
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3



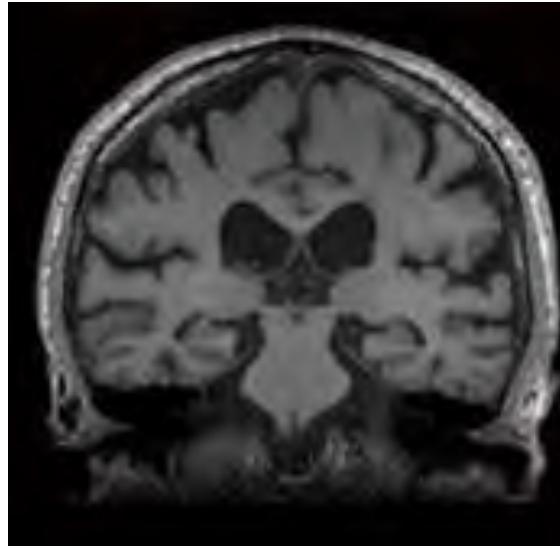
2



1

Cognitive assessment – Stanford Memory Clinic

- History (dementia onset)
- Physical exam
- Cognitive exam
- Brain MRI
- Blood: B12, thyroid, others



normal



Alzheimer's

Recent and emerging biomarkers:

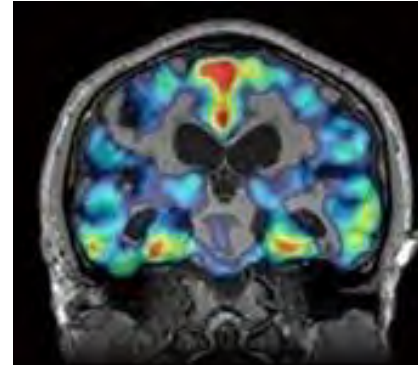
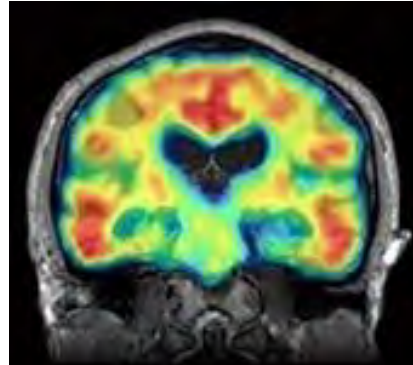
- blood amyloid and tau
- cerebrospinal fluid amyloid and tau
- amyloid and tau PET scans

Amyloid and tau PET scans

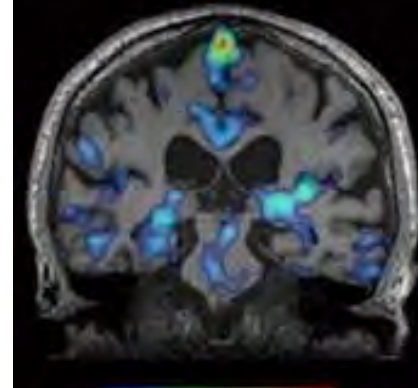
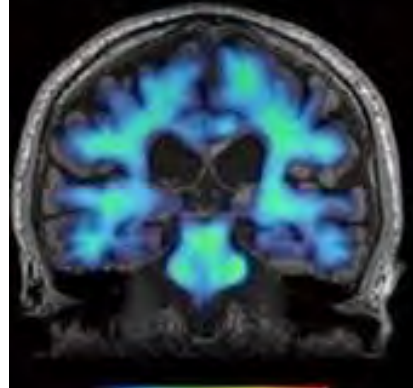
Amyloid PET
(abnormal 15-20 yrs
before symptoms)

Tau PET
(abnormal just
Before symptoms)

Alzheimer's patient



Normal
age-matched control



Dementia prevention strategies

No prevention evidence for current drugs



Physical exercise:
Epidemiology
~40% risk dec
Multiple RCTs
(goal 30 min/5 days)



Sleep:
Epidemiology
No RCTs



Diet:
Epidemiology
~30% risk dec
No RCTs



Cognitive exercise:
Effects on Executive function –
transfer to other functions?

RCTs = Randomized Clinical Trials

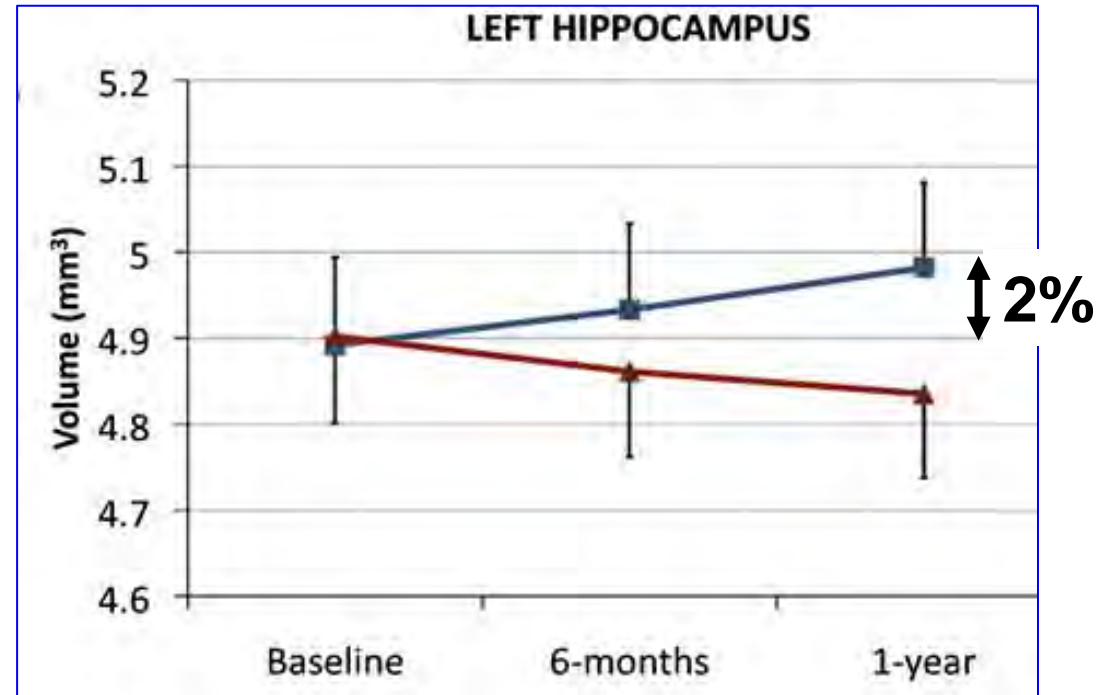
Walking reverses of Hippocampal Age-related Atrophy!



10 → 40 min/day walk 1 year

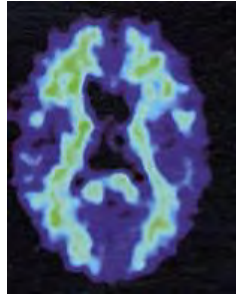


hippocampus
1-2%/yr atrophy

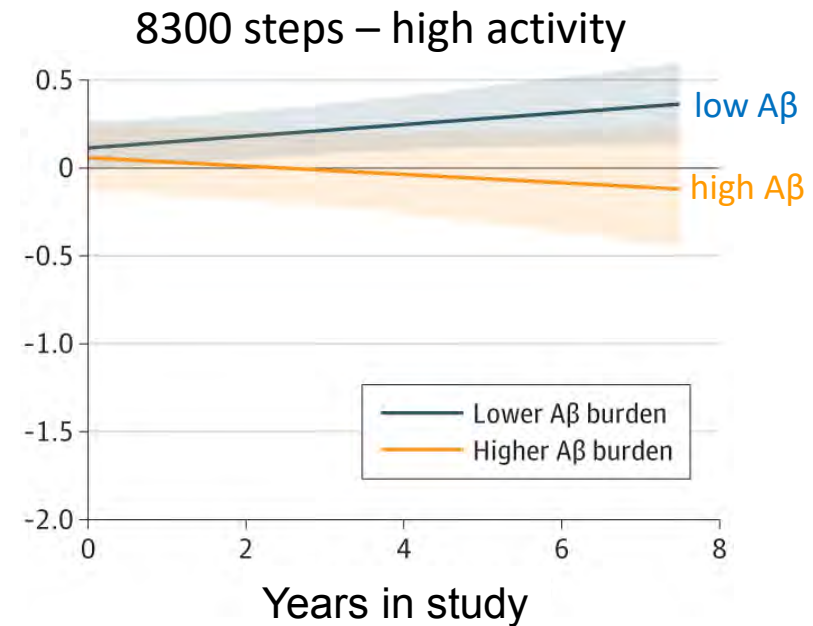
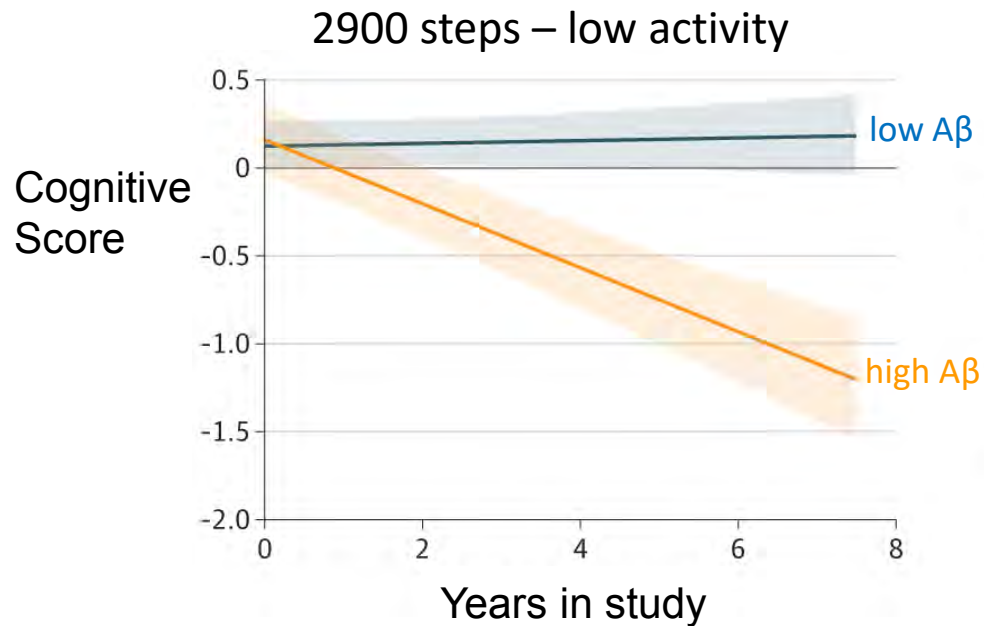
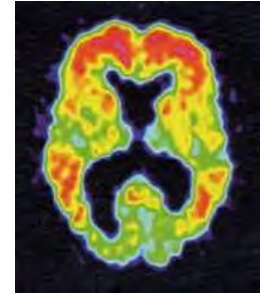


High physical activity – resilience to amyloid

low A β



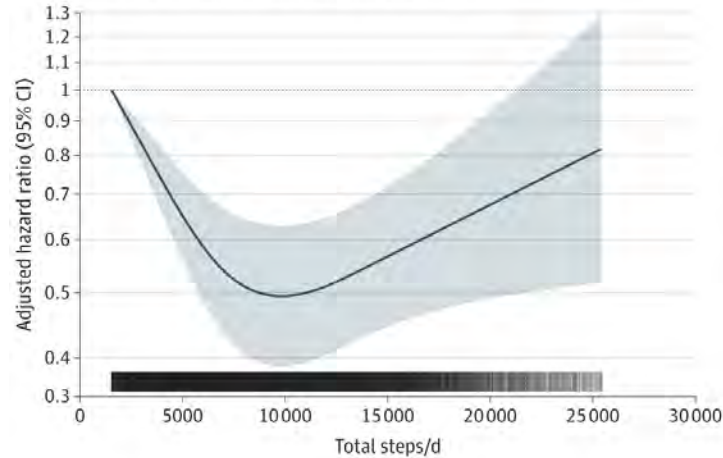
high A β



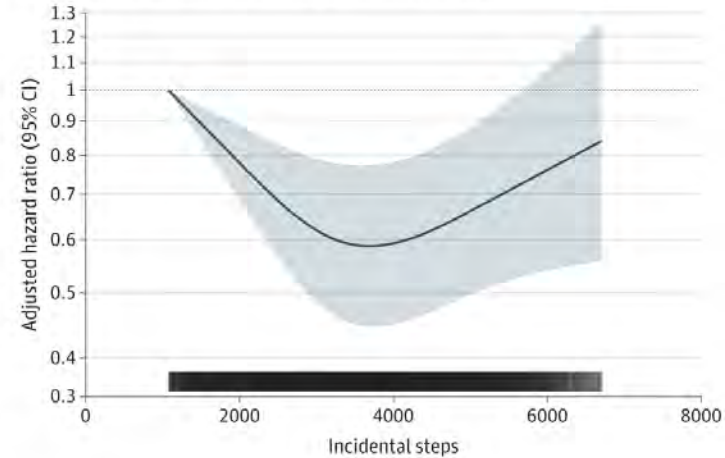
Step count and risk of dementia

UK Biobank Registry
78,430 adults aged 40-79
wrist accelerometer
7-year follow up

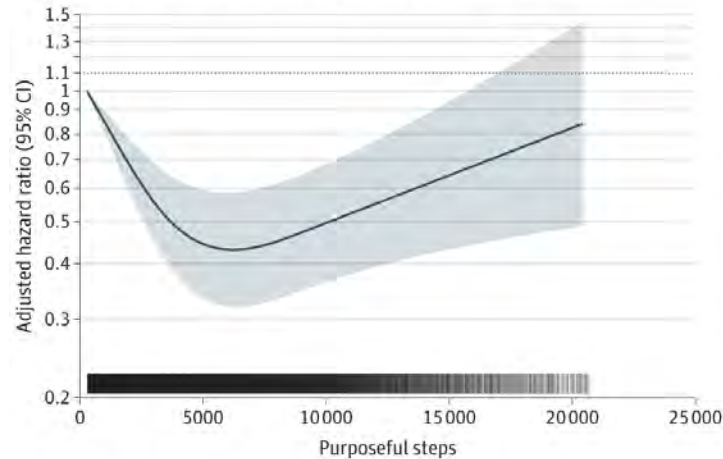
A Total steps/d and incidence of all-cause dementia



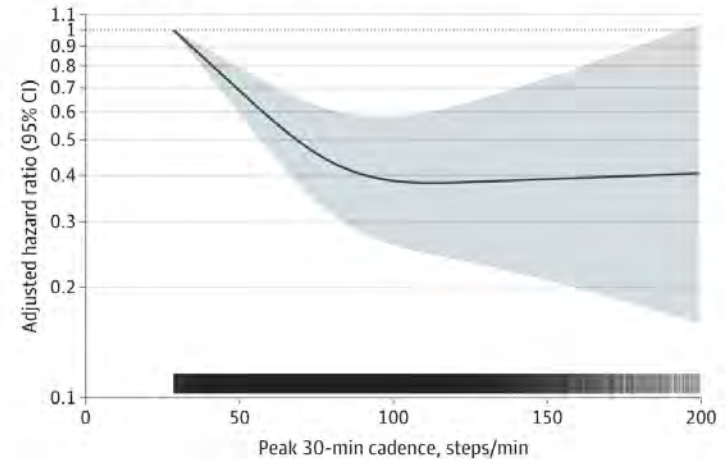
B Incidental steps and incidence of all-cause dementia



C Purposeful steps and incidence of all-cause dementia



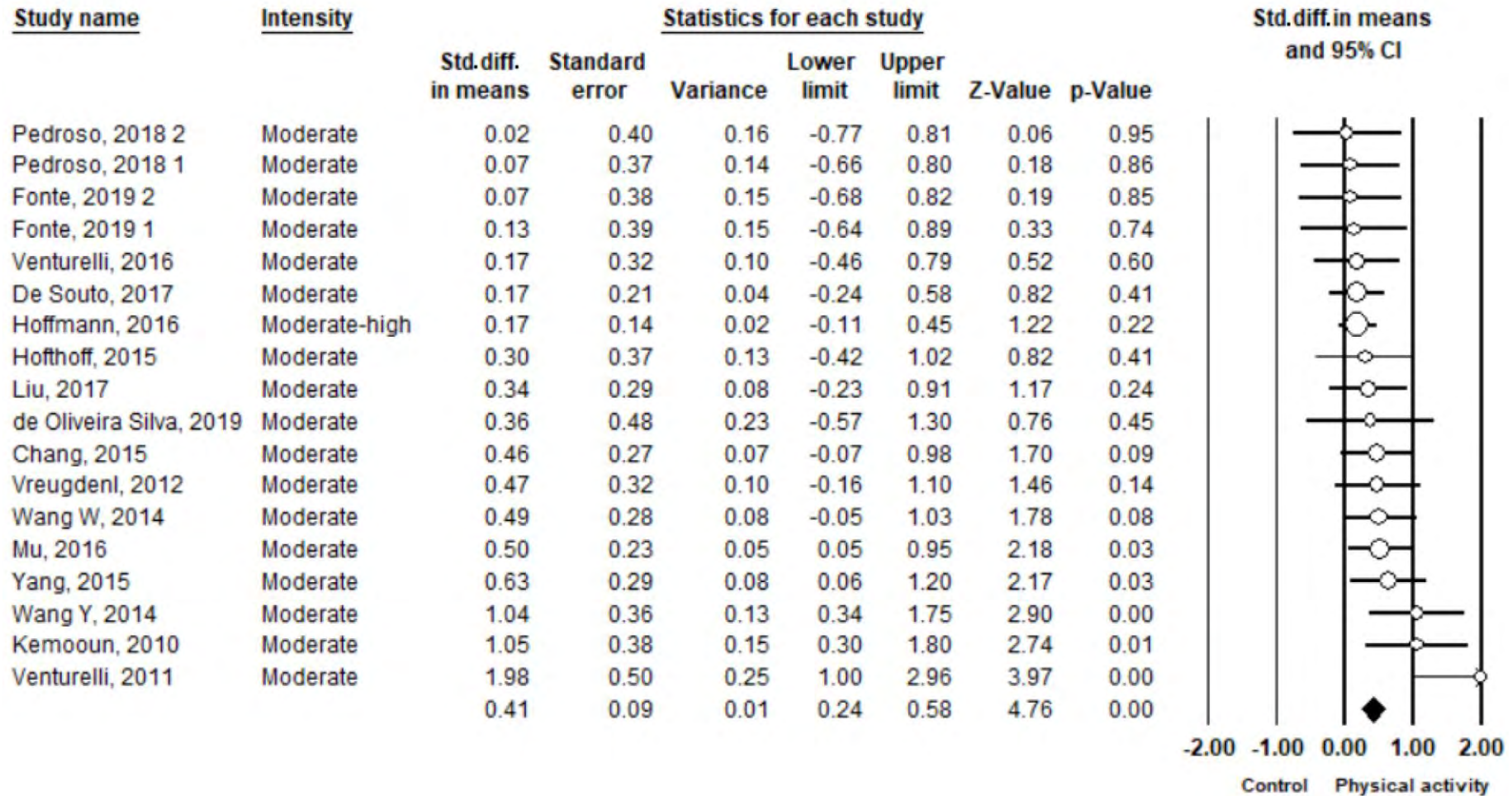
D Peak 30-min cadence and incidence of all-cause dementia



Optimal dose 9800 steps; 50% risk reduction
25% reduction dose 3800

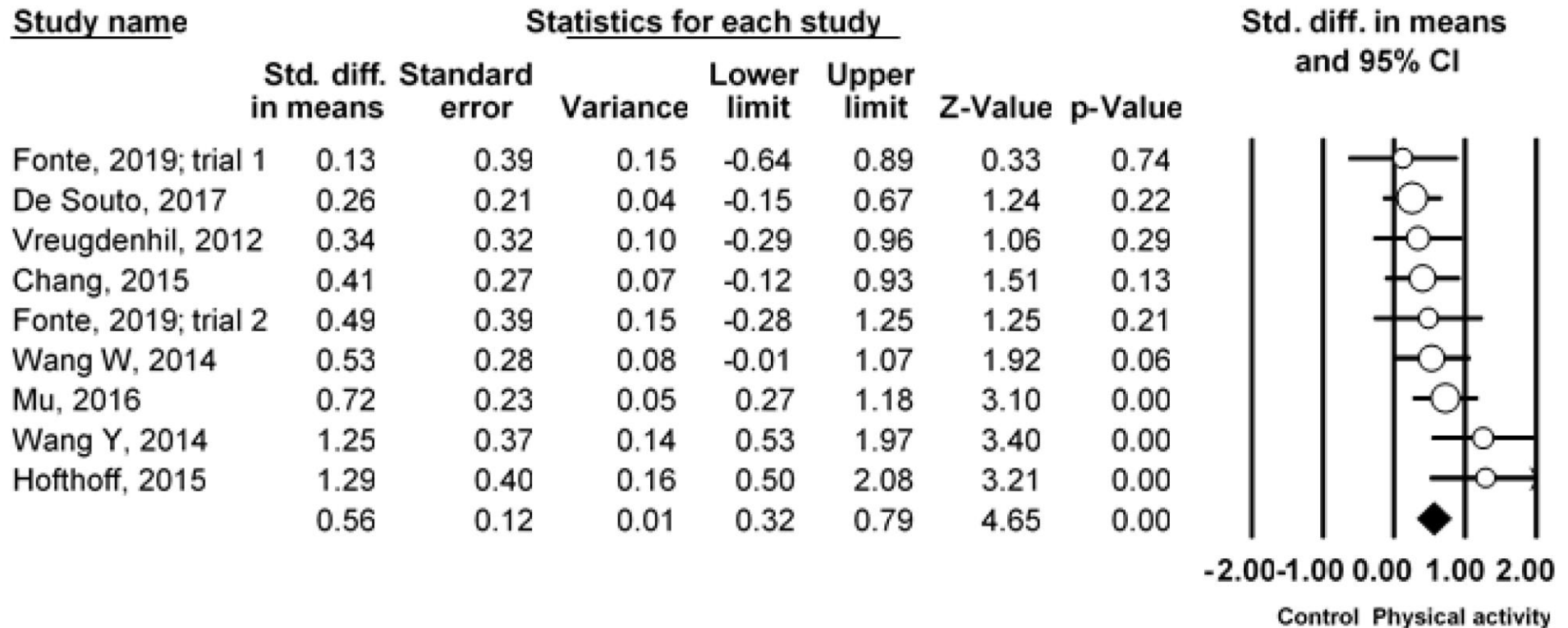
Effect of physical activity on global cognition in Alzheimer's disease

Meta analysis

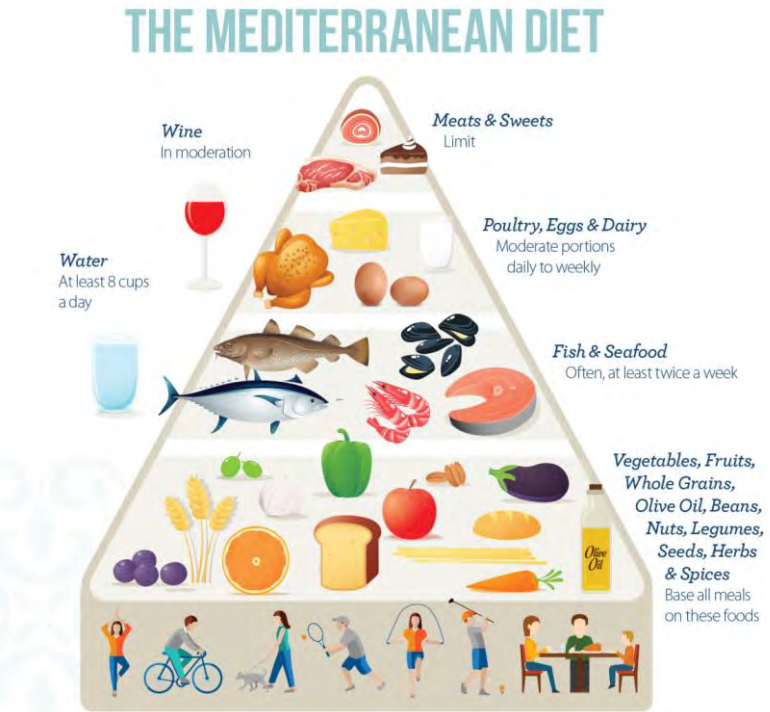


Effect of physical activity on activities of daily living in Alzheimer's disease

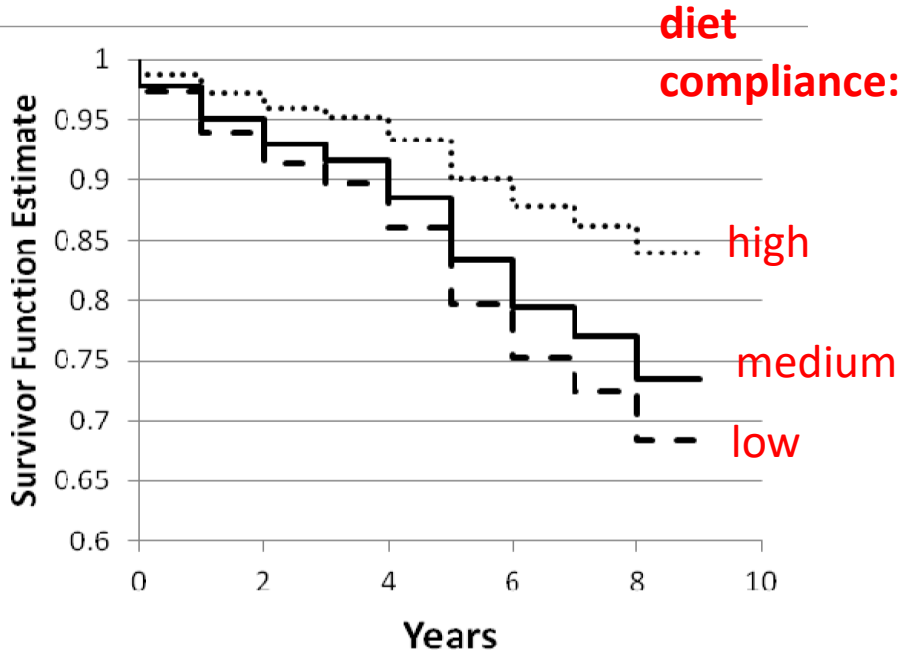
Meta analysis



Mediterranean diet: longitudinal studies



Alzheimer onset

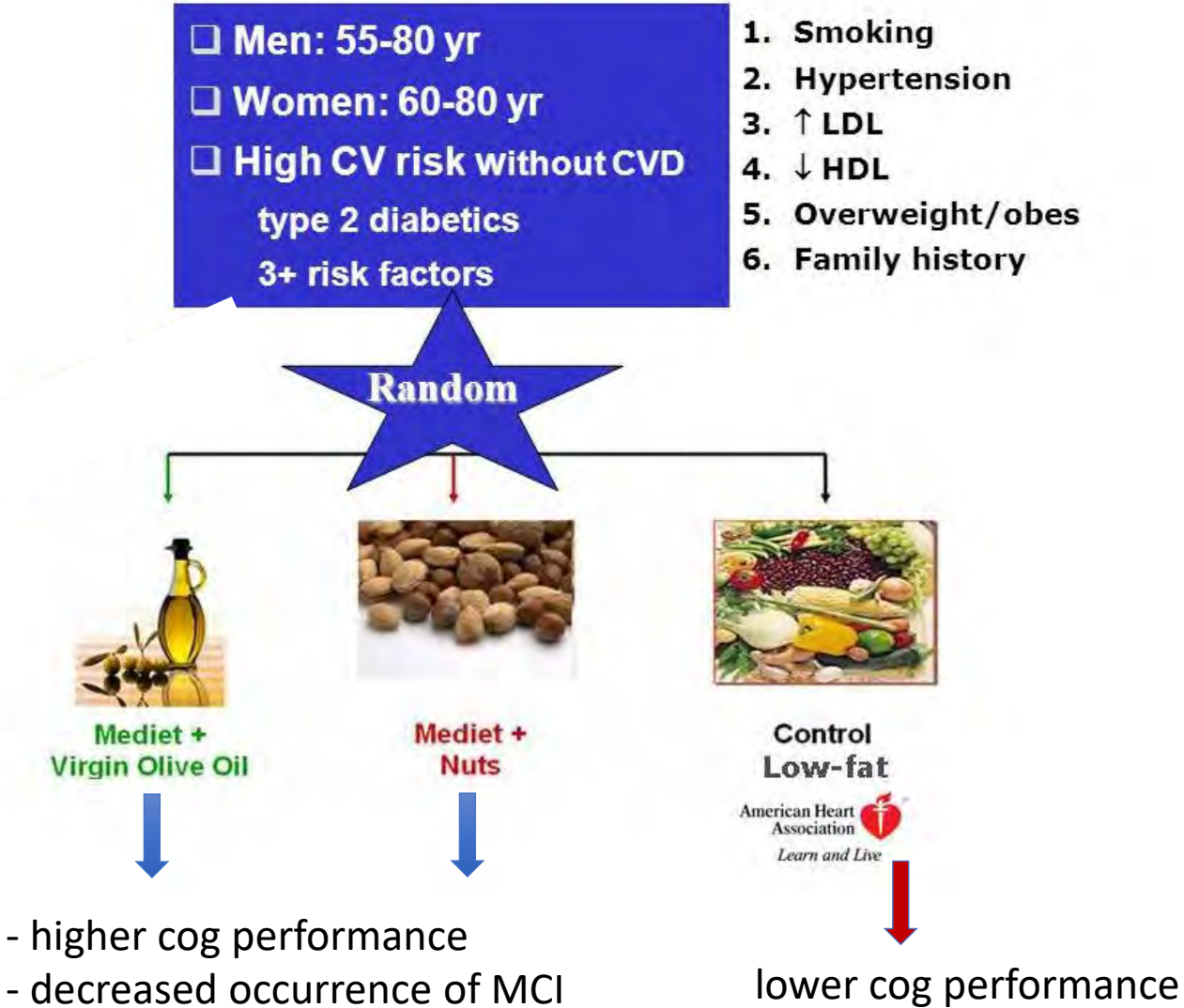


20-40% risk reduction for dementia

Wu and Sun
Scientific Reports 2017
Abbatecola et al
Curr Opin Clin Nutr Metab Care 2018

Mediterranean diet – prospective trial

PREDIMED: RCT 6.5 years (Valls-Pedret et al, JAMA Intern Med 2015)



Ongoing:
MIND study
Med-DASH RCT
3-year at risk AD

Diet / Supplements



Omega-3 FA

- AD 5/6 studies no effect except 1 study (mild AD subgroup) Thomas et al, BioMed Res 2015
- MCI 4/5 small studies mild improvement;
- Normal aging: no effect (3/3 studies); Jiao et al, Am J Clin Nutr 2014



Vitamin E

- Mild/mod Alzheimer's 2000 IU/d: 19% reduction rate decline ADLs; no cog effects (Dysken et al, 2014)
- Normal elderly; 400 IU/day: PREADVISE trial (2017) – no effect



Vit D: 'normal' level (controversial) 20-40 ng/mL

< 10 ng/mL : 2.2X; < 20 ng/mL: 1.5X increased risk

- 3 small interventional studies: improved executive function (1-15 mo)

Traditional FDA approved therapies

Do not delay onset or slow progression



- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

- Memantine (Namenda)

Aducanumab – amyloid antibody Two phase 3 trials

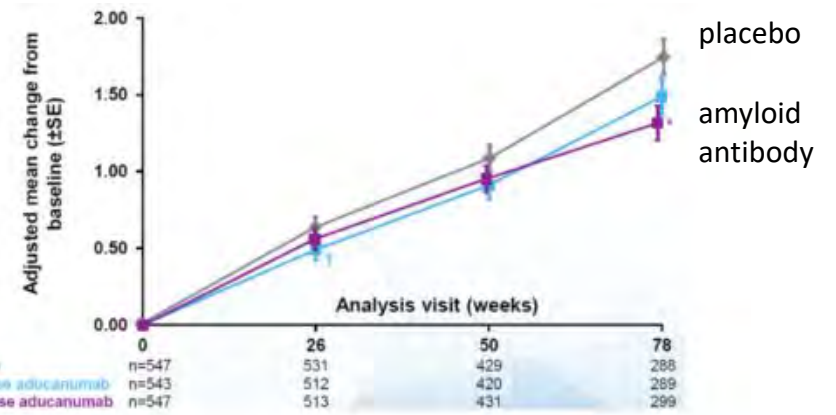
FDA approved 2021

Amyloid PET scan

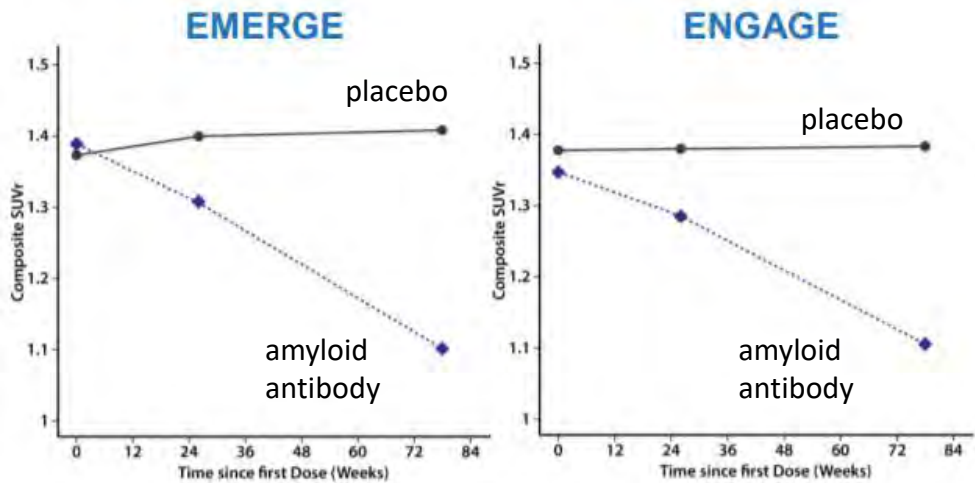
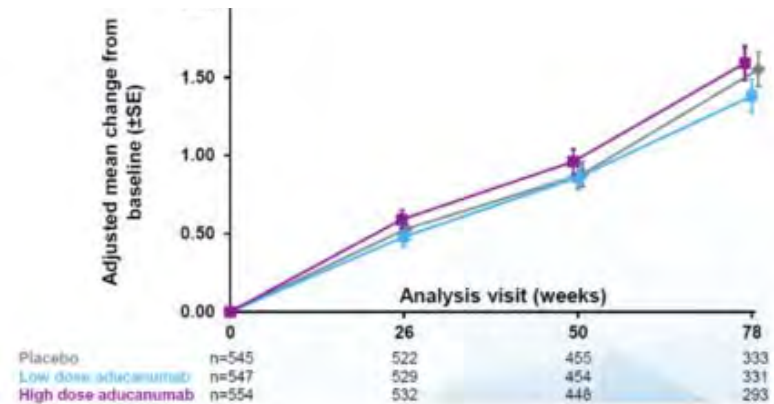


Cognitive score: CDR-SB: functional rating scale 0 -18

Emerge



Engage

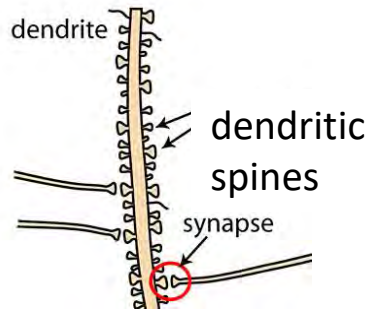


Young blood in old and AD mice improves cognition

Tony Wyss-Coray
Stanford Neurology



Aged mice



old blood

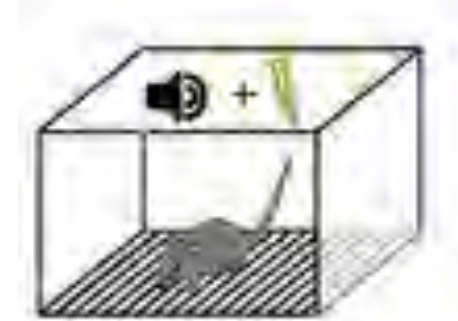


low spine density

young blood



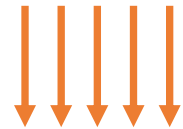
high spine density



Villeda et al *Nature Med* 2014

Clinical studies to translate mouse discoveries

Two small proof-of-concept safety studies in Alzheimer's disease completed



Multiple infusions of plasma
or plasma fraction from
young donors (~35 yrs old)

Patient Assessment:

Safety ✓

Daily activities of living

Memory tests ✓

Functional brain imaging

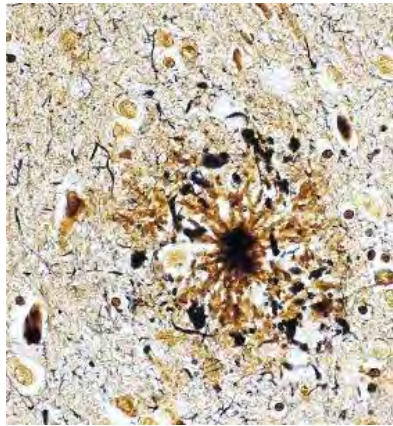
Blood tests

Sharon Sha, M.D.

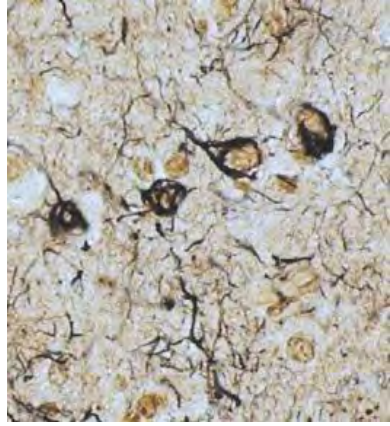


Stanford
MEDICINE

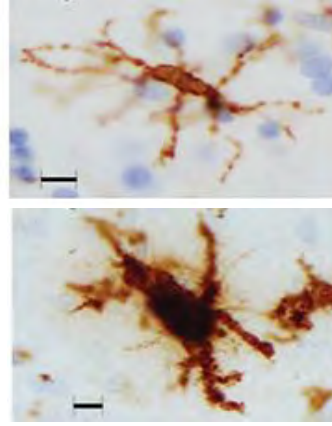
Developing a more powerful drug – addressing multiple mechanisms



Amyloid plaques



Tau tangles



Neuro-inflammation



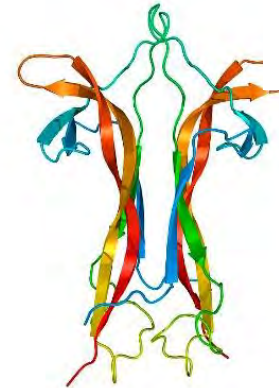
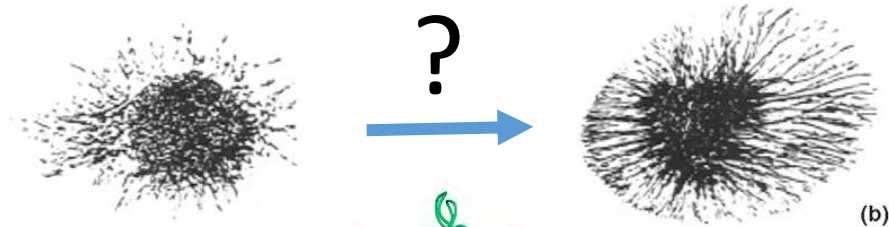
Rita Levi-Montalcini

Discovery of Nerve Growth Factor (NGF)



Levi-Montalcini, *Science* 1987

sensory neurons

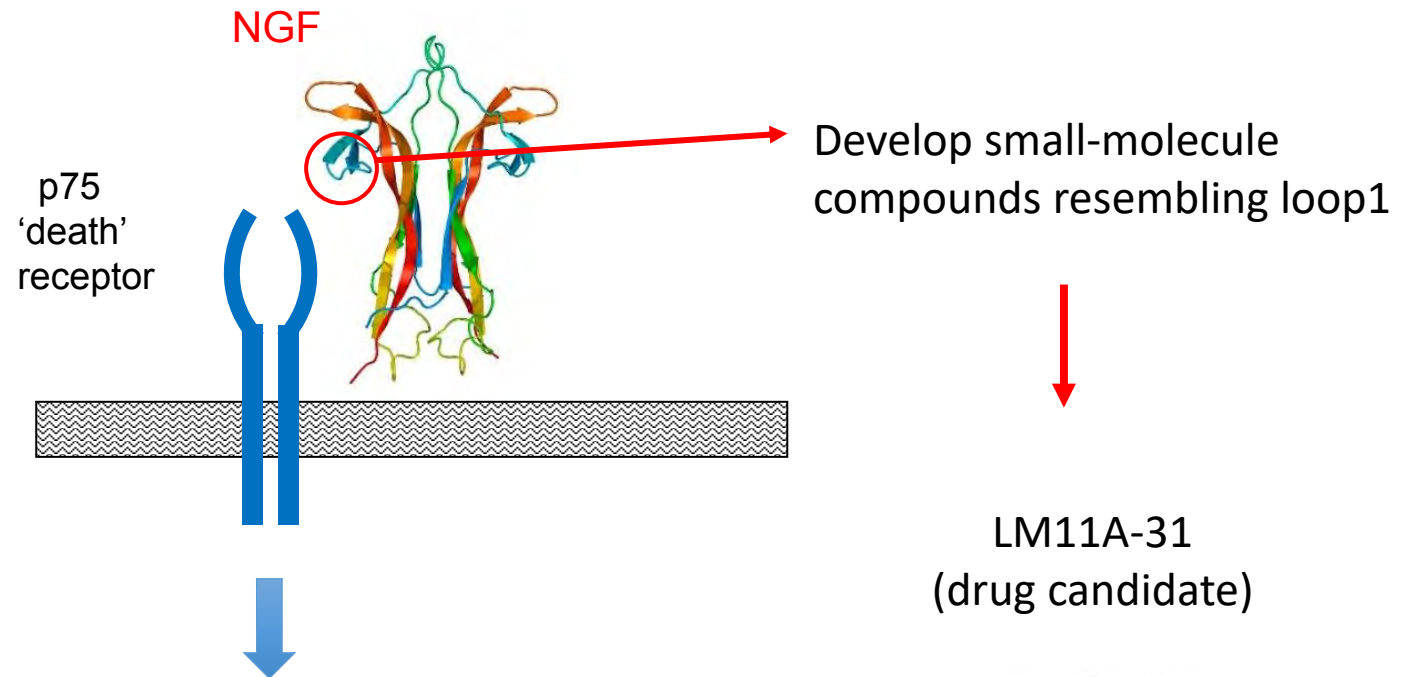


Nerve Growth Factor (NGF)

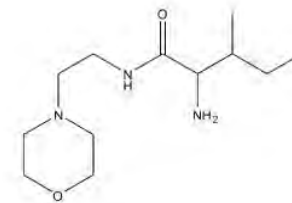


Nobel prize in medicine 1986

Inventing drug to prevent neuron and synapse degeneration: LM11A-31



- prevent neuron and synapse degeneration
- promote neurite outgrowth



Basic studies in cell cultures

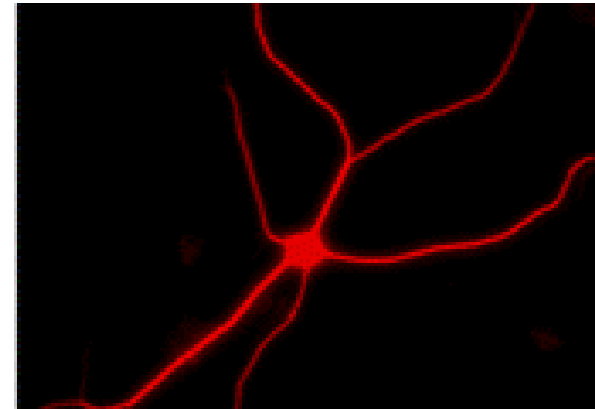
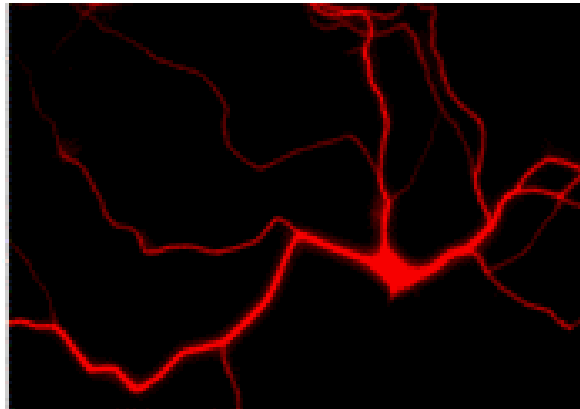
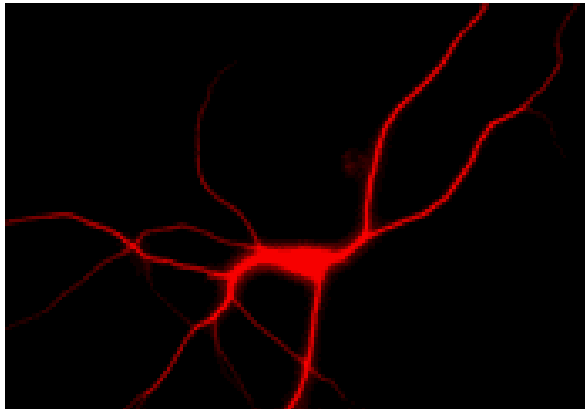
Neurons from
mice or humans



culture
media

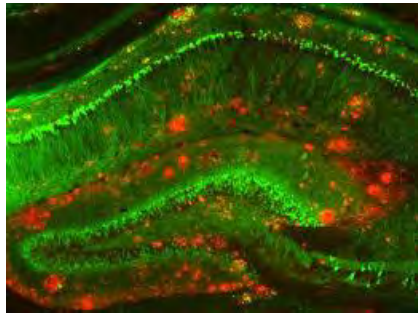
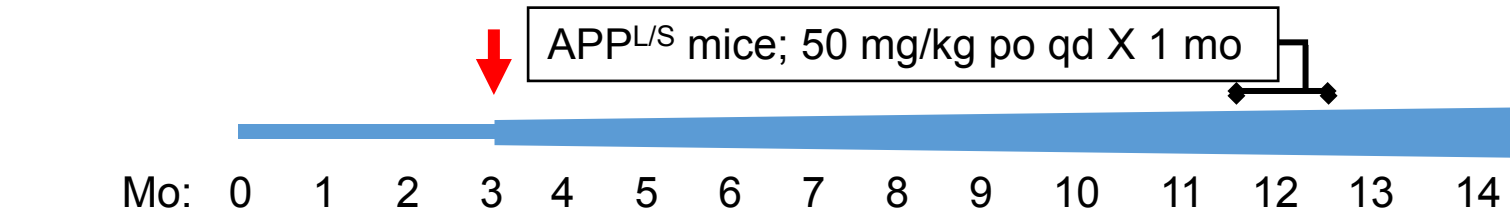
amyloid

amyloid
+ C31

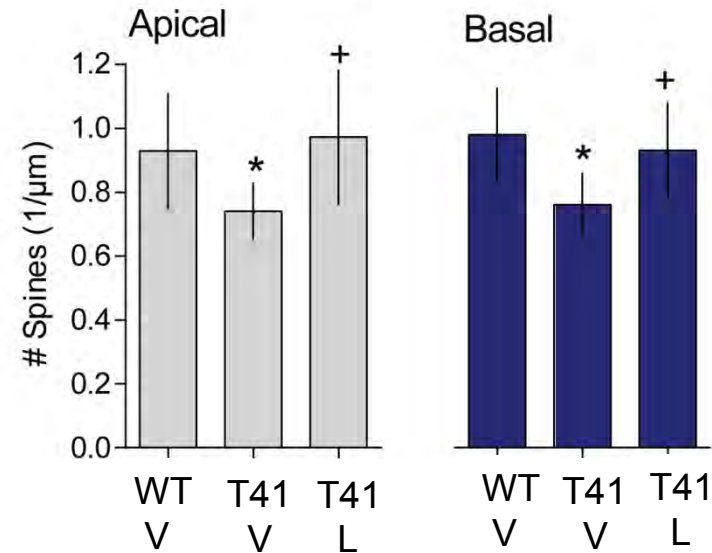
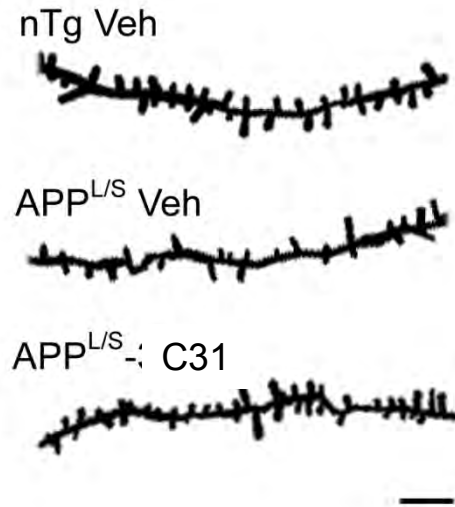


“Resilience in a dish”

LM11A-31 reverses late-stage spine degeneration

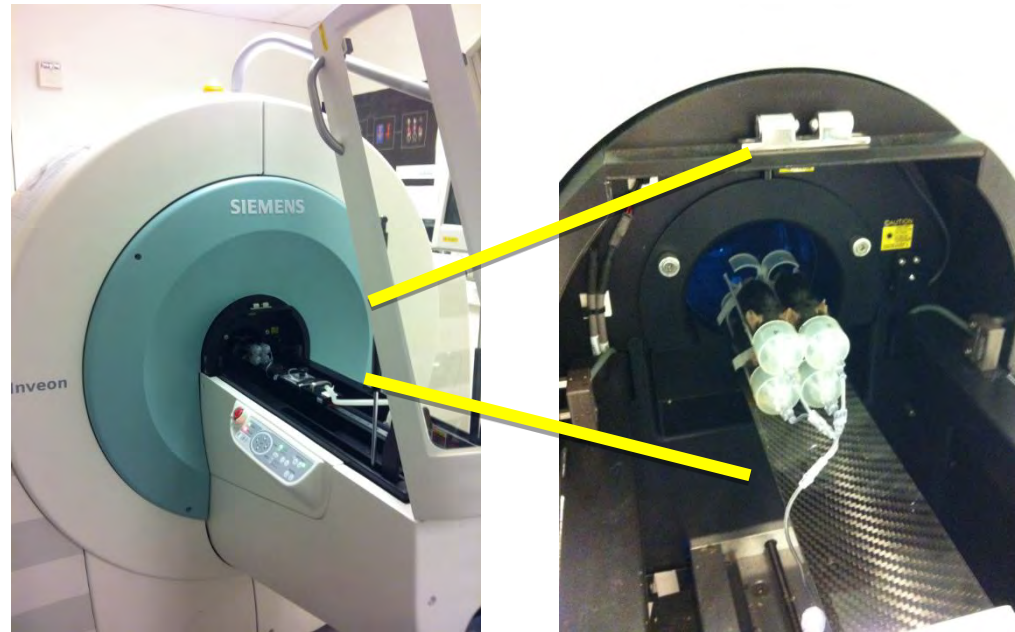


no change in amyloid level

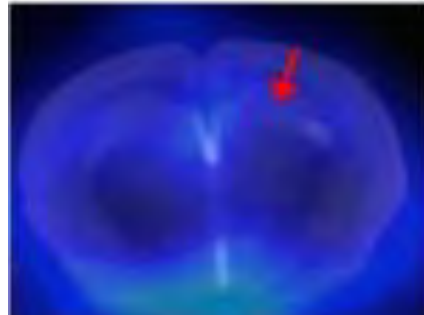


CT-PET detection of brain inflammation

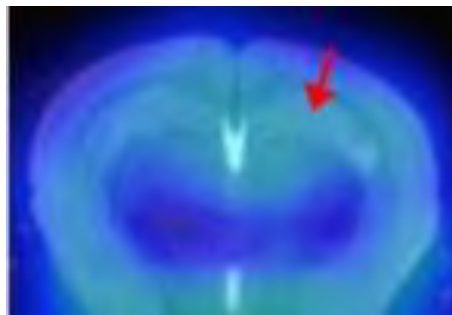
Michelle James / Frank Longo - Stanford



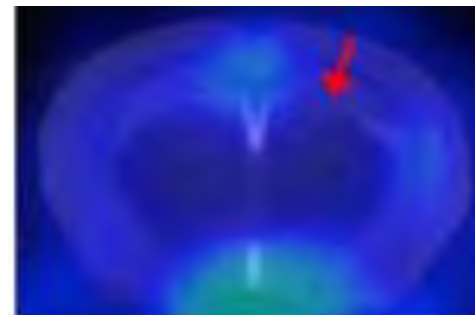
normal
mouse



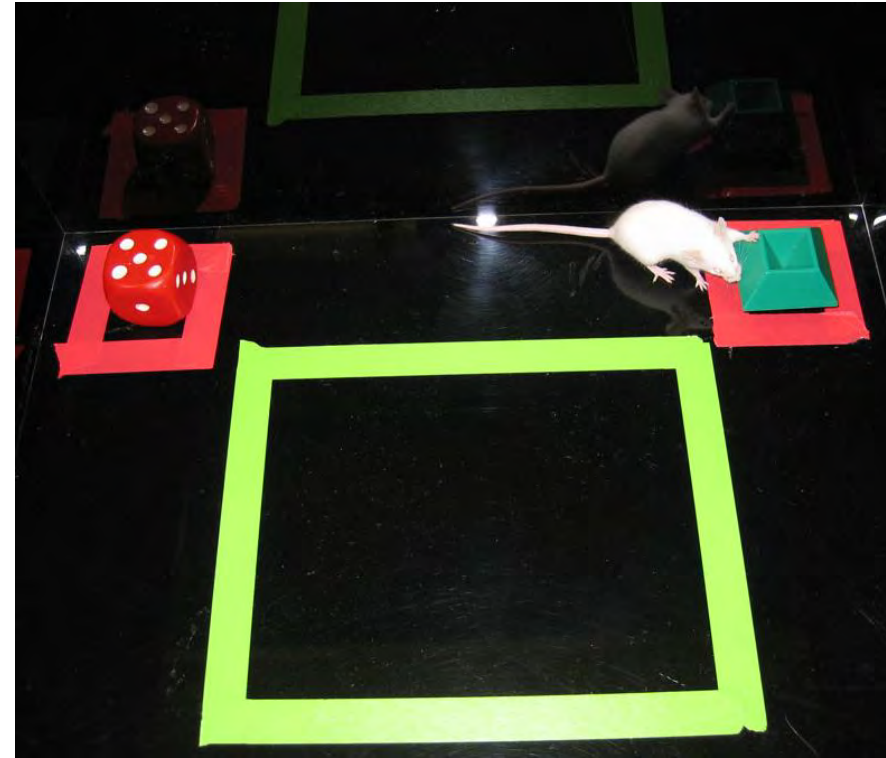
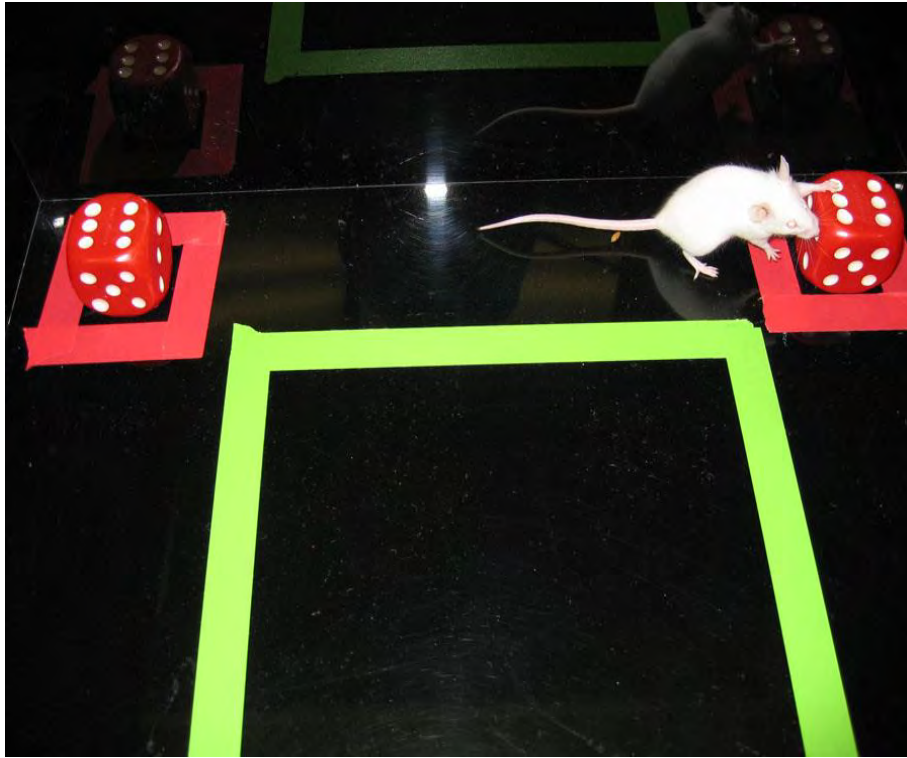
AD mouse +
placebo



AD mouse
+ test drug

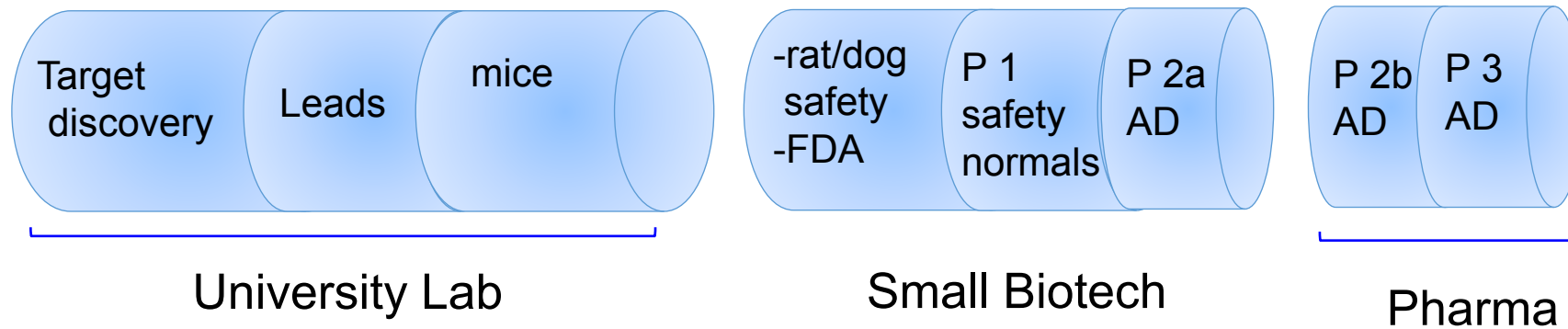


Testing Alzheimer's Therapies



web

The Drug Pipeline and 'Valley of Death'



Phase 2a RCT safety and exploratory endpoint trial

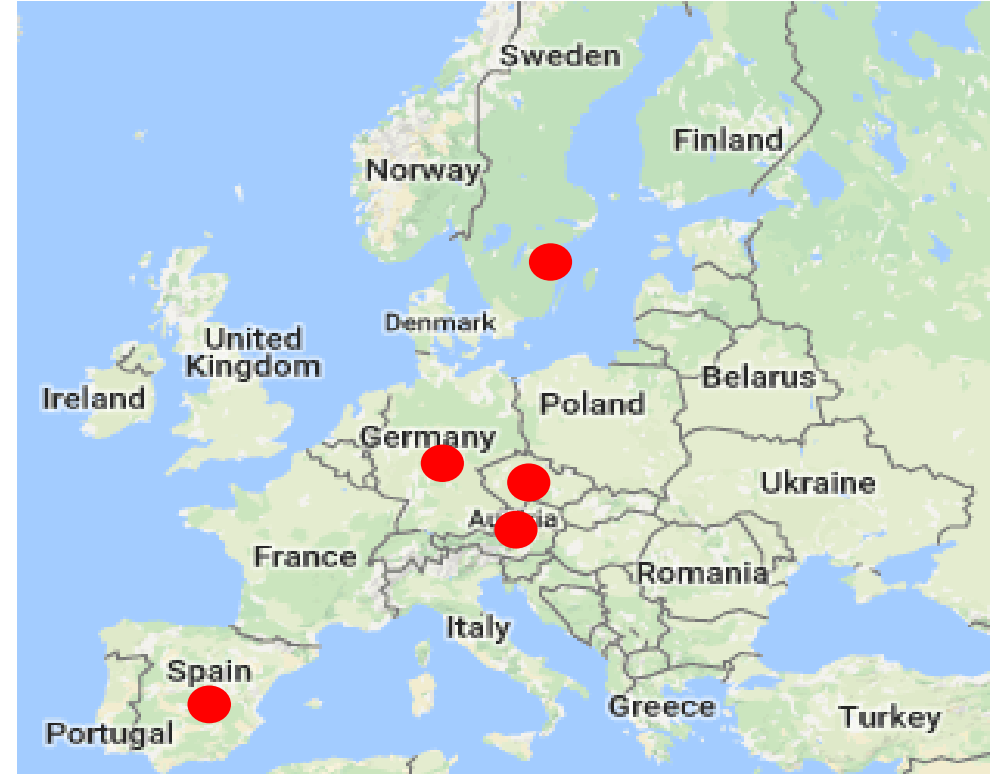
Mild-moderate Alzheimer's disease

PI: M. Windisch (Pharmatrophix-NeuroScios)

Co-PI: A. Börjesson-Hanson (Karolinska)

Subjects enrolled in 18 sites in 5 countries

6-month treatment trial

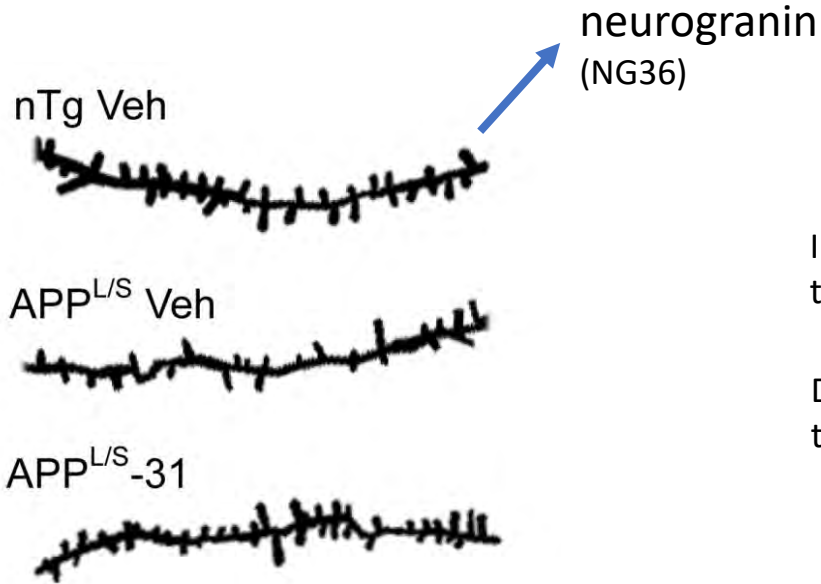


Barcelona Alzheimer's Treatment and Research Center



LM11A-31 reduces biomarker of synaptic spine loss

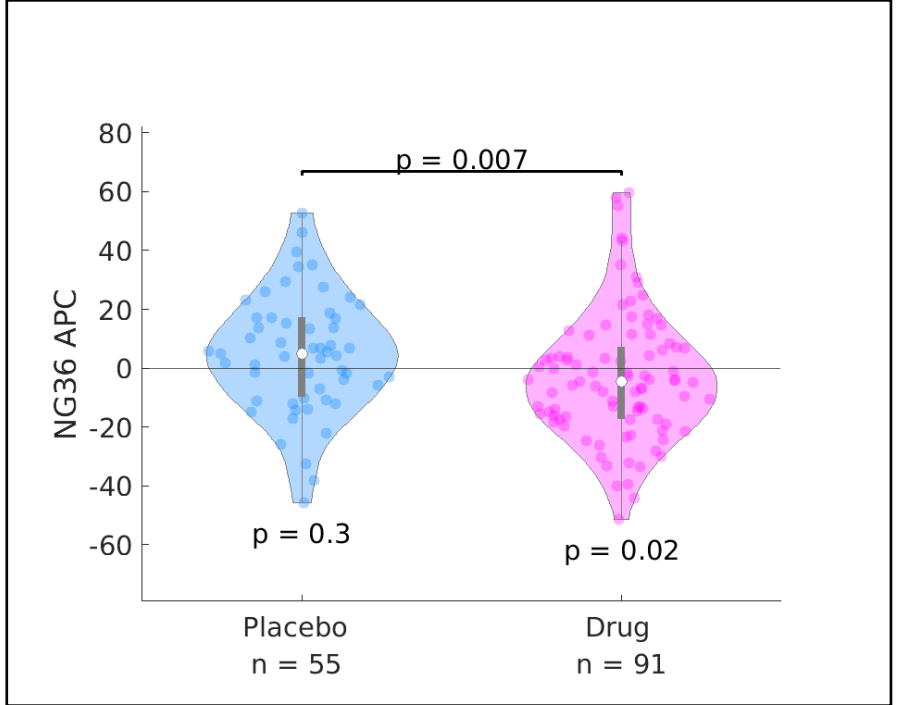
mouse




Increase over time

Decrease over time

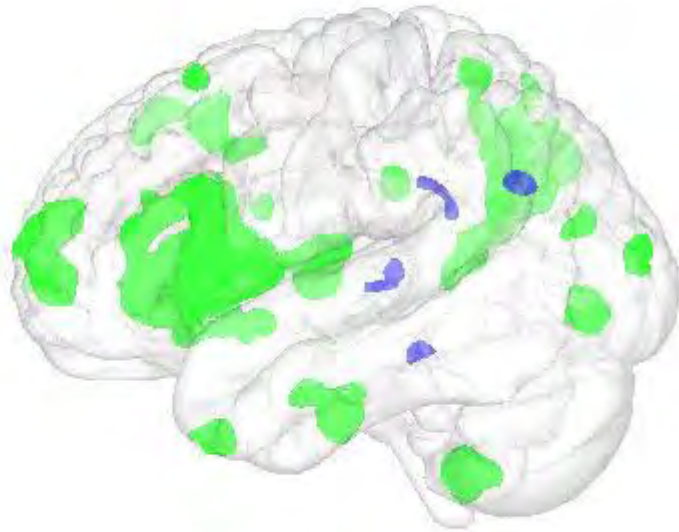
Human – cerebrospinal fluid



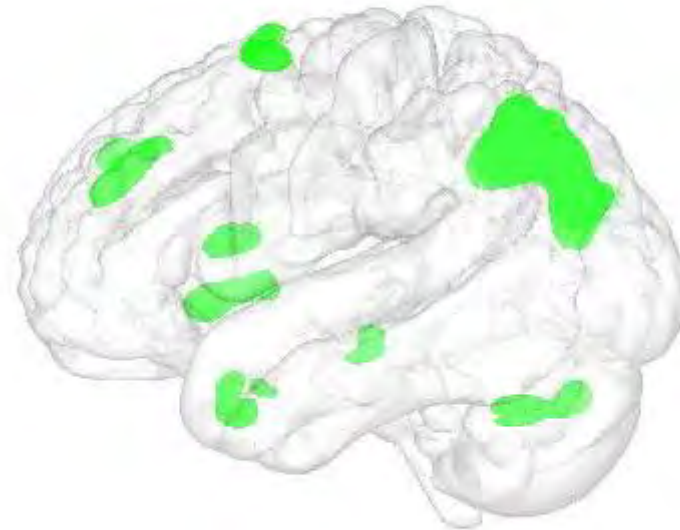
Phase 2a trial – treatment results

 = slowing of brain degeneration

MRI scans

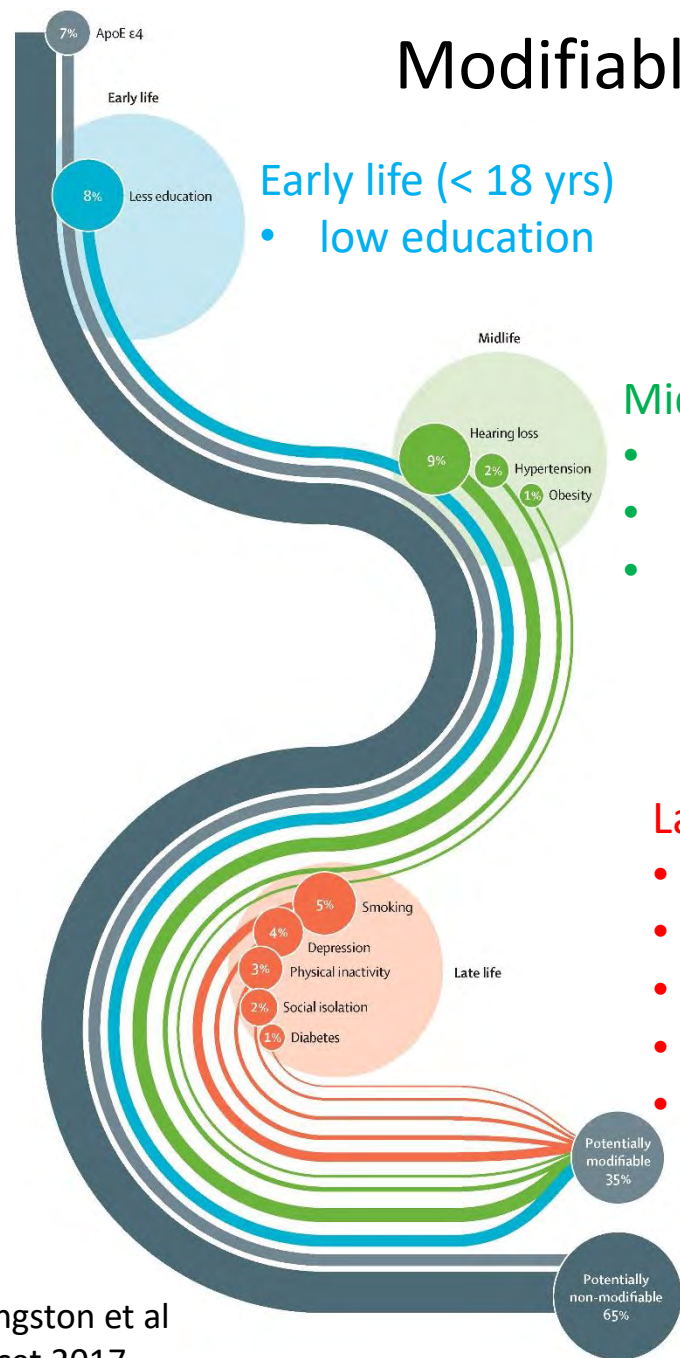


FDG PET scans



Next step: Phase 3 trial

Modifiable dementia risk factors



Early life (< 18 yrs)

- low education

Midlife (45-65 yrs)

- hypertension
- obesity
- hearing loss

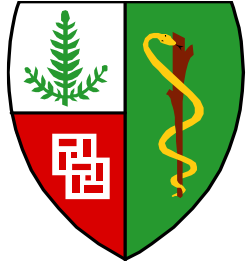
Later life (> 65 yrs)

- smoking
- depression
- physical inactivity
- social isolation
- diabetes

Exercise
Diet
Cognitive engagement / purpose
Sleep
Optimize medical conditions (HTN, DM)

- 'Western' diet
- Anti-cholinergic medications (Benadryl, Paxil, Elavil, Ditropan)

Iqbal Farrukh and Asad Jamal Alzheimer's Disease Research Center at Stanford



Progress in Alzheimer's prevention and treatment

- age-related neurodegenerative mechanisms
- imaging and large-scale blood biomarkers
- deep biology treatment approaches