Recent Advances in the Diagnosis and Treatment of Alzheimer's Disease

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Auguste D: Clinical Presentation

"What is your name?“

"Auguste.“

"Family name?“

"Auguste.“

"What is your husband's name?“
- she hesitates, finally answers:

"I believe ... Auguste.“

"How old are you?“

"Fifty-one.“

"Where do you live?“

"Oh, you have been to our place“

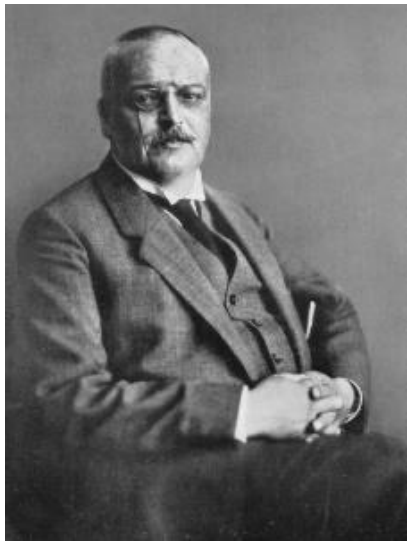
"Are you married?“

"Oh, I am so confused.“

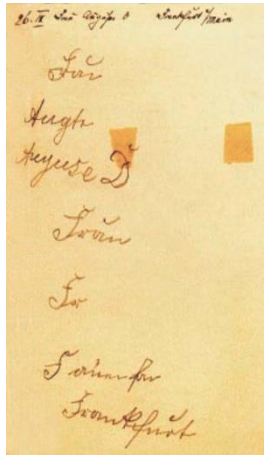
"Where are you right now?“

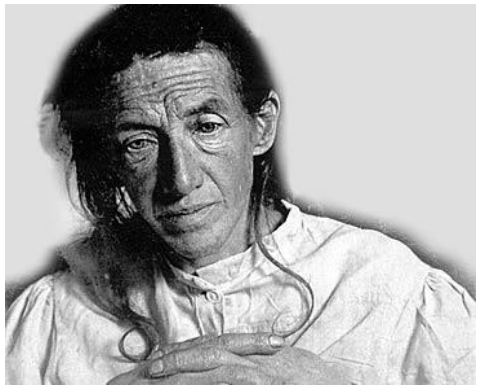
"Here and everywhere, here and now, you must not think badly of me.“

Memory impairment, getting lost,
can no longer do household chores,
language deficit, personality change,
hallucination, agitation, paranoia



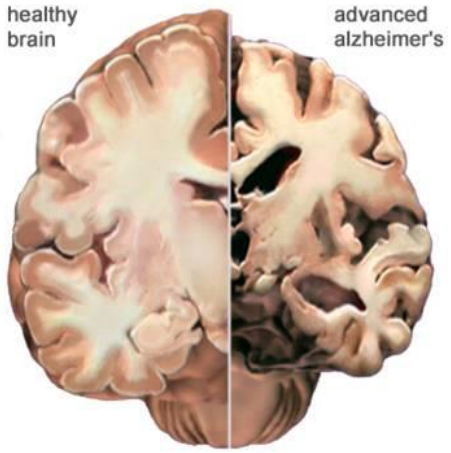
Alois Alzheimer (1864 – 1915)

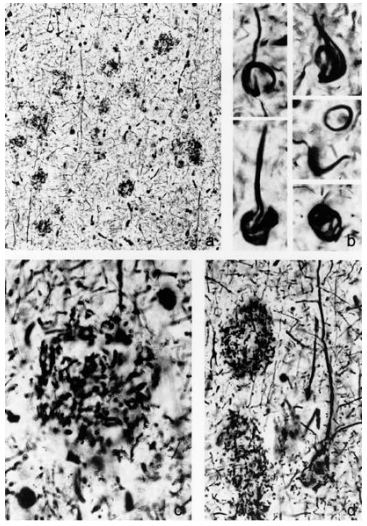


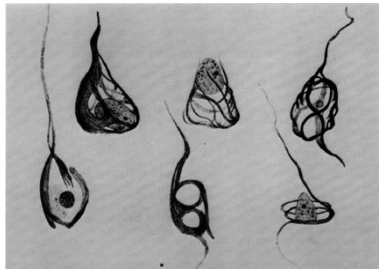


Auguste Deter (1850 - 1906)
Age at diagnosis 51 death at 56

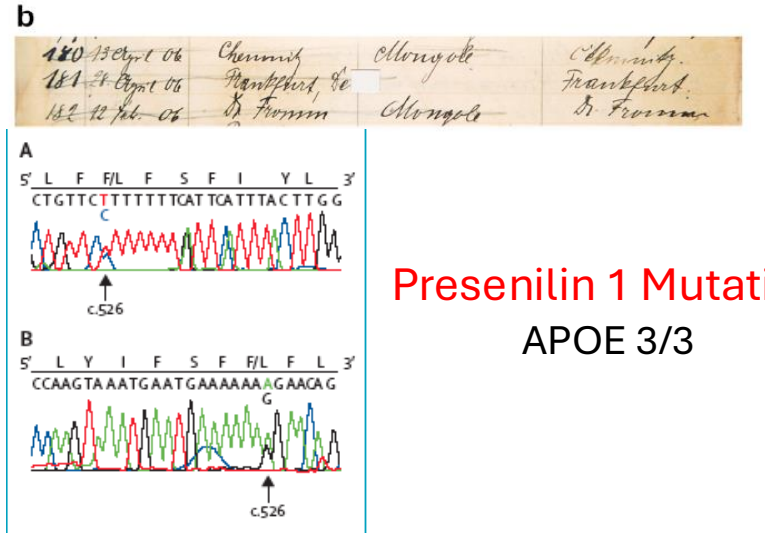
Auguste D: Neuropathology and Genetics







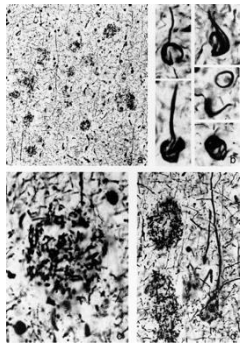
From Graeber et al., 1998, 2013



Presenilin 1 Mutation

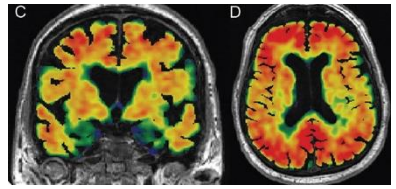
APOE 3/3

Alzheimer's Disease: From Clinical to Biological Definition



Clinical Syndrome
Autopsy/Neuropathology
No Treatment

In Vivo Biomarkers
(Amyloid/Tau PET, CSF, blood)
Disease-Modifying Treatments
Prevention Trials



1906

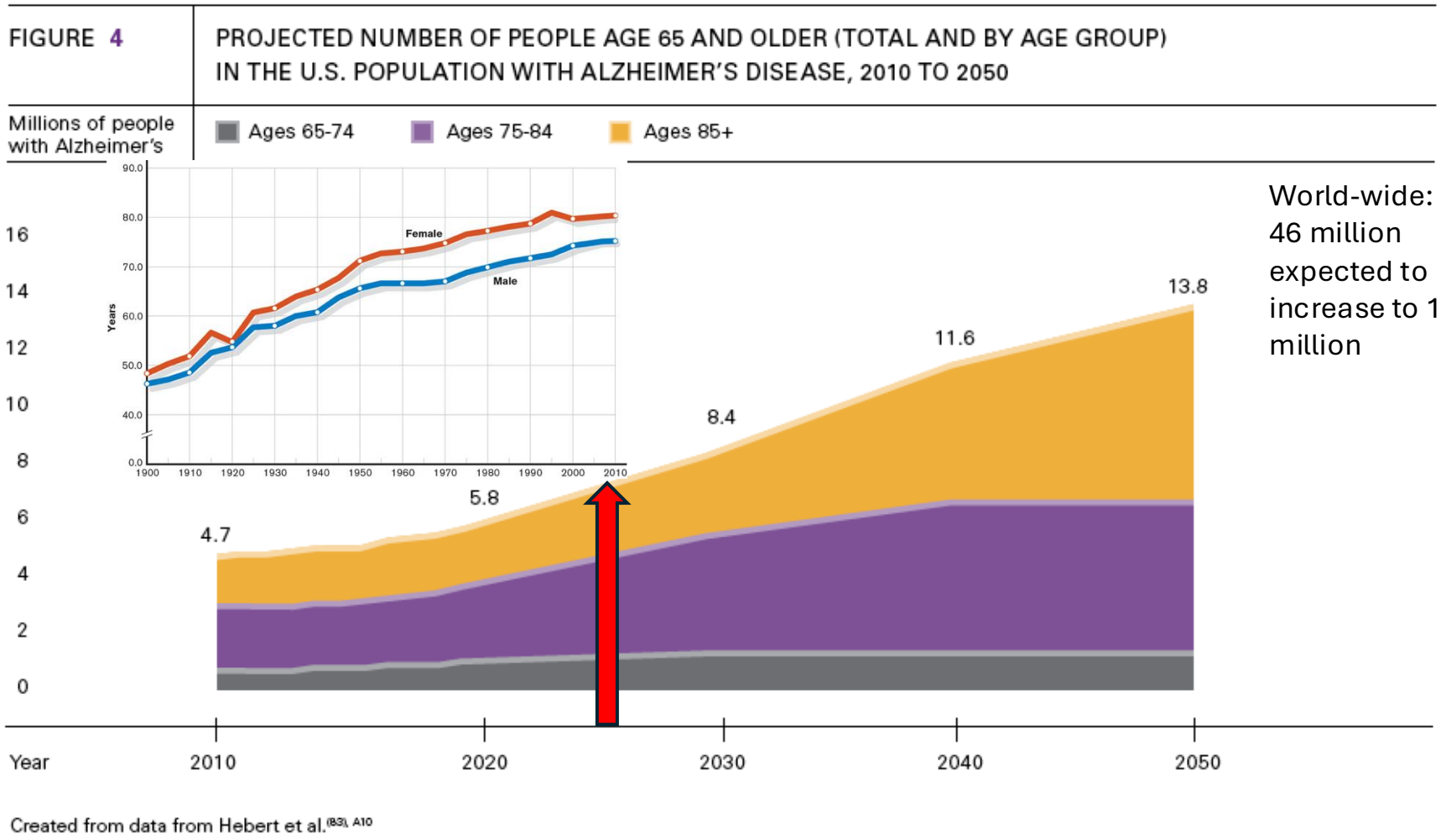
2026

1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

Dementia → **MCI** → **Preclinical**

Biological diagnosis of AD in biomarker positive individuals regardless of clinical stage/ symptoms

The Alzheimer's Epidemic



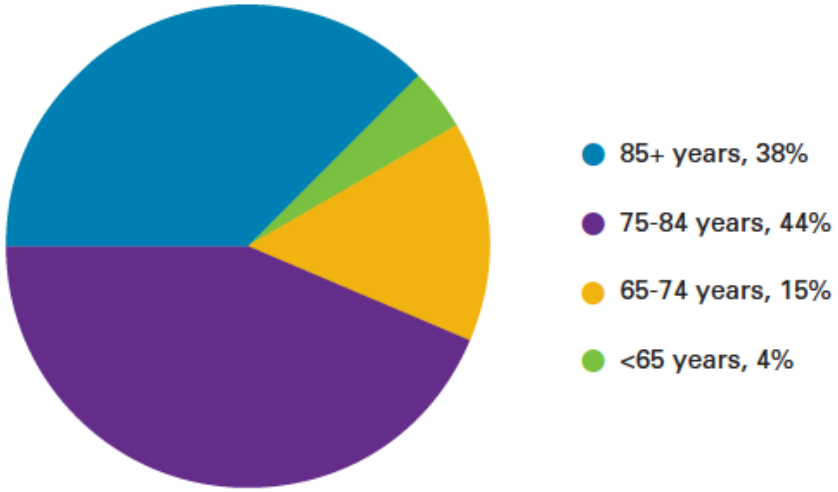
World-wide: 46 million expected to increase to 131 million

Source: 2013 Alzheimer's Disease Facts and Figures

alzheimer's association®

The Alzheimer's Epidemic

figure 1 | Proportion of People With Alzheimer's Disease in the United States by Age



Percentages may not total 100 because of rounding.
Created from data from Hebert et al.[114], A3

Source: 2014 Alzheimer's Disease Facts and Figures

alzheimer's association®

Alzheimer's Disease: Risk Factors

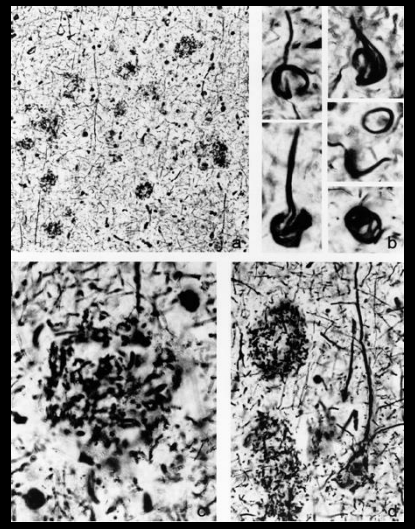
Non-Modifiable

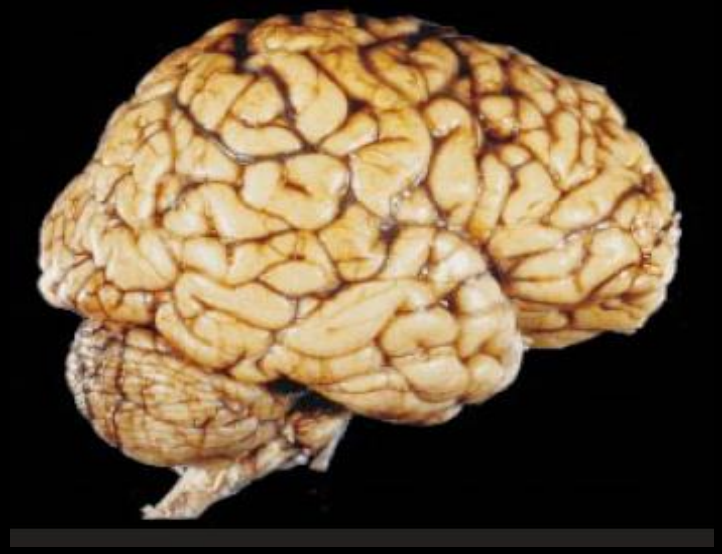
- Age
- Genetics: APOE4, Presenilin, APP

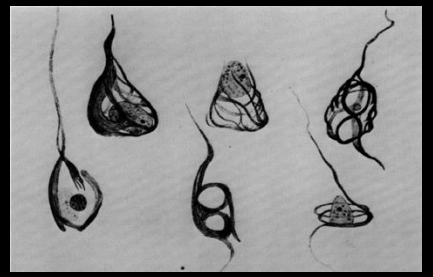
Modifiable

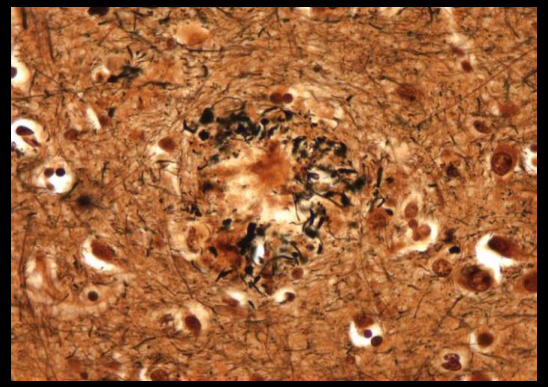
- Cardiovascular/Cerebrovascular Risk Factors
  - hypertension, diabetes, hyperlipidemia, obesity, smoking, physical inactivity
- Traumatic Brain Injury (TBI)
- Late-Life Depression
- Socioeconomic
  - low education
  - poverty
  - social isolation
  - healthcare access disparities

Alzheimer's Disease Neurobiology: A Tale of Two Proteins

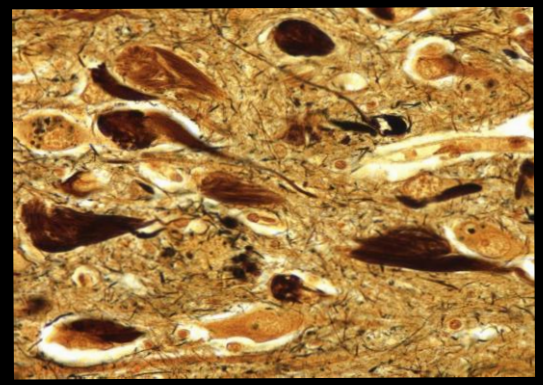






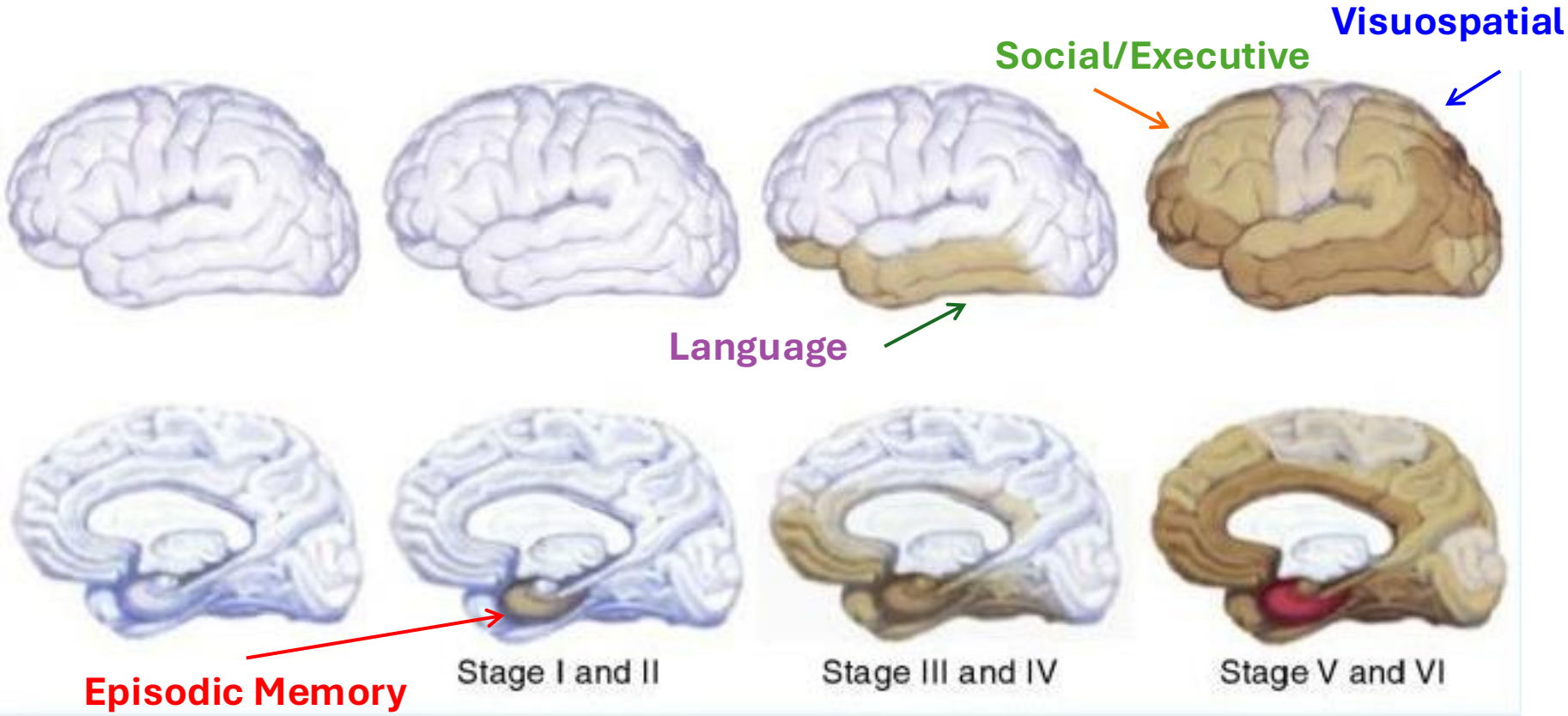


Aβ amyloid plaque
(cerebral amyloidosis)



Tau neurofibrillary tangles
(neurodegeneration)

Braak Stages: Neurofibrillary Tangles (NFTs)/Tau-Mediated Neurodegeneration



Location and Extent of NFT's Correlates with Clinical Symptoms/Severity

Preclinical → MCI → Dementia

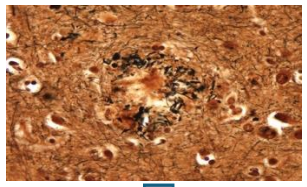
The Alzheimer's Disease Continuum

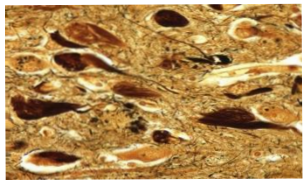
- Neuropsychological, biomarker, and autopsy data support the notion of an Alzheimer's Disease (AD) clinico-pathological continuum

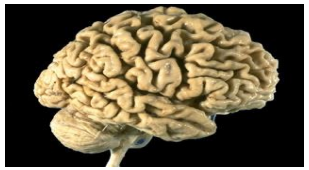
- AD continuum characterized by the transition from an asymptomatic/preclinical phase to a clinical phase (MCI and dementia)

- Biomarkers allow in vivo identification of AD pathology in cognitively normal individuals at risk for dementia, with important implications for early diagnosis, prognosis, and treatment

The Alzheimer's Disease Continuum/Amyloid Cascade







Clinical Diagnosis

Autopsy Confirmation

Preclinical
(10-20 years)

Clinical

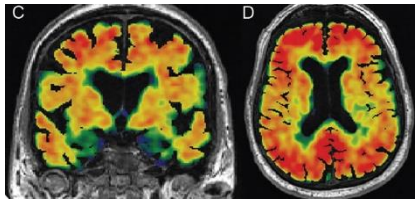
Amyloid Accumulation

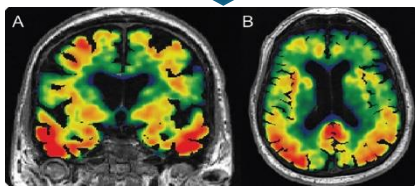
Tau Accumulation

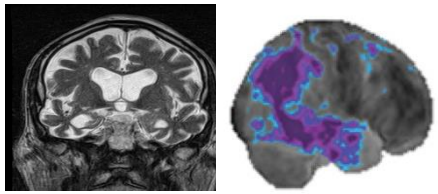
Neuronal Loss

Mild Cognitive Impairment (MCI)

Dementia







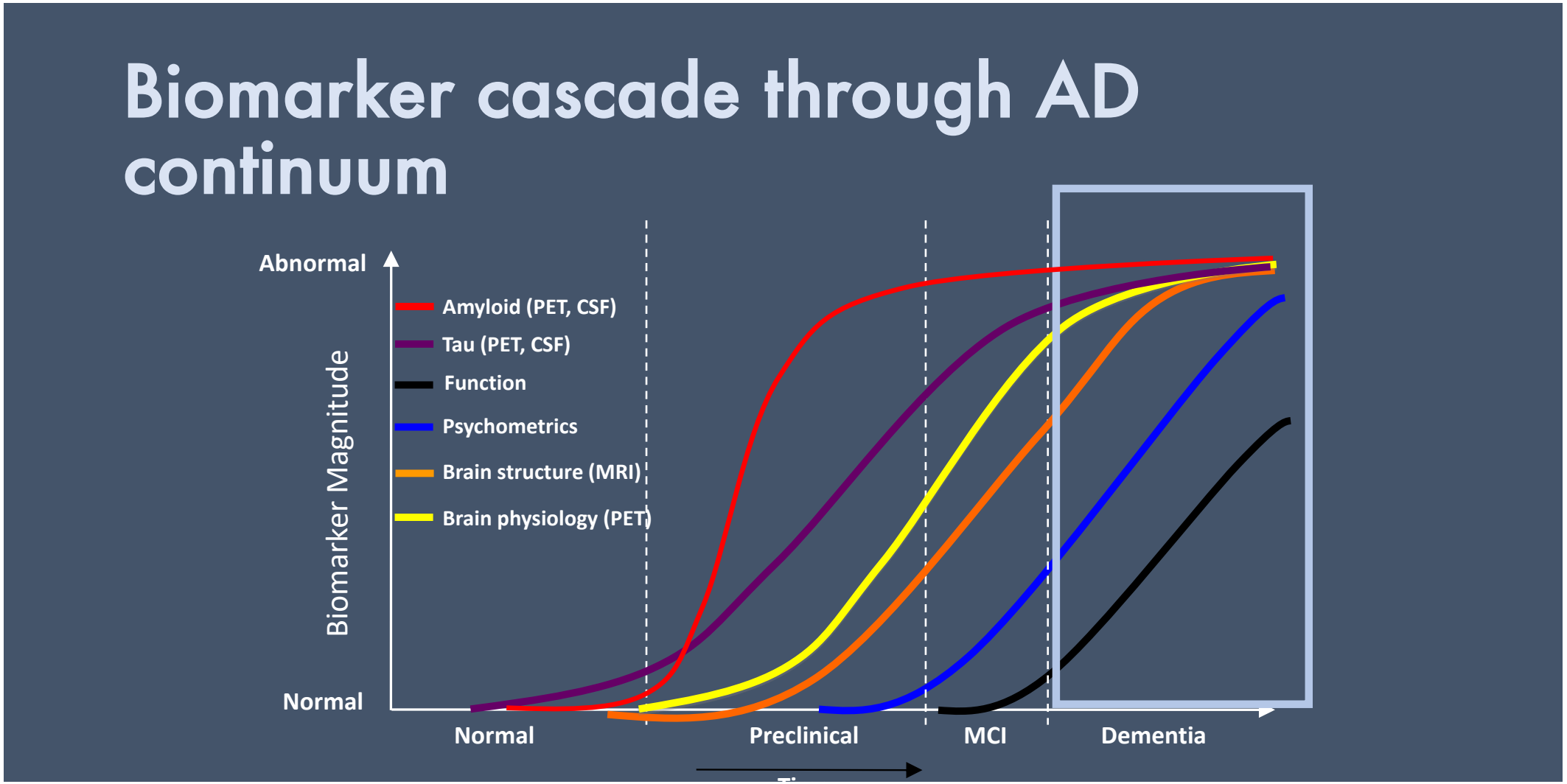
Biomarkers

Amyloid PET
CSF, Blood

Tau PET
CSF, Blood

MRI, FDG PET

Biomarkers Support Amyloid Cascade Hypothesis



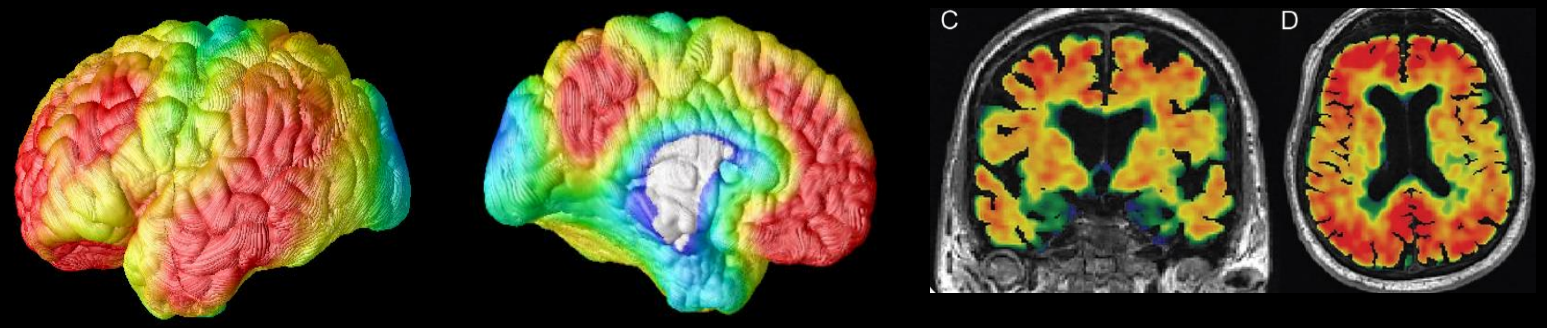
Modified from Jack CR Jr et al. *Lancet Neurol*. 2010;9:119

Penn University of Pennsylvania | Alzheimer's Disease Research Center

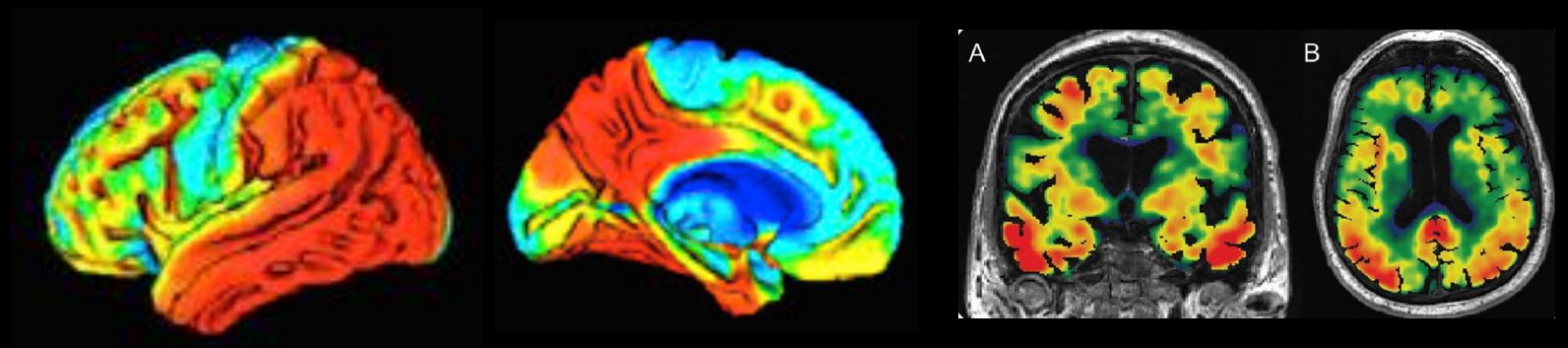
Wolk, 2023

PET Biomarkers of Amyloid and Tau Pathology in Alzheimer's Disease

Amyloid PET
Aβ Plaques



Tau PET
Neurofibrillary Tangles

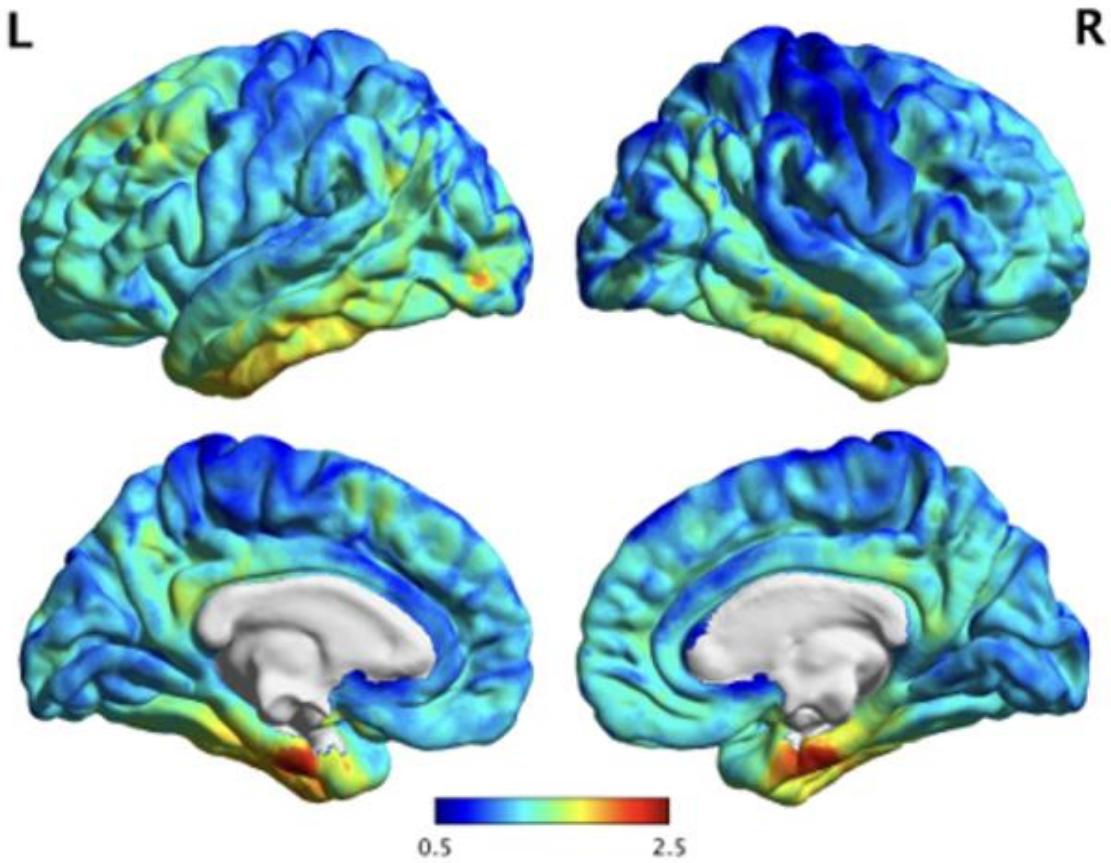


Reiman et al *PNAS* 2009; Scholl et al, *Neuron* 2016

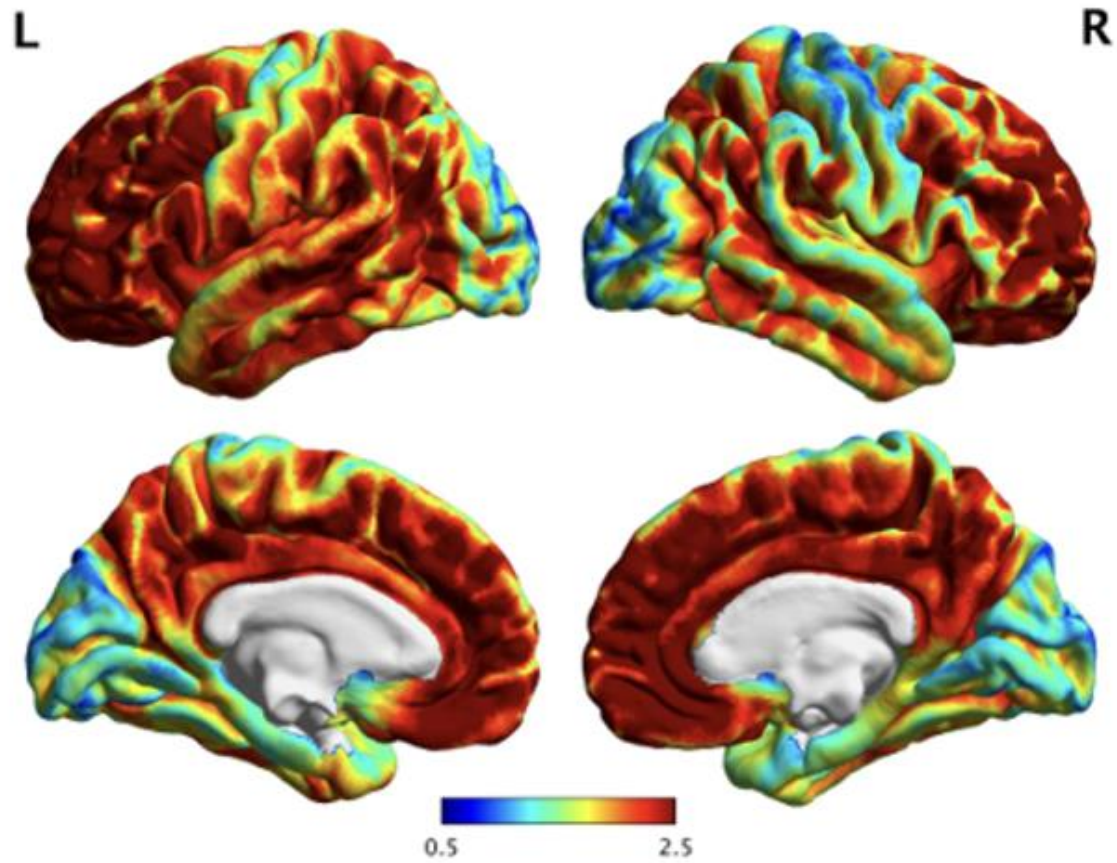
Jack et al., 2016

ADRC 700002

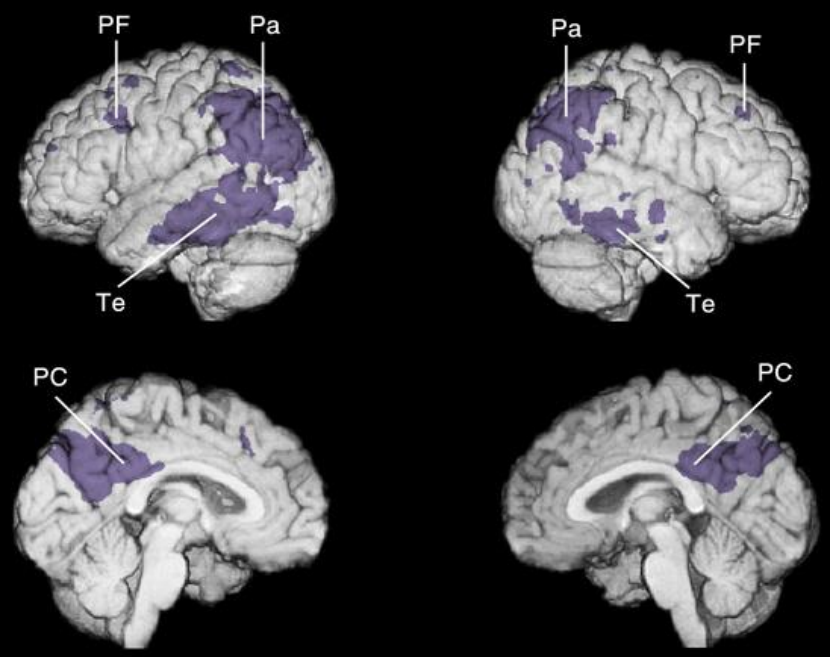
FTP



FBP

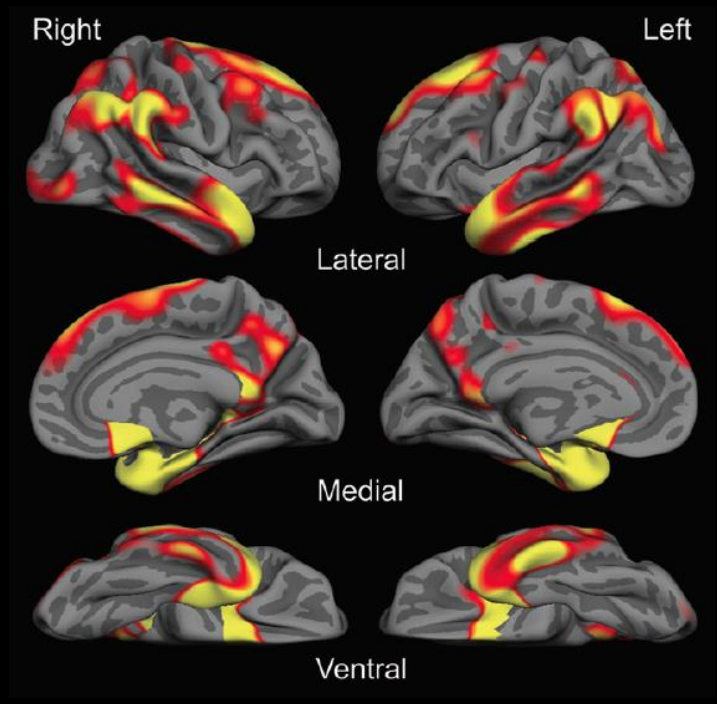


Imaging Biomarkers of Neurodegeneration in Alzheimer's Disease



From Reiman et al, New Engl J Med 1996

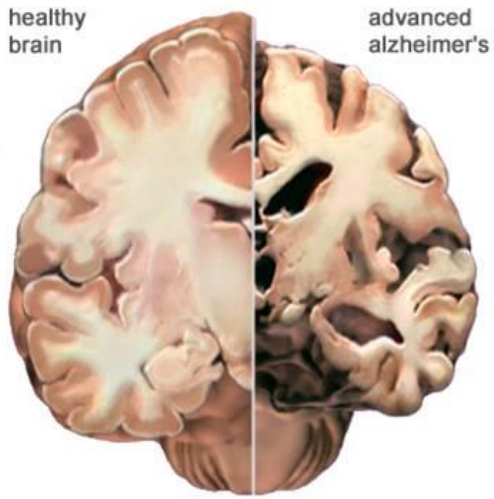
FDG PET Hypometabolism

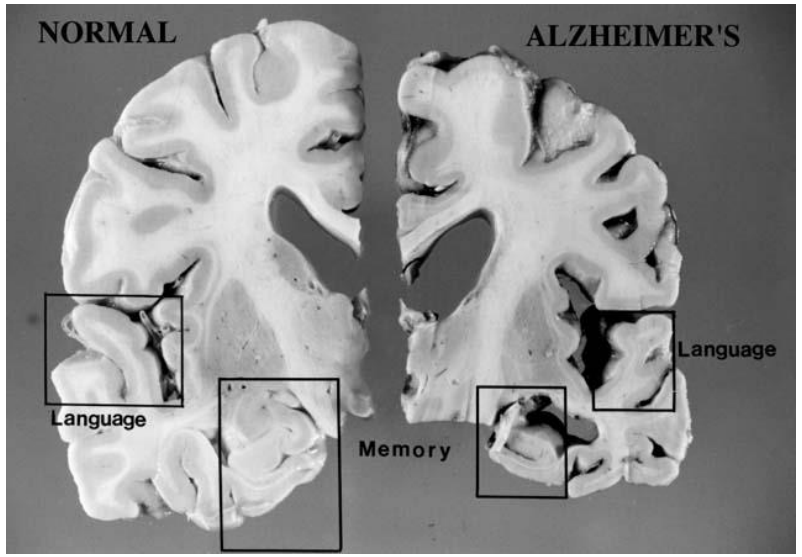


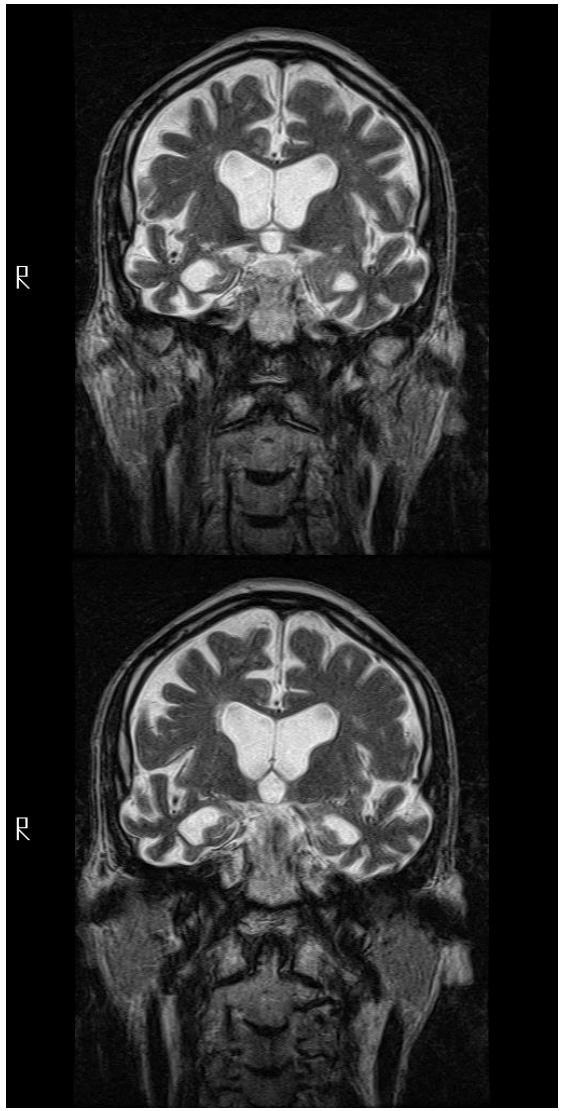
Dickerson et al., 2009

MRI Atrophy

MRI: Hippocampal Atrophy in Alzheimer's Disease







P-tau217 Blood Test: 90% Accurate in Predicting AD Pathology/Amyloid PET Status

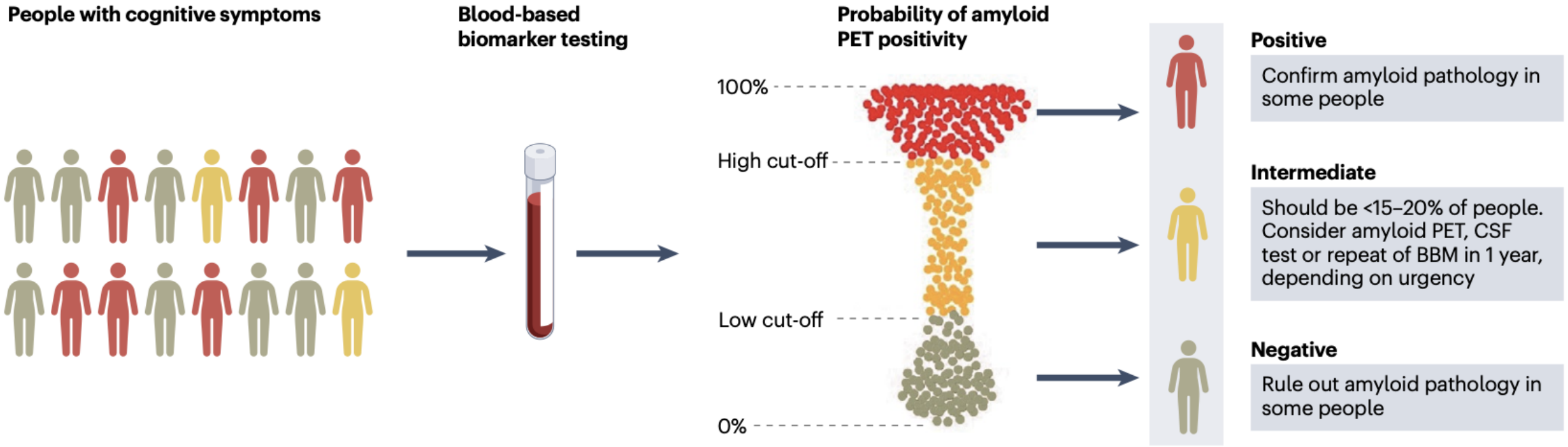
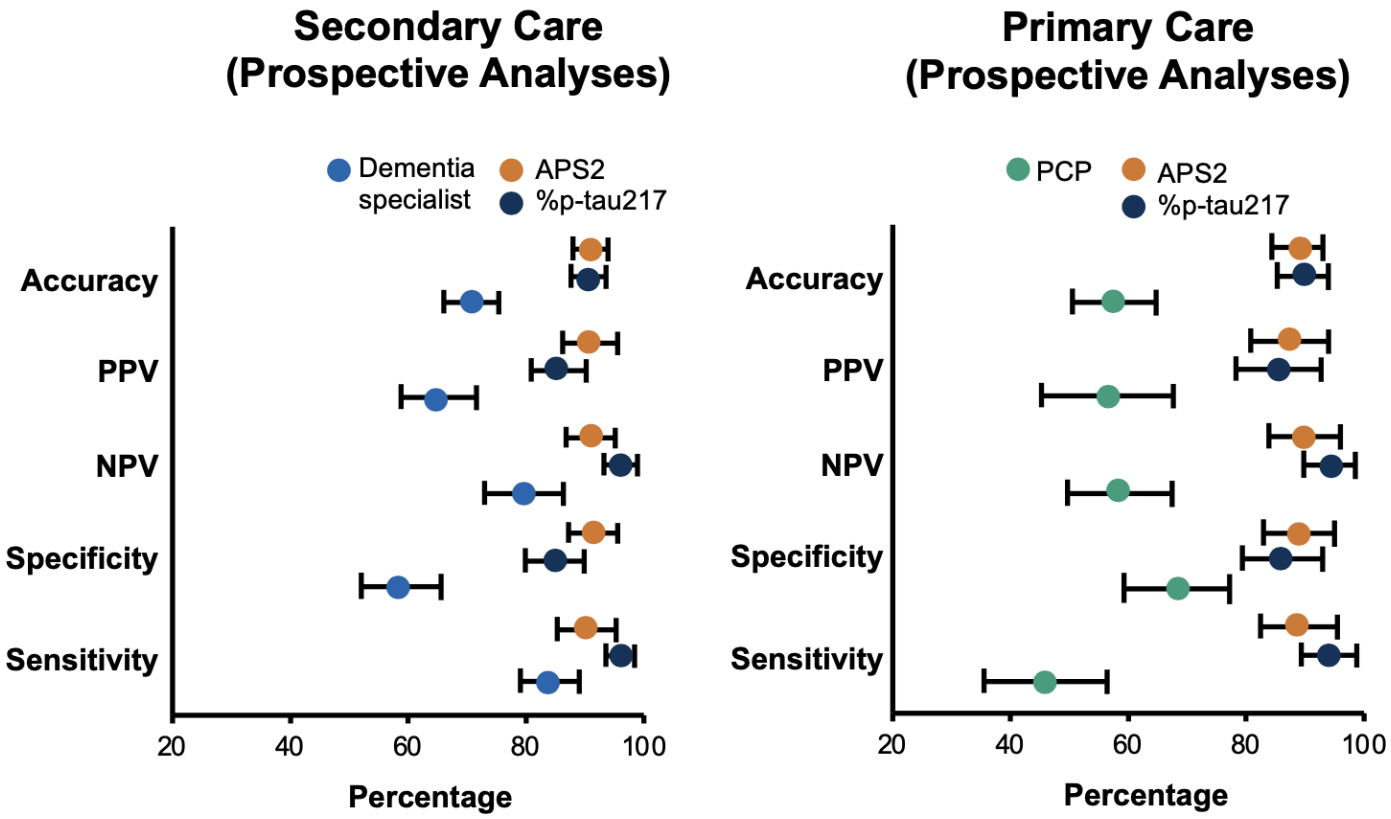


Fig. 2 | The two cut-off approach for blood biomarker tests of amyloid pathology. Use of two cut-off values for blood biomarker (BBM) testing in a group of people with cognitive symptoms leads to three categories of results: positive, intermediate and negative, increasing the accuracy with which people can be classified as having or not having amyloid pathology. Ideally, no more than 15–20% of individuals would be classified as having intermediate results. Interpretation of positive and negative results depends on the clinical suspicion of Alzheimer disease (Tables 3 and 4). CSF, cerebrospinal fluid. Adapted from ref. 78, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Schindler et al., 2024

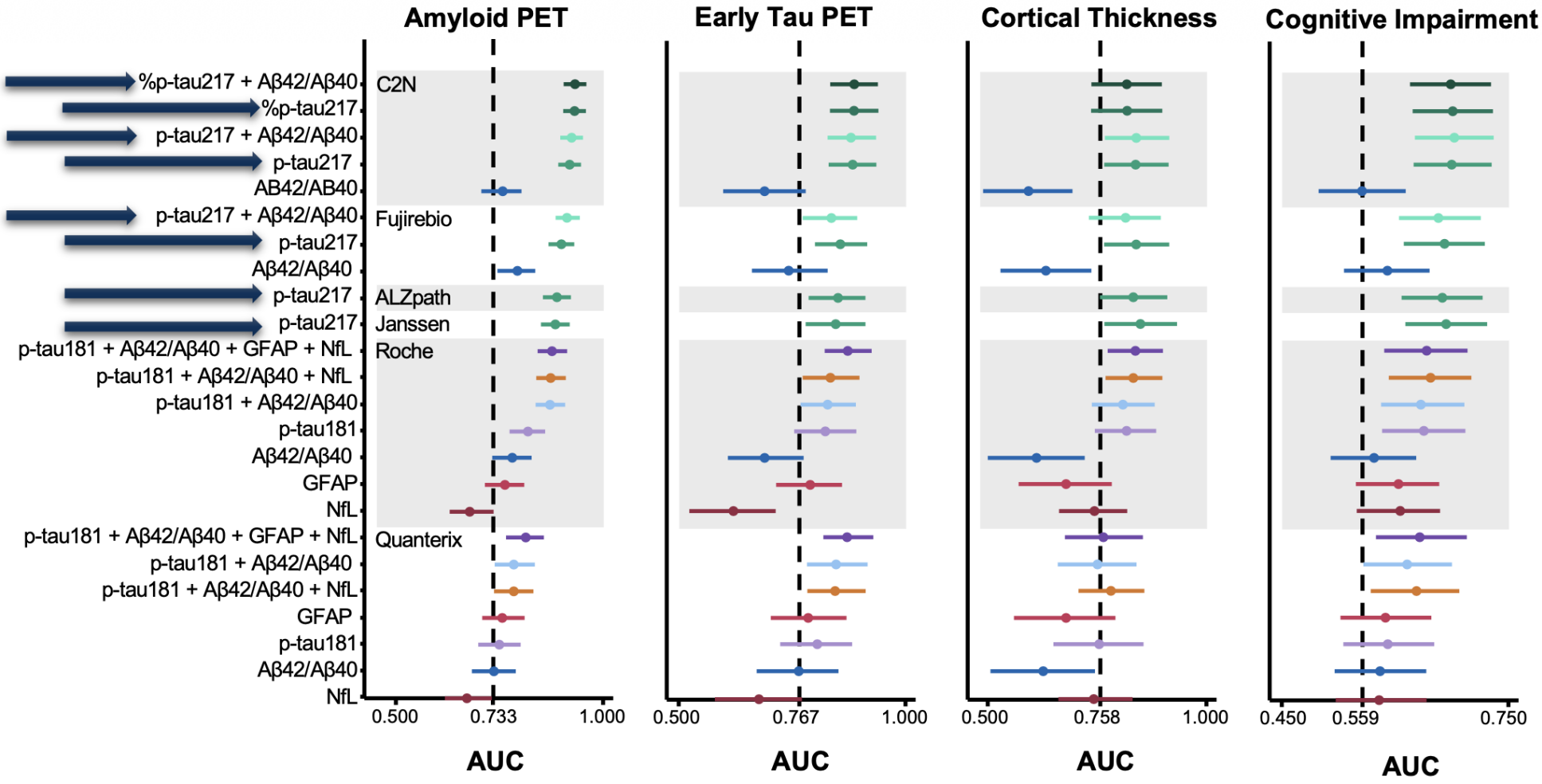
Plasma %P-Tau217 With and Without Aβ42/Aβ40 Is Highly Accurate[1]

- Plasma %p-tau217 combined with Aβ42/Aβ40 plasma ratio (APS2) improved diagnostic accuracy in both primary and secondary care
  - Clinical diagnosis is incorrect ~40% of the time in primary care and ~25% of the time in specialty care
  - Biomarker testing increased the diagnostic accuracy to >90% in both care settings



1. Palmqvist S et al. *JAMA*. 2024;332:1245-1257.

Plasma P-Tau217 Tests Are the Best Predictors of Biological and Clinical Markers of AD[1]



FNIH
Foundation for the National Institutes of Health

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

ADNI
Alzheimer's Disease Neuroimaging Initiative

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

1. Schindler SE et al. *Alzheimers Dement.* 2024;20:8074-8096.

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Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

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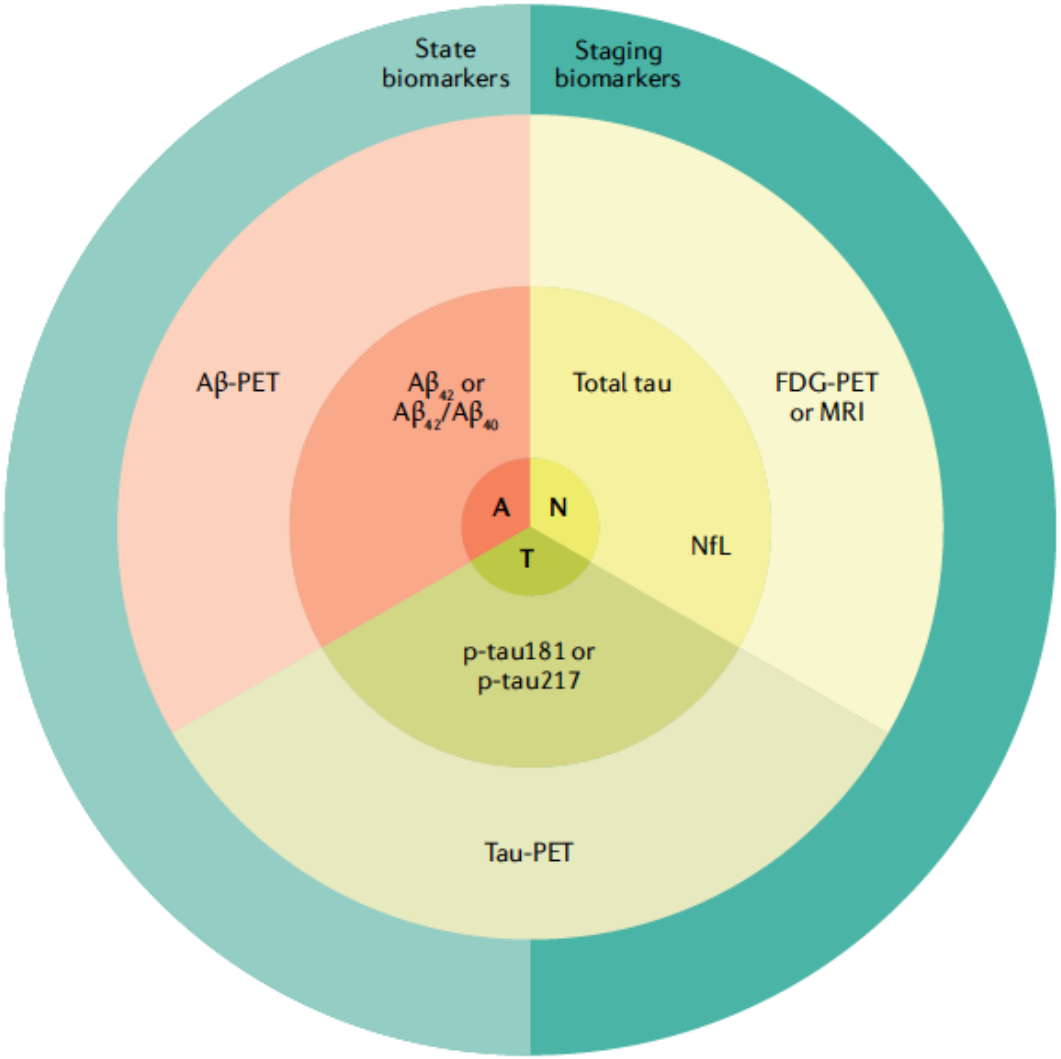
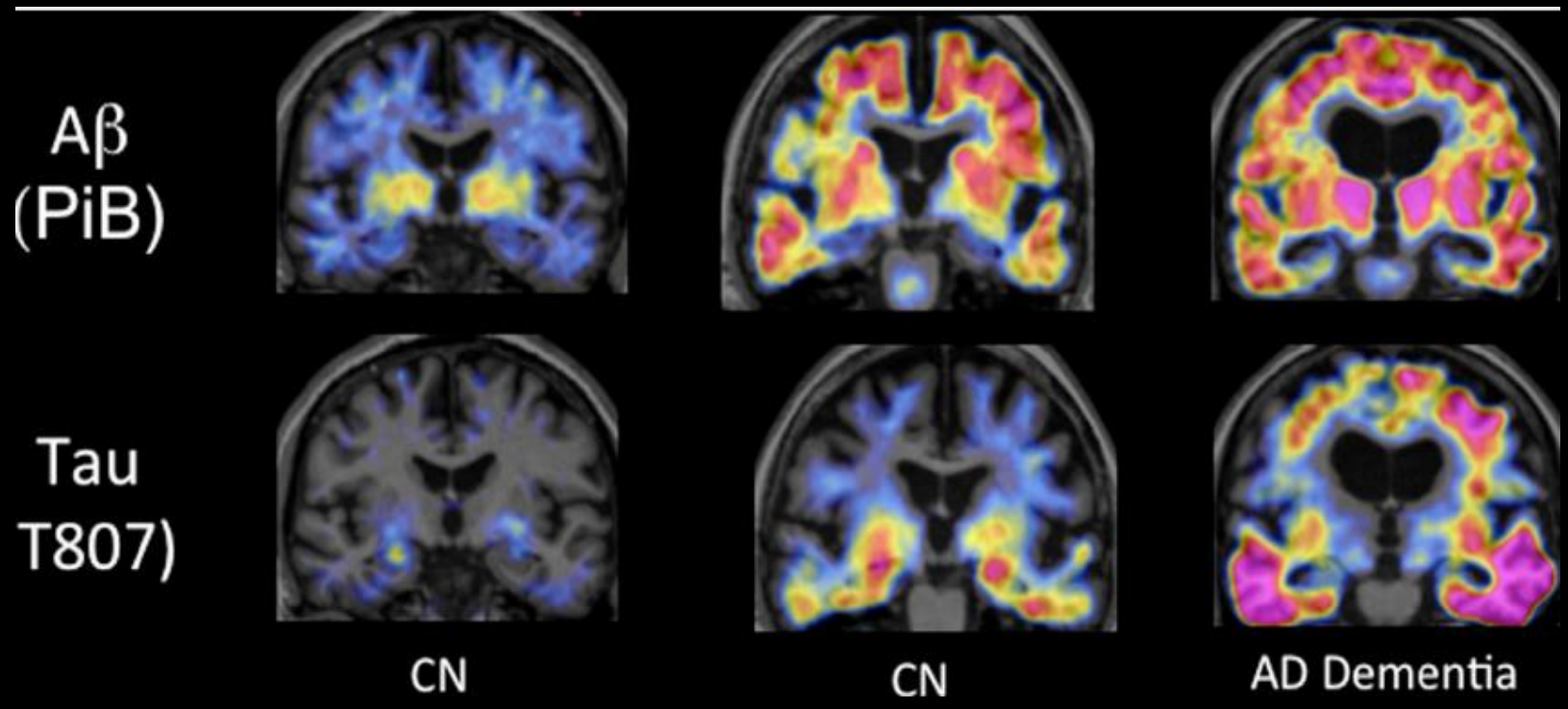
[e]*Office of Drug Evaluation, FDA, Silver Spring, MD, USA*

The ATN (Amyloid/Tau/Neurodegeneration) Framework



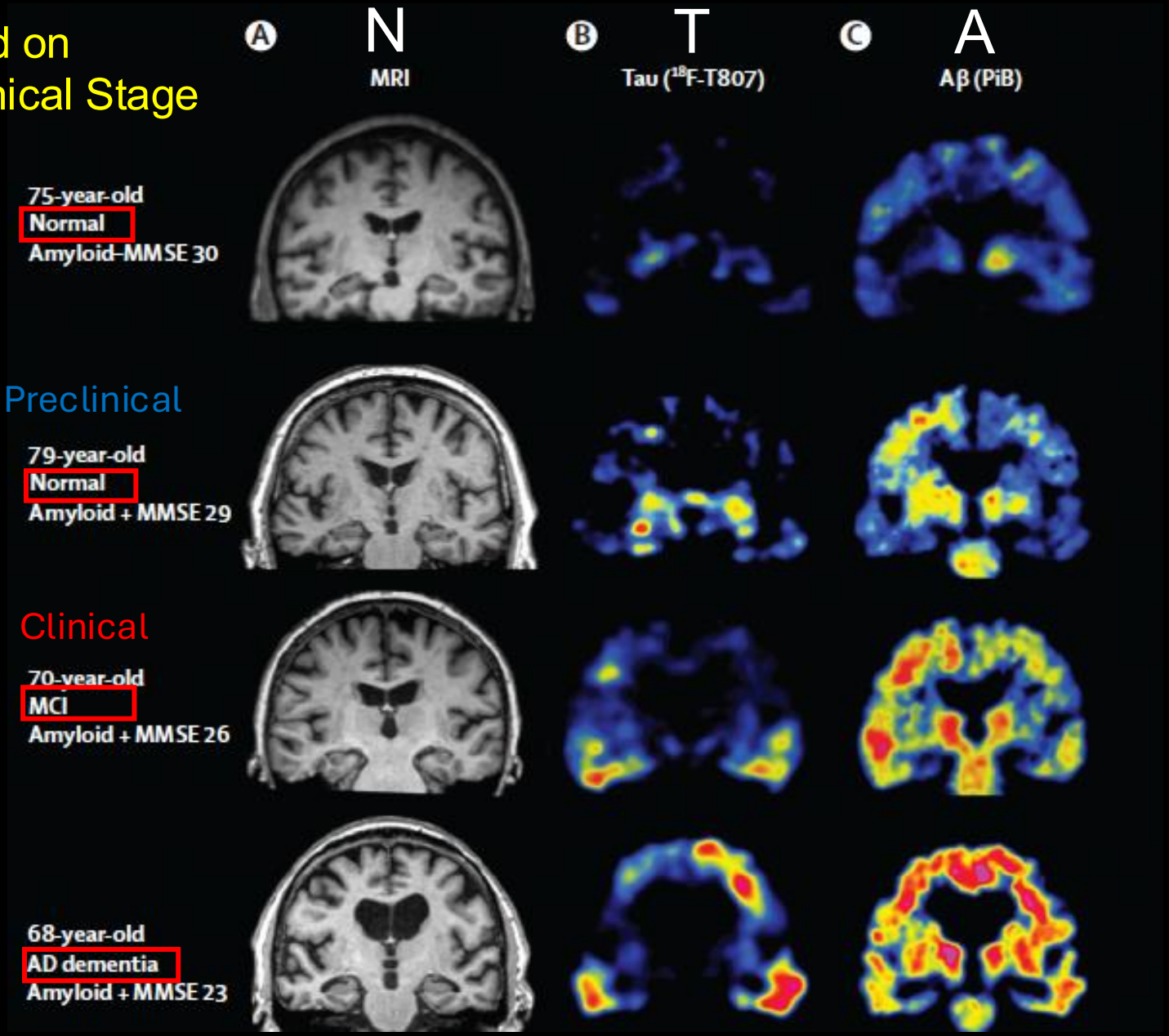
Knopman, 2021

	Preclinical	Clinical
Cognitively Normal Biomarker Negative	Cognitively Normal Biomarker Positive	Cognitively Impaired Biomarker Positive



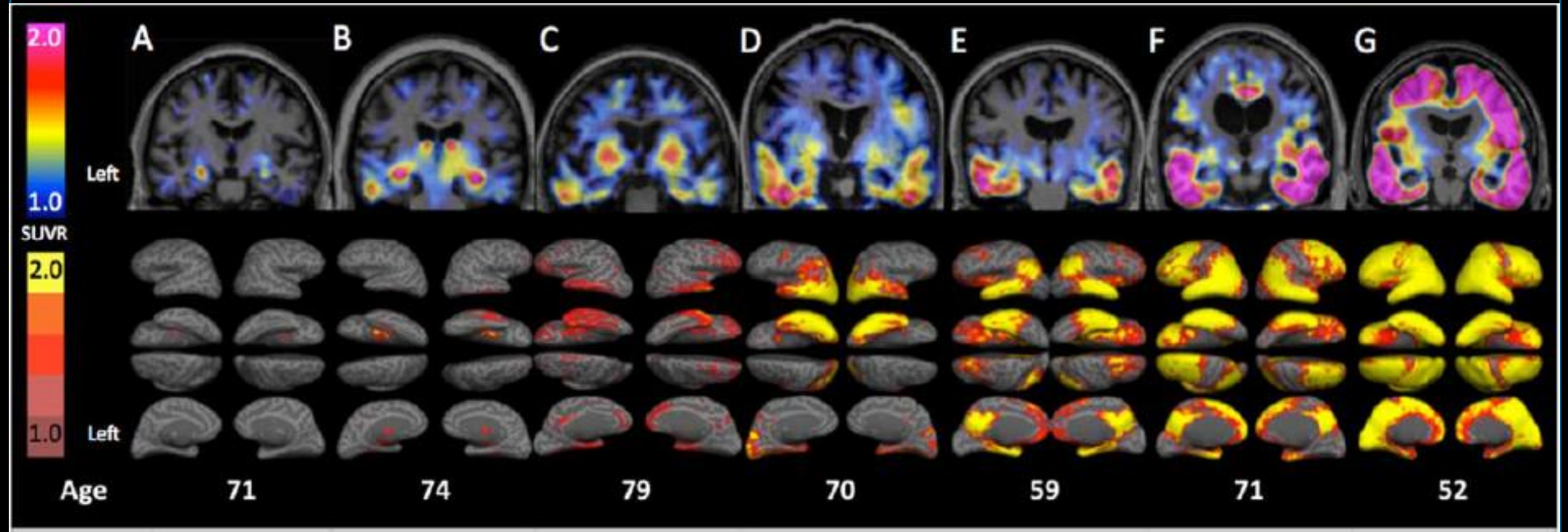
Modified from Sperling, 2014

Classification Based on Biomarker Status and Clinical Stage



Modified from Villemagne et al., 2015

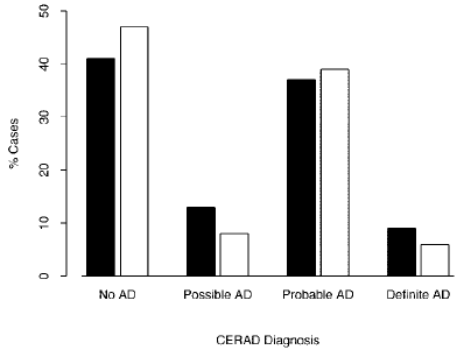
Tau PET Across the AD Continuum (Johnson et al., 2016)

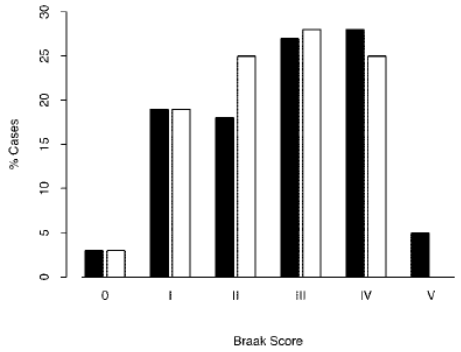


MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
PET Braak	0, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

Preclinical → Clinical

Preclinical AD: Neuropathology





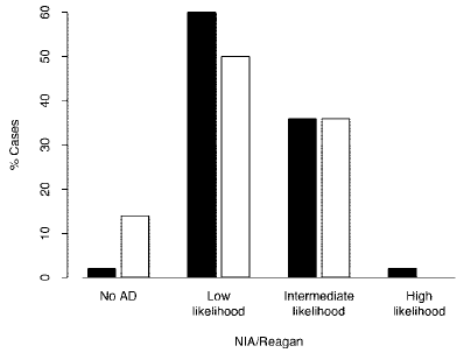
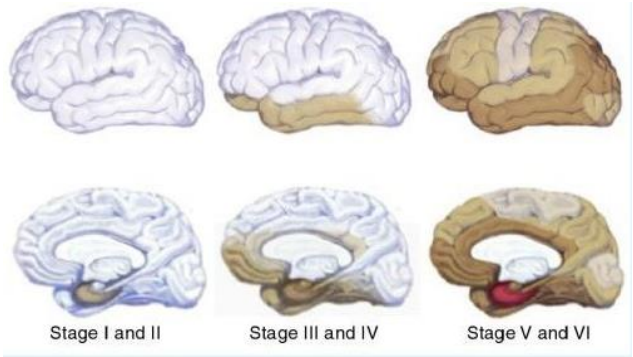


Table 2 *Selected pathologic characteristics of subjects without cognitive impairment in the Religious Orders Study (ROS) and the Memory and Aging Project (MAP)*

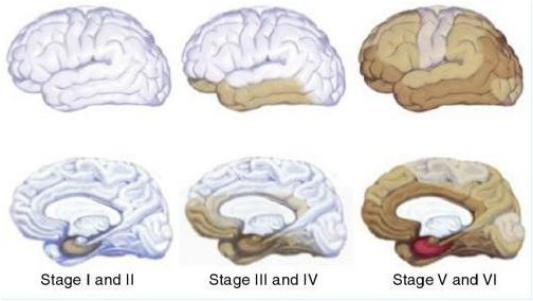
Pathologic characteristics	ROS	MAP
CERAD AD		
Not present	40 (40.8)	17 (47.2)
Possible	13 (13.3)	3 (8.3)
Probable	36 (36.7)	14 (38.9)
Definite	9 (9.2)	2 (5.6)
Braak Score		
0	3 (3.1)	1 (2.8)
I	19 (19.4)	7 (19.4)
II	18 (18.4)	9 (25.0)
III	26 (26.5)	10 (27.8)
IV	27 (27.6)	9 (25.0)
V	5 (5.1)	0
VI	0	0
NIA-Reagan AD		
Not present	2 (2.0)	5 (13.9)
Low likelihood	59 (60.2)	18 (50.0)
Intermediate likelihood	35 (35.7)	13 (36.1)
High likelihood	2 (2.0)	0
Infarcts		
Not present	75 (76.5)	30 (83.3)
Present	23 (23.5)	6 (14.7)
Lewy bodies		
Not present	84 (83.6)	32 (88.9)
Nigral	7 (7.1)	1 (2.8)
Limbic	5 (5.1)	2 (5.6)
Neocortical	2 (2.0)	1 (2.8)

Values are n (%).



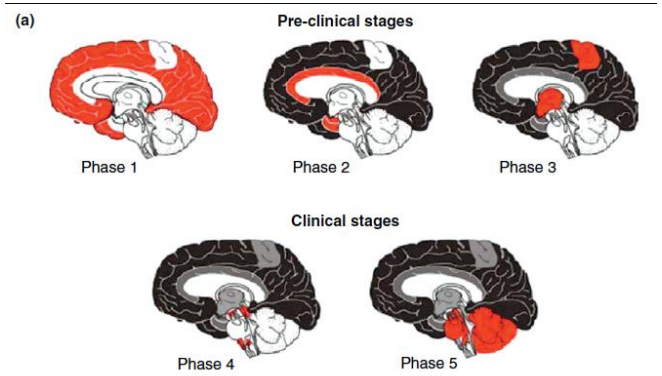
Bennett et al., 2013

NFT/Tau

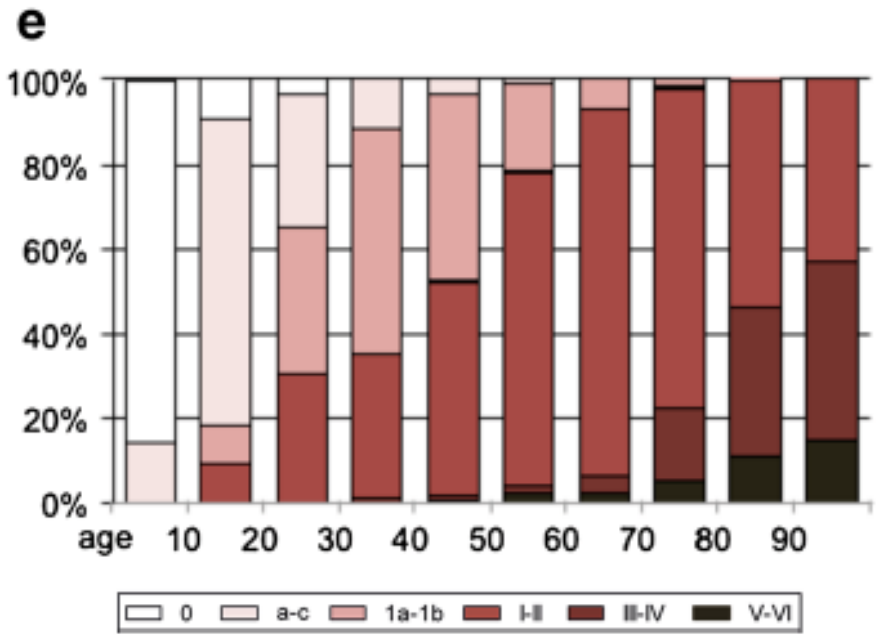


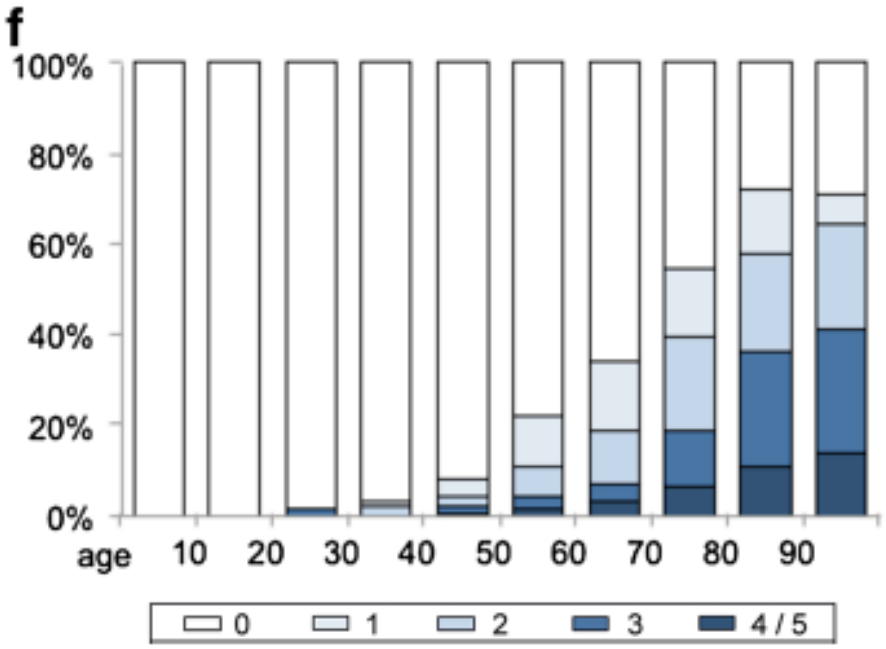
Braak Stage

Aβ/Amyloid



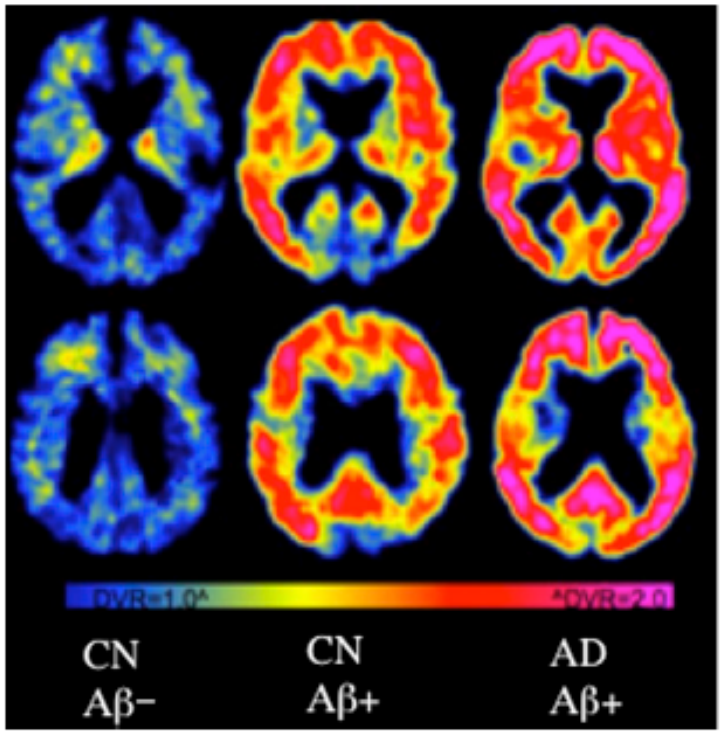
Thal Phase





Braak et al., 2014
(NC, n=2366, ages 1-100)

Amyloid PET Across the AD Continuum



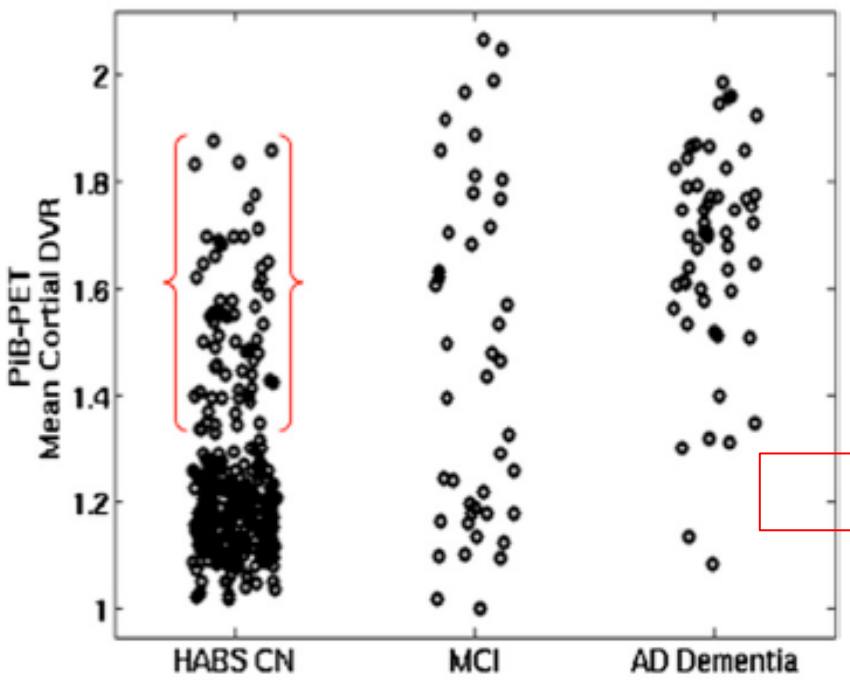
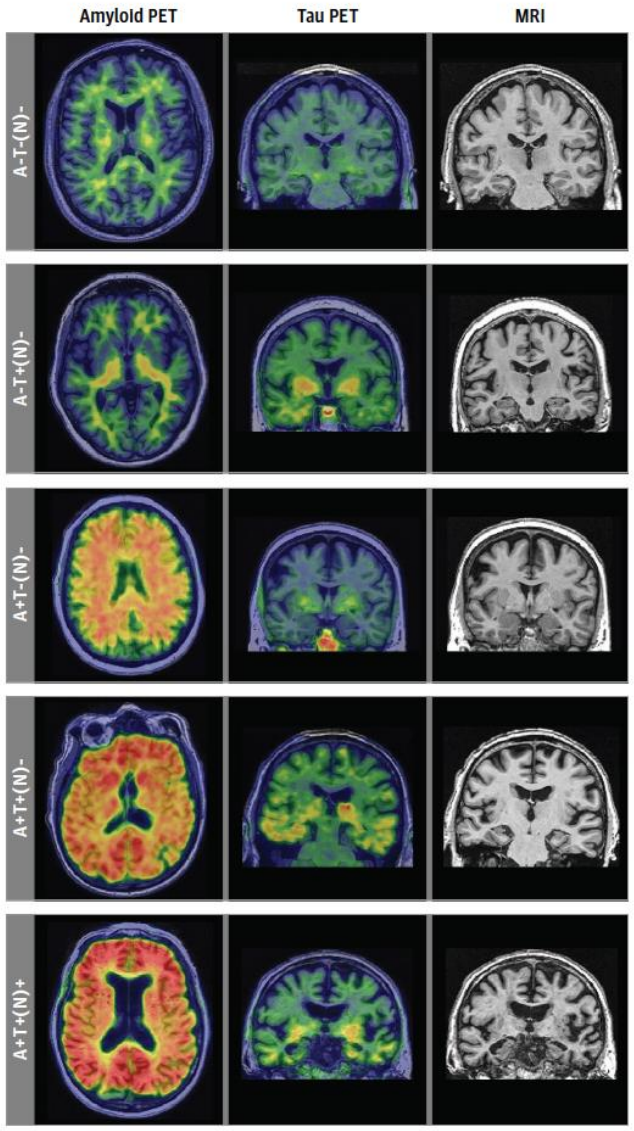


Figure 1. PET Amyloid Imaging with ^{11}C-PiB
Left: representative PET images from three older individuals; clinically normal older individual without evidence of elevated Aβ accumulation (CN Aβ−), clinically normal older individual with elevated Aβ accumulation (CN Aβ+), and patient with AD dementia with very elevated Aβ accumulation (AD Aβ+) in frontal and parietal heteromodal cortices.
Right: scattergram of PiB distribution value ratios (DVRs) by diagnostic group; Harvard Aging Brain Study clinically normal older individuals (HABS CN), mild cognitive impairment (MCI), and AD dementia. Approximately 30% of HABS CN demonstrate elevated Aβ accumulation in the range of MCI and AD dementia Aβ+.

Sperling, 2014

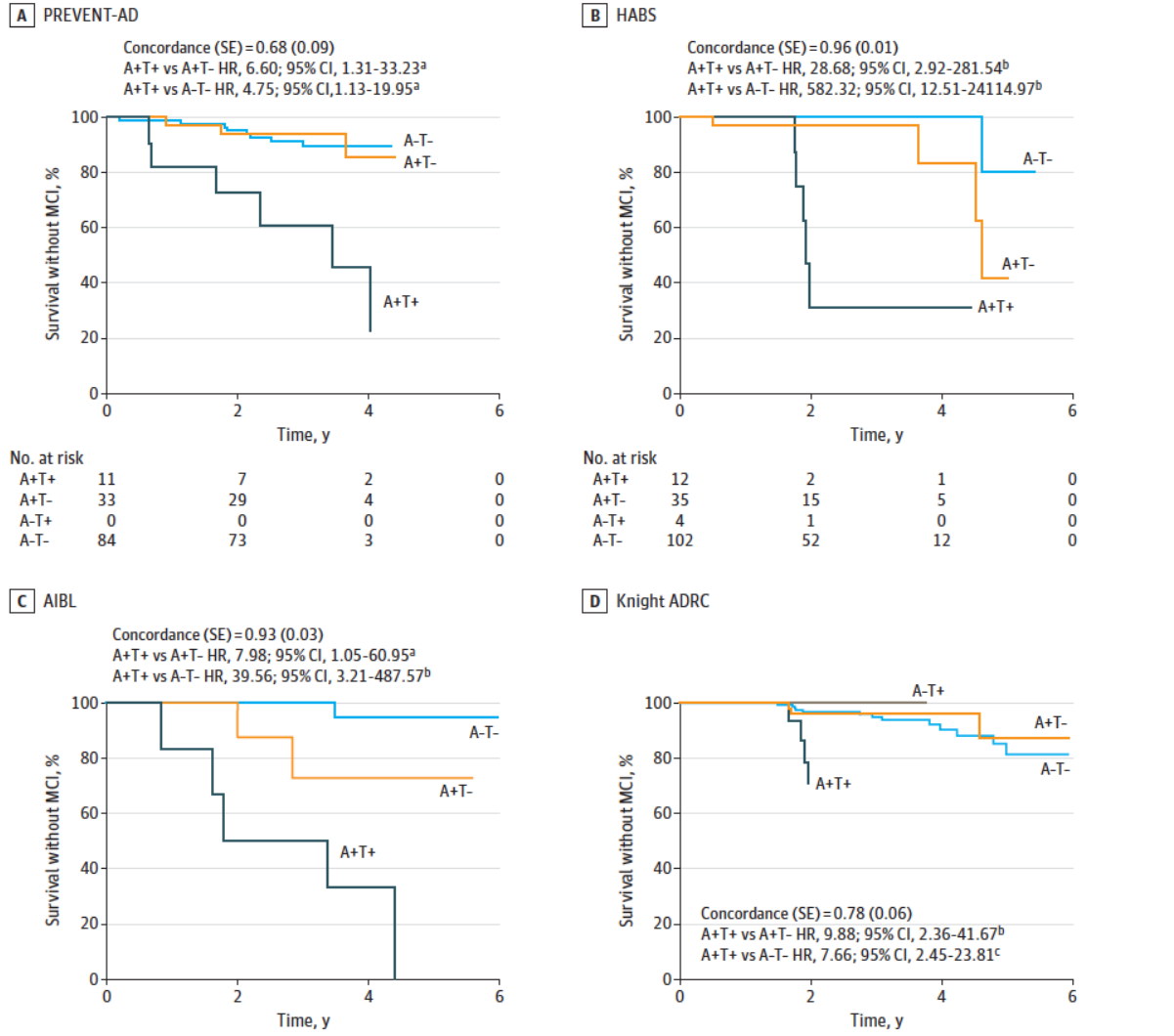
Biomarkers Predict Clinical Conversion in Cognitively Normal Individuals

Figure 1. Amyloid, Tau, and Neurodegeneration Biomarker (AT[N]) Examples



Jack et al., 2019

Figure 3. Survival Curves Reflecting Time From Positron Emission Tomography (PET) Scan to Mild Cognitive Impairment (MCI) Classification for the 4 Biomarker Groups, Across Cohorts



Strikwerda-Brown et al., 2022

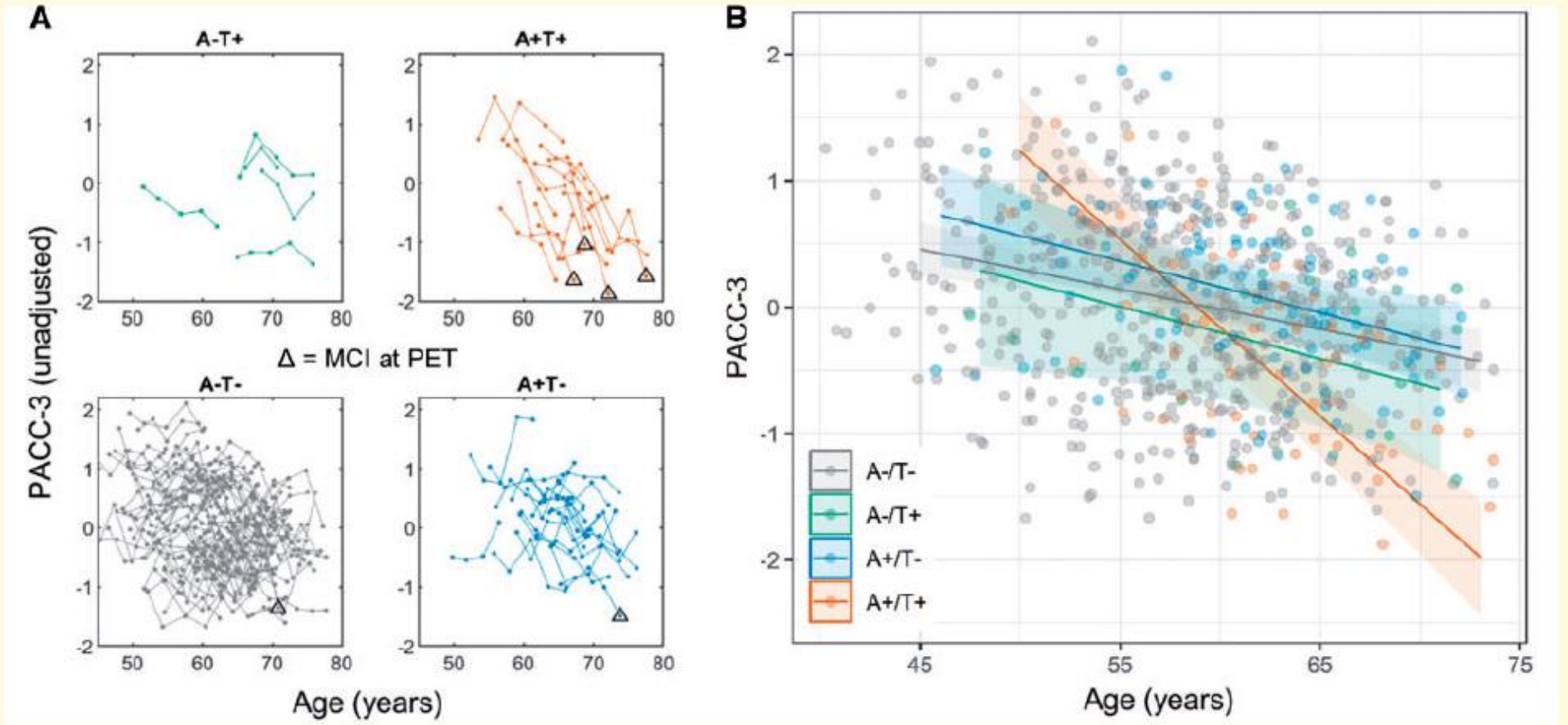


Figure 2 Observed and group-modelled cognitive performance by biomarker group. Observed longitudinal PACC-3 performance organized by biomarker groups (**A**). Triangles indicate individuals with mild cognitive impairment at their cognitive assessment most proximal to PET imaging. Individuals who had elevated global PiB DVR and entorhinal MK-6240 SUVR (*top right*) had more precipitous decline in scores over time several years prior to mild cognitive impairment diagnosis and prior to imaging. The difference in rates of cognitive decline between biomarker groups was characterized using linear mixed effects analysis (model outcomes given in Table 3). Panel **B** shows the group-level modelled PACC-3 simple slopes and confidence levels over the range of ages present in each group, with the individual observed PACC-3 performance displayed in the background (points). Results of the linear mixed effects model indicated a significant group × age interaction. Tukey-adjusted pairwise comparisons indicated that the A + T + group (orange in plots) declined approximately three times faster on average during the retrospective observation period compared to all other groups.

Betthauser et al., 2020

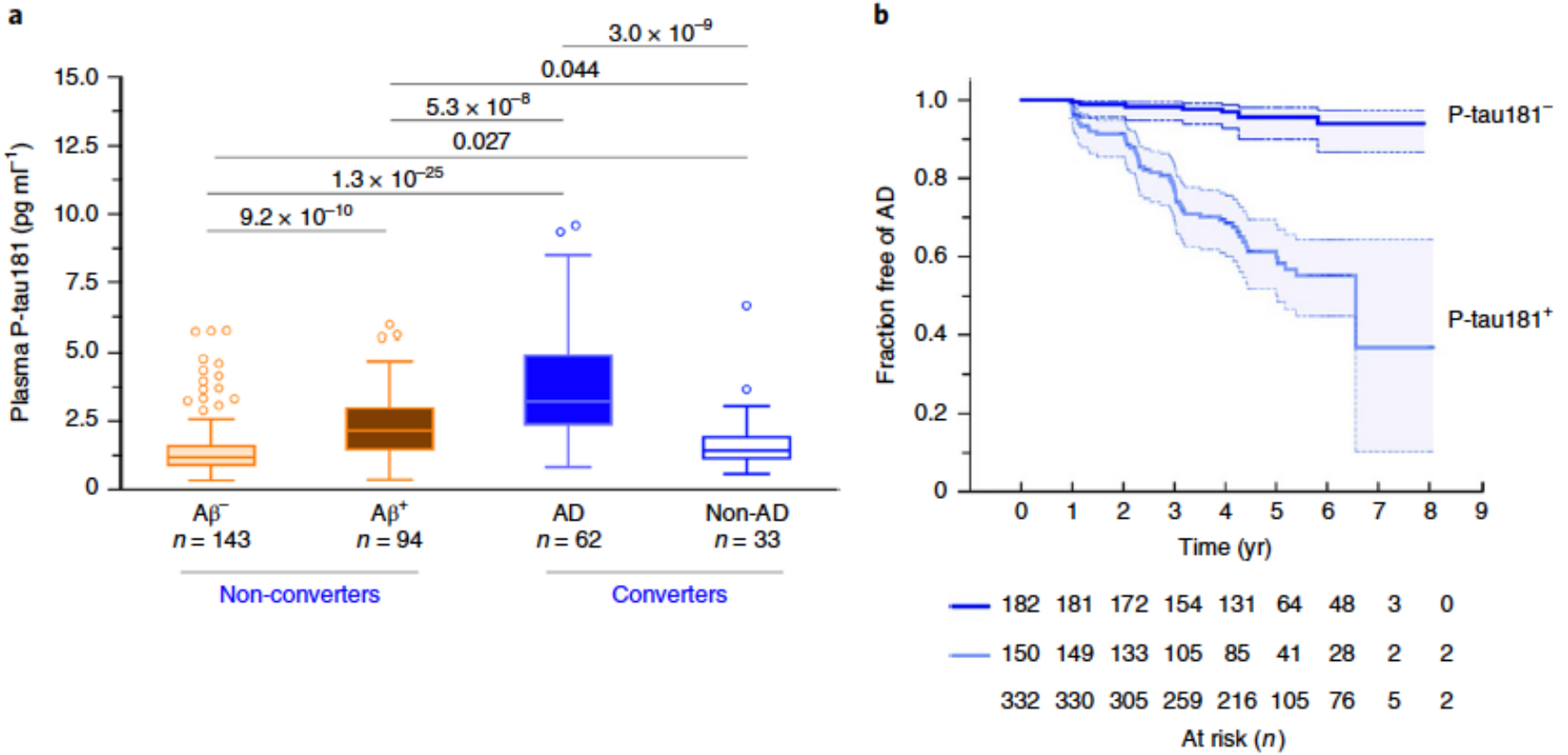
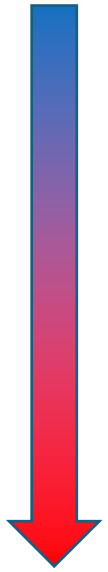


Fig. 3 | Plasma P-tau181 and progression to AD dementia. a, Plasma P-tau181 concentrations in Aβ⁺ and Aβ⁻ individuals who did not develop dementia, developed AD dementia or developed non-AD neurodegenerative disease during clinical follow-up. *P* values derived from univariate general linear models adjusted for age, sex and years of education (as described in Methods); individual measures are shown in Extended Data Fig. 3e; boxes show interquartile range, the horizontal lines are medians and the whiskers were plotted using the Tukey method. **b**, Survival curves for progression from cognitively unimpaired or MCI to AD dementia among participants with normal versus abnormal baseline plasma P-tau181 levels ($n=332$). Plasma P-tau181 data were binarized, using the Youden-based cutoff of 1.81 pg ml^{-1}, for differentiation of Aβ⁻ cognitively unimpaired who did not convert to AD dementia from those who progressed to AD dementia.

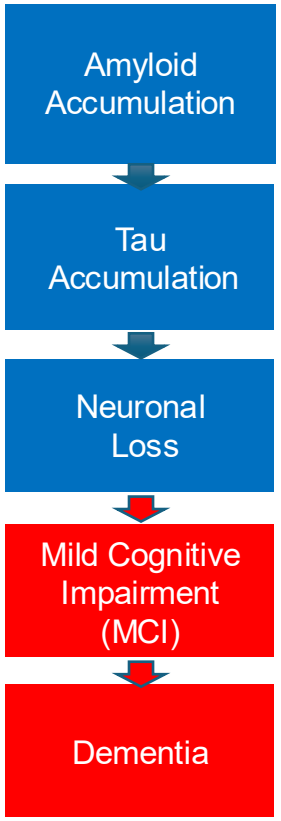
Janelidze, 2020

Alzheimer's Disease Treatment

Preclinical



Clinical



Disease Modifying
(Anti-Amyloid)

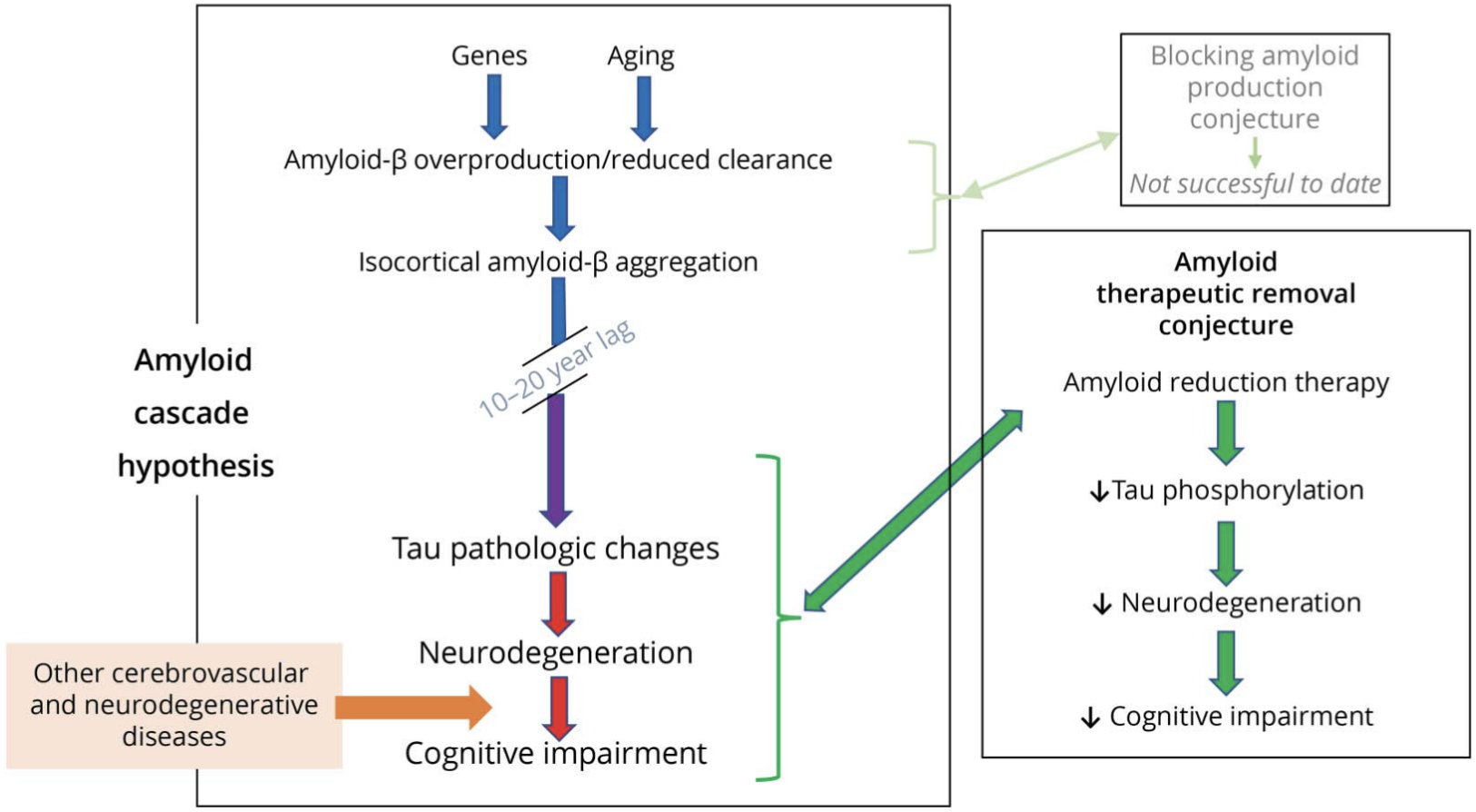
Symptomatic
(donepezil,
galantamine,
rivastigmine,
memantine)

Preclinical
Prevention
Delay Onset

MCI/Mild Dementia Stage
Slow Progression

Moderate/Severe Dementia Stage
Slow Progression

Figure 1 Amyloid Cascade Hypothesis of Alzheimer Disease Pathogenesis and Its Related Therapeutic Conjectures

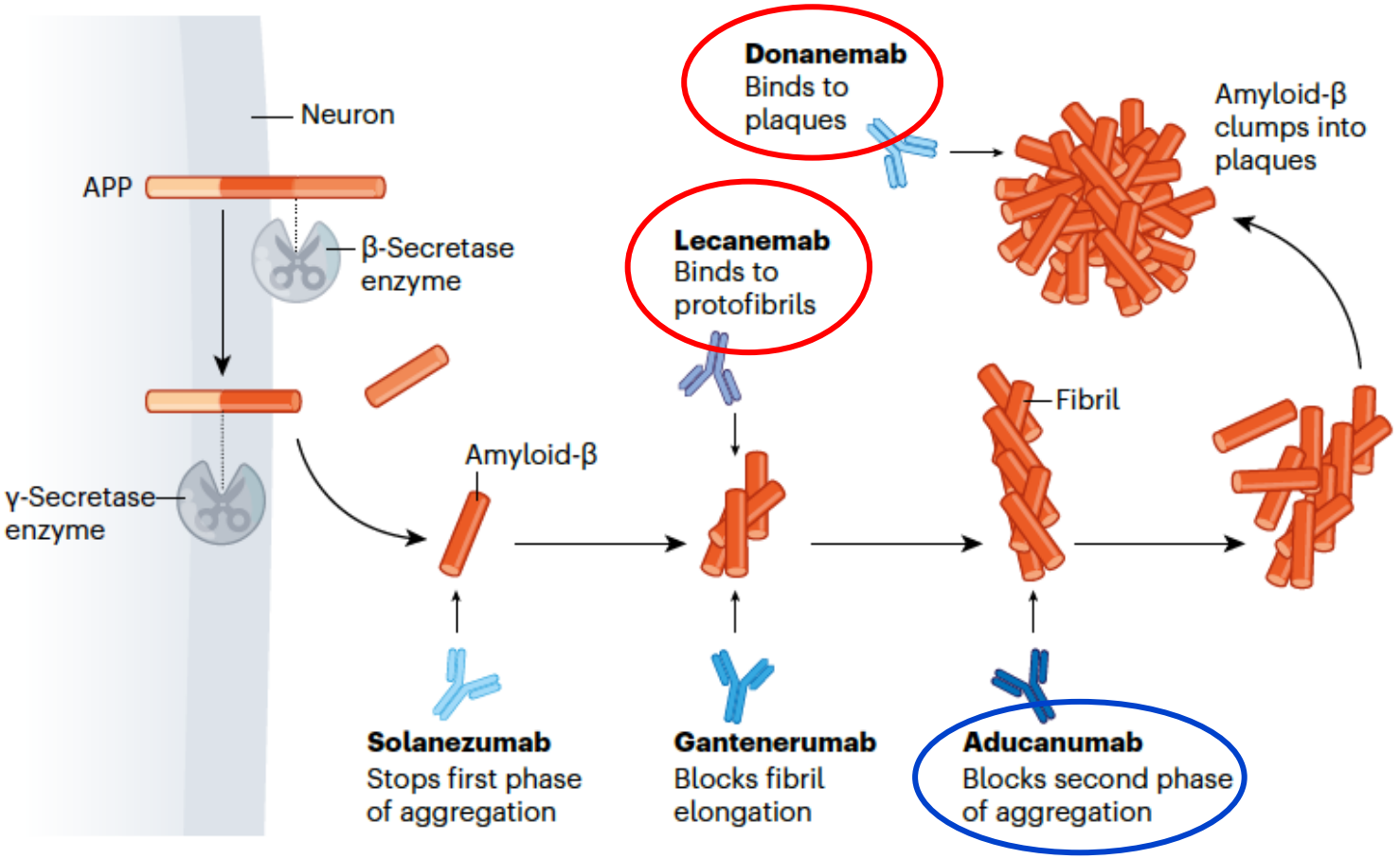


The model posits that elevations of aggregated amyloid-β peptide occur asymptomatically and induce downstream consequences including tauopathy and other neurodegenerative changes, eventually culminating in cognitive impairment. Blue arrows indicate clinically covert pathologic changes, the purple arrow indicates pathologic changes with early symptomatic consequences, and the red arrows indicate changes with overt clinical consequences. Green arrows indicate therapeutic intervention and hypothesized alterations in downstream pathologic and clinical consequences. The orange arrow indicates the influence of other cerebrovascular and non-Alzheimer neurodegenerative pathologic processes that modify the clinical expression of Alzheimer pathology.

Knopman, 2023

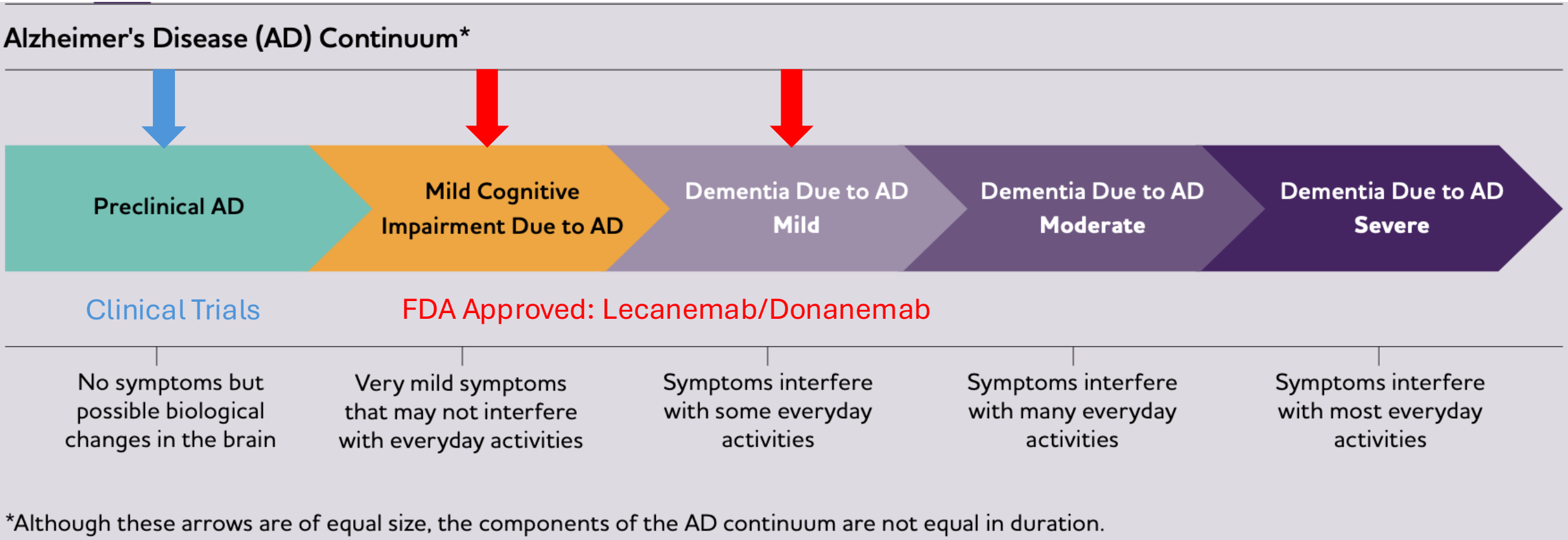
ANTIBODIES AGAINST AMYLOID

Several clinical trials are testing whether drugs called monoclonal antibodies can stem the symptoms of Alzheimer's by preventing the toxic clumping of amyloid-β proteins. This process starts when enzymes cleave the amyloid precursor protein (APP). Amyloid-β proteins elongate into fibrils and then nucleate into plaques. All of the drugs bind to amyloid-β, but their primary targets in the process are different.



Abbott, 2022

Approval of Disease-Modifying (anti-amyloid) Treatments Based on Clinical Stage



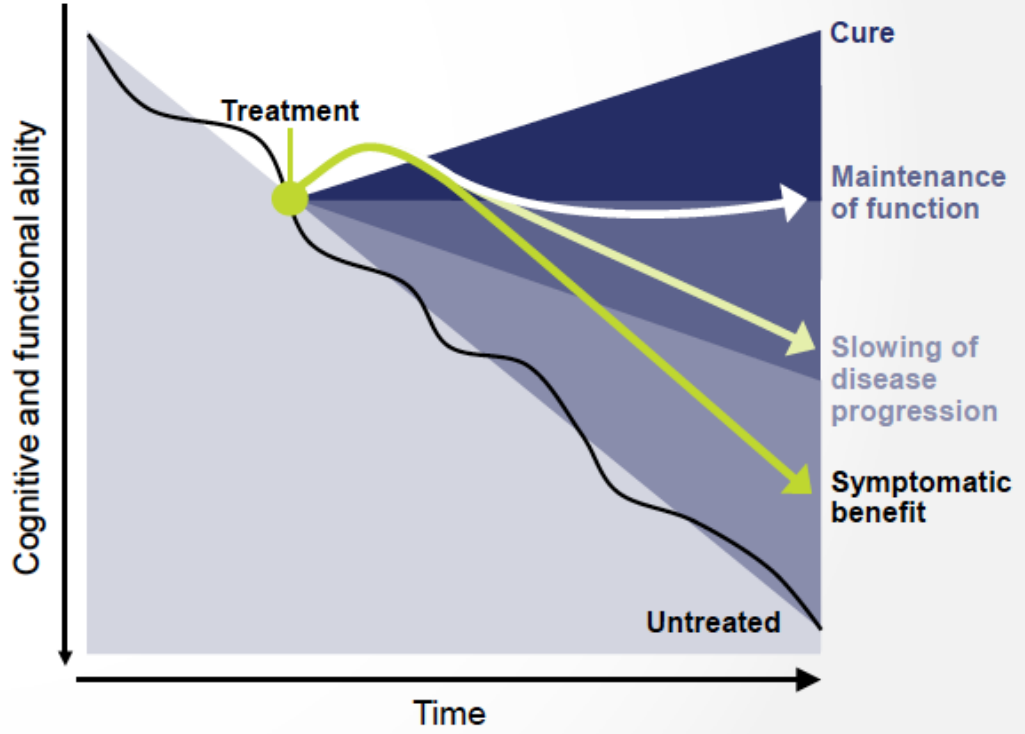
*Although these arrows are of equal size, the components of the AD continuum are not equal in duration.

alzheimer's association

Symptomatic and disease-modifying treatments

- A **symptomatic treatment** can provide an initial benefit, but the patient will continue to decline[3,4]
- A **disease-modifying treatment** would either stop or slow the progressive decline of the patient[3,4]
- A **cure** for AD would reverse the disease progress and restore the patient to their original level of functioning[4]

Theoretical ways in which a treatment could affect the course of AD[4]

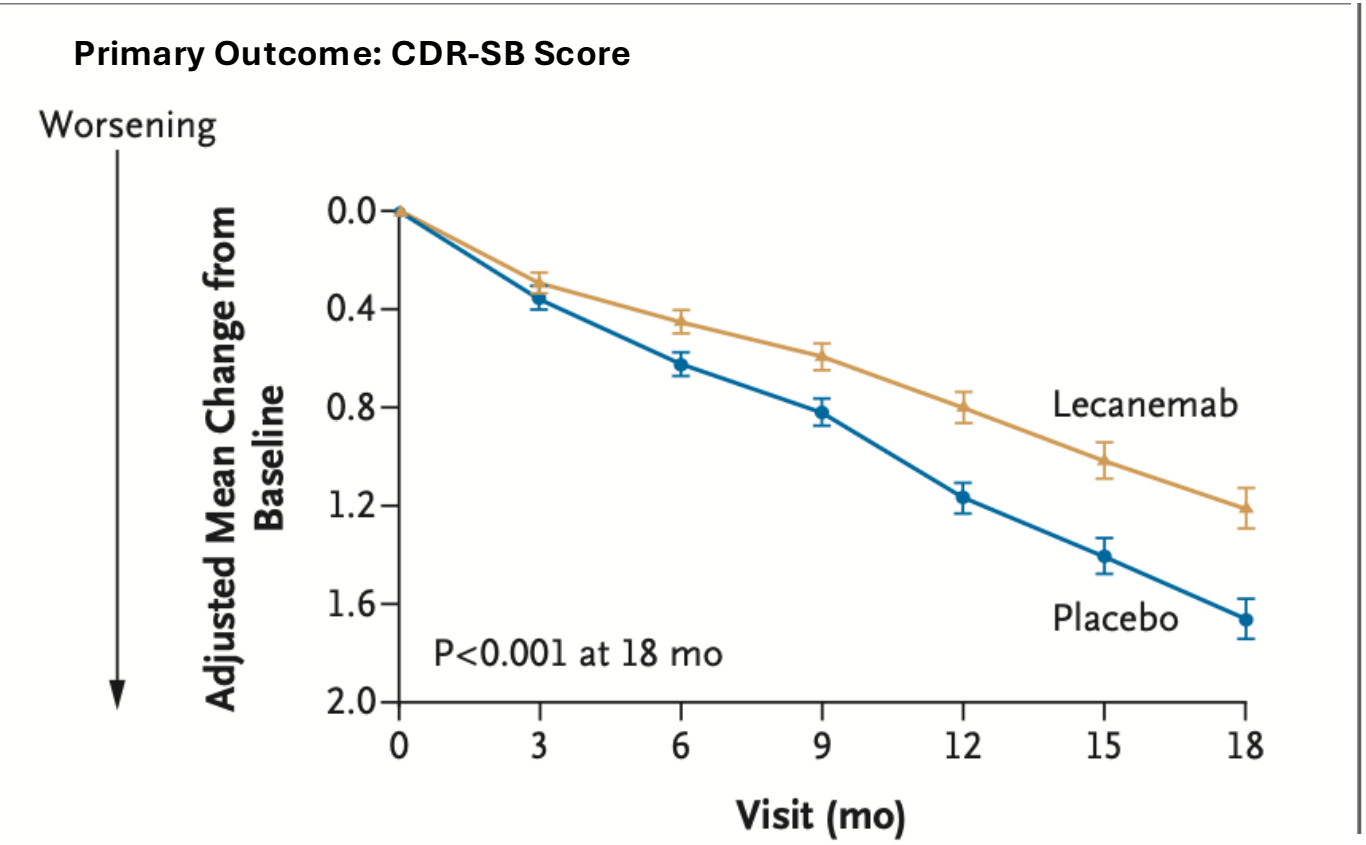


1. Winblad et al. Lancet Neurol 2016;15(5):455–532; 2. Cummings et al. Alzheimers Res Ther 2021;13(1):98;
3. Cummings & Fox. J Prev Alzheimers Dis 2017;4(2):109–115; 4. Adapted from: Van Dam & De Deyn. Nat Rev Drug Discov 2006;5(11):956–970

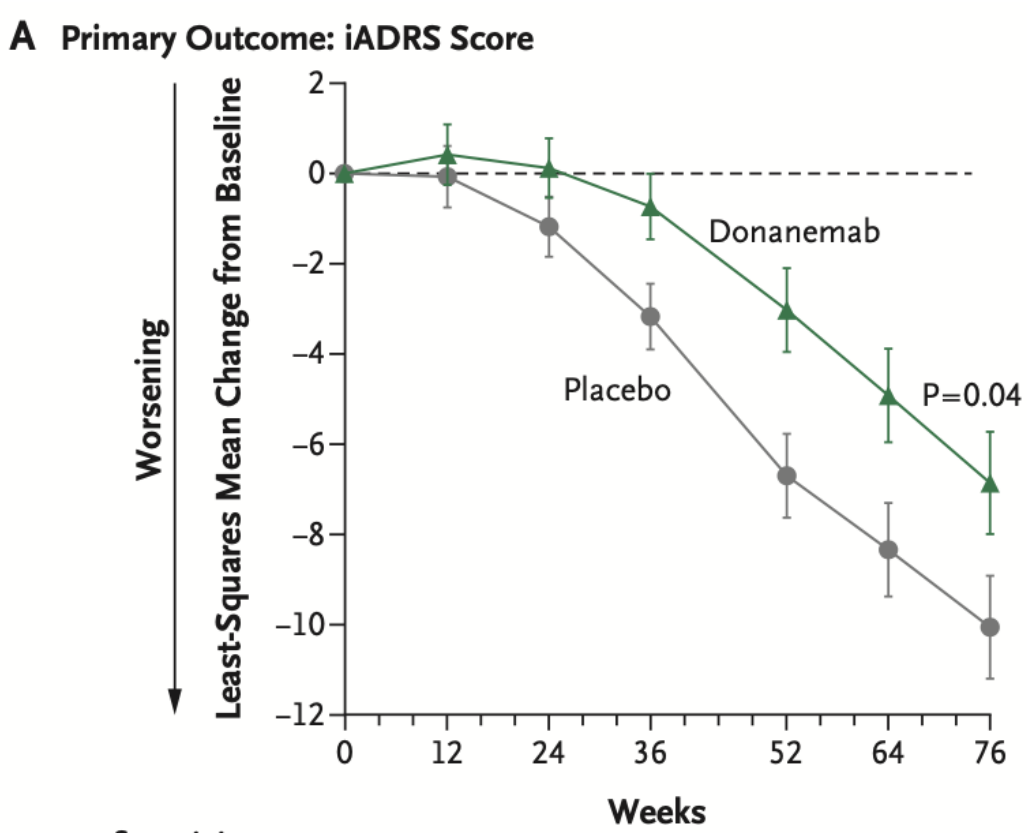
Atri, 2023

Lecanemab/Donanemab: Clinical Outcomes

25-35% slowing of cognitive decline compared to placebo



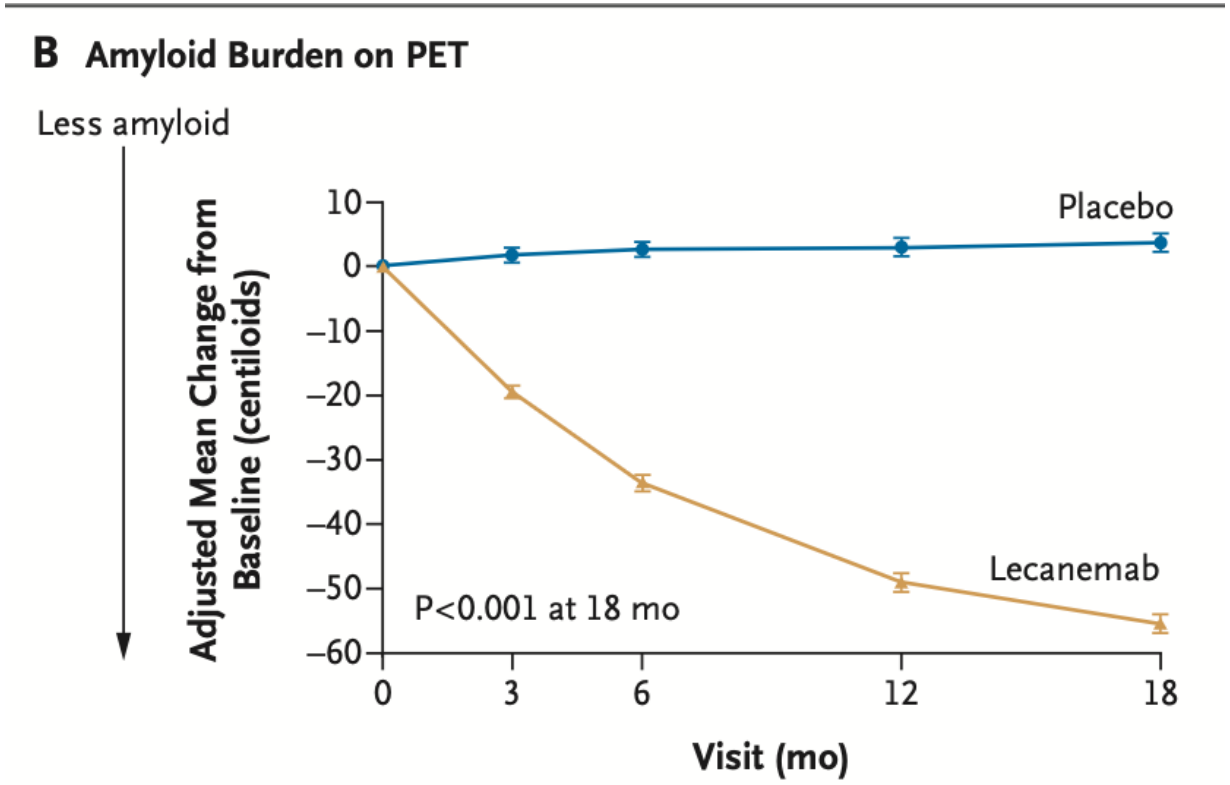
van Dyck et al., 2023



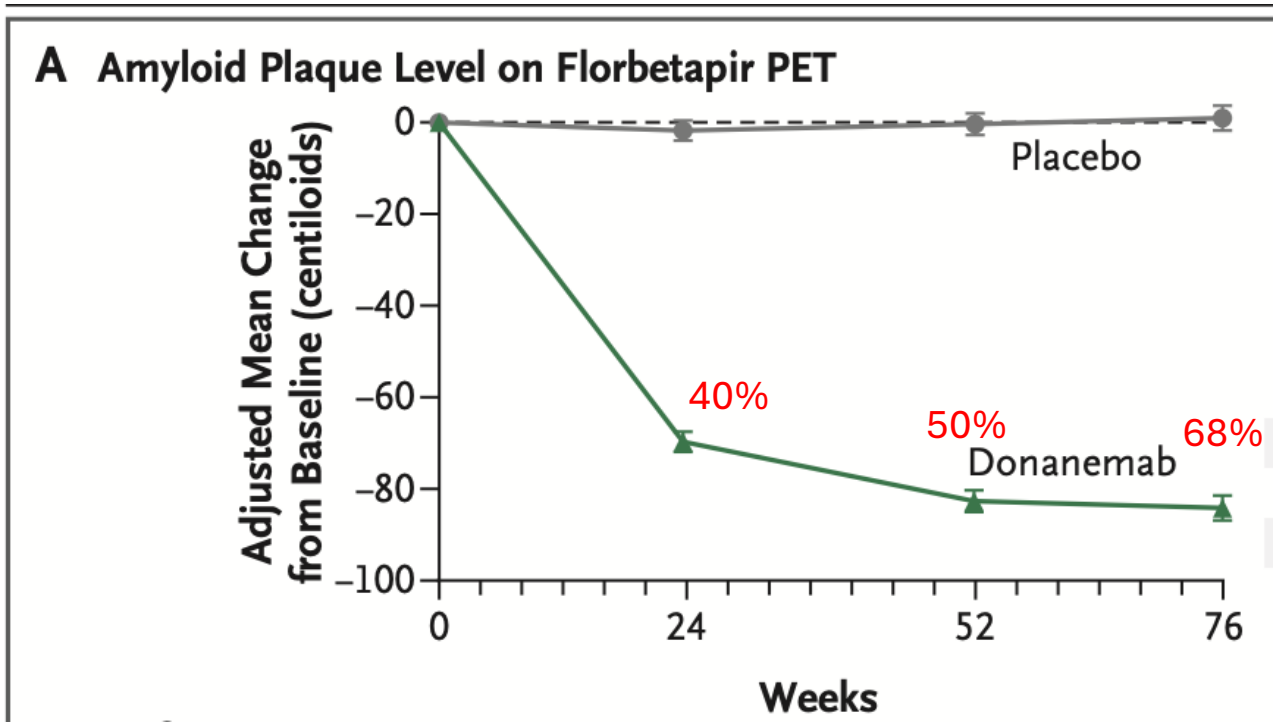
Mintun et al., 2021

Lecanemab/Donanemab: Biomarker Outcomes

Dramatic lowering of PET amyloid burden:
70-80% convert to amyloid negative status

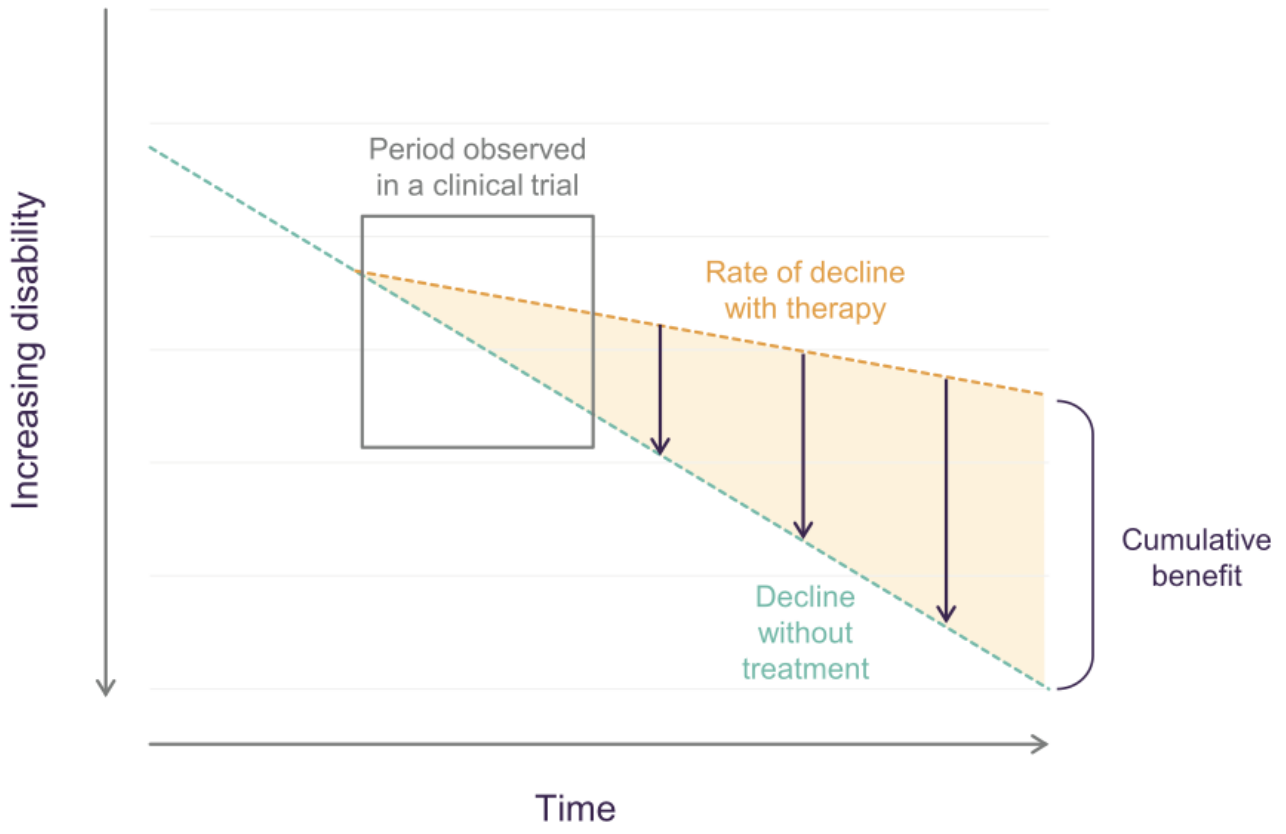


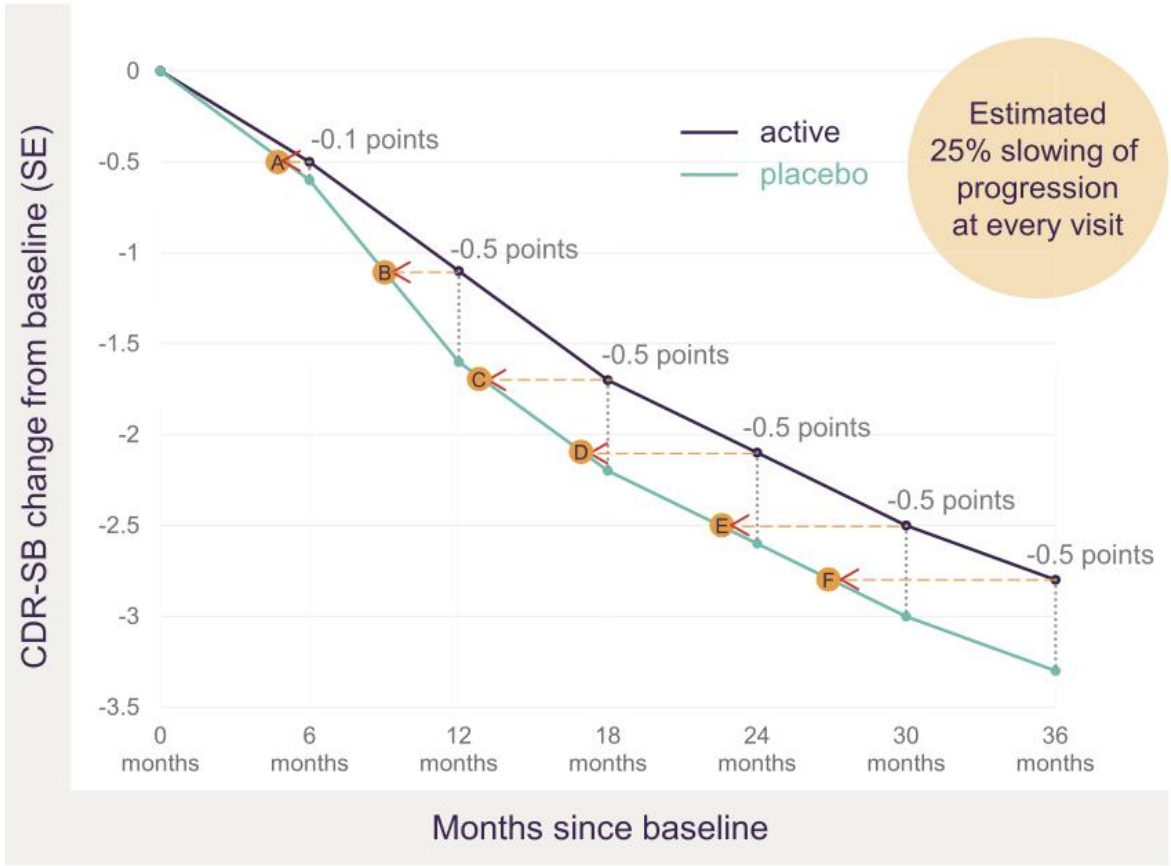
van Dyck et al., 2023



Mintun et al., 2021

Cumulative Treatment Benefit Over Time

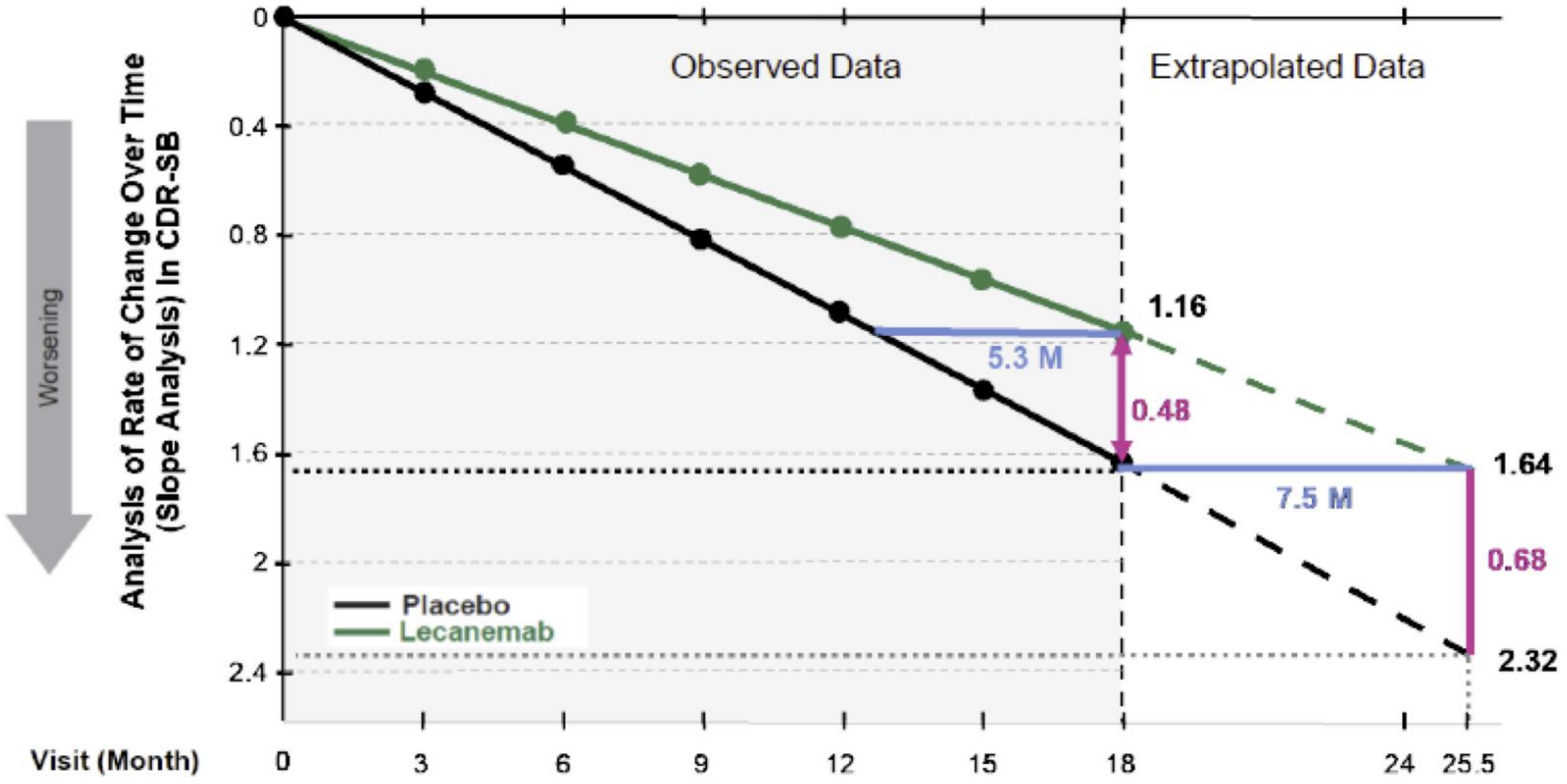




	A	B	C	D	E	F
points	-0.1	-0.5	-0.5	-0.5	-0.5	-0.5
months difference vs. placebo	-1.5	-3	-4.5	-6	-7.5	-9

Petersen, 2023

- 32% slowing of slope annually [(95%CI: 18% to 46%), p=0.00001] on lecanemab vs. placebo
  - Projected treatment difference at 25.5 months based on slope showed -0.68 treatment difference
- Increasing separation over time between lecanemab & placebo

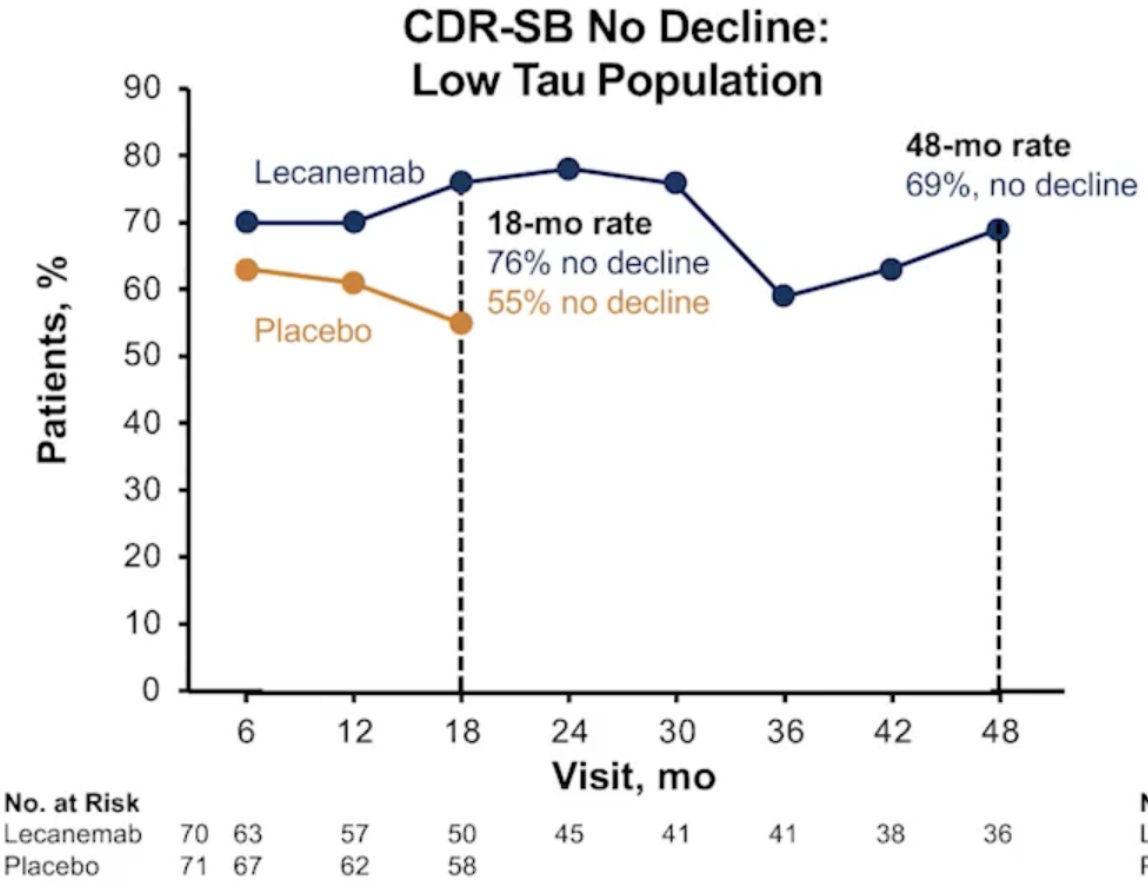


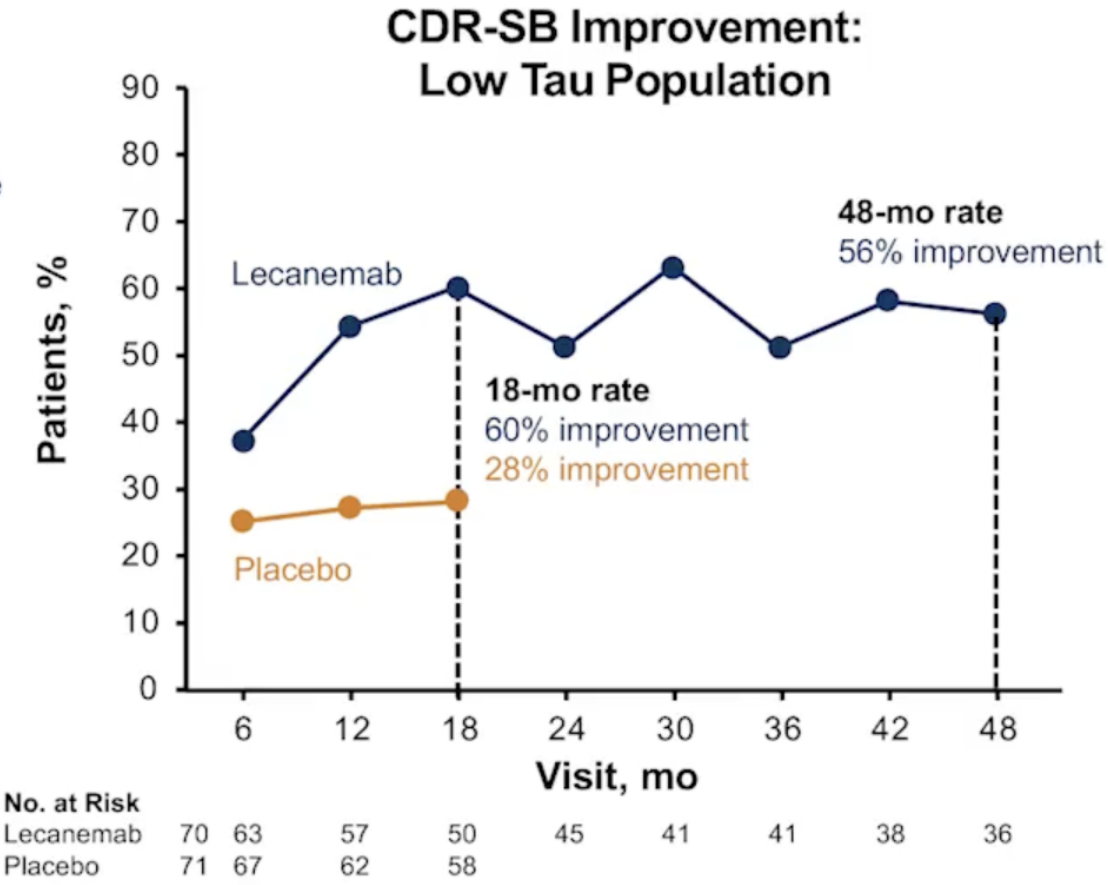
- Lecanemab takes 25.5 months to reach same level as placebo at 18 months

Note: Rate of change over time (mean slope) based on change from baseline in the CDR-SB was analyzed using linear mixed effects (LME) model. LME model included time, treatment by assessment time as covariate with random intercept and slope. CDR-SB, Clinical Dementia Rating-Sum-of-Boxes.

Van Dyck et al. NEJM 2023; Cohen et al. CTAD2022

Low Tau Patients Treated With Lecanemab Saw Greater "No Decline" and "Improvement" Rates vs Placebo[1]





Lecanemab, %	No Decline	Improvement
ADAS-Cog14	51	51
ADCS MCI-ADL	64	58

1. van Dyck CH et al. AAIC 2025. Abstract 4-4-DEV.

PeerView

Brosch, 2025

Lecanemab/Donanemab Eligibility Criteria

- MCI or mild dementia due to AD
- Age: 50-90
- MMSE: 20-30
- Positive amyloid PET scan or CSF biomarker confirmation of AD (positive blood biomarker test not sufficient)
- APOE genotype
- Can be receiving symptomatic treatment with cognitive enhancing agents (cholinesterase inhibitors, namenda)
- Care partner/family member

Lecanemab/Donanemab Exclusion Criteria

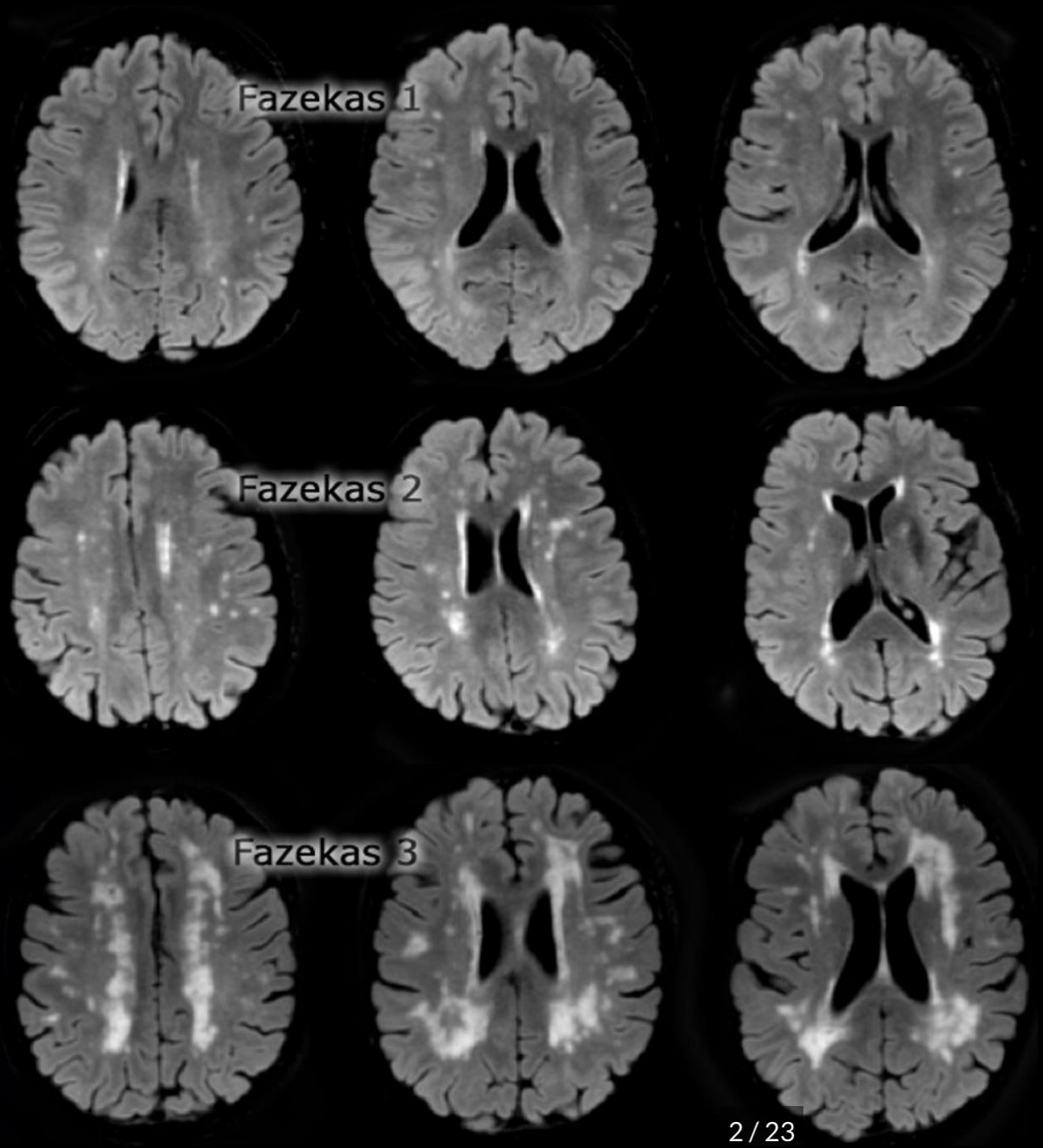
- MCI or mild dementia due to non-AD etiology
- Contraindications to MRI or evidence of:
  - >4 microhemorrhages, or single macrohemorrhage (>10mm)
  - superficial siderosis
  - cortical infarcts, >2 lacunes
  - severe deep with matter disease, Fazekas grade 3
  - brain tumors, vascular malformations
- Recent history of stroke/TIA (12 months), any history of seizures
- Patient on anticoagulants, bleeding disorders, antiplatelets (ASA 81mg) acceptable, should not receive tPA
- History of immunological disorders, treatment with immunosuppressants, immunoglobulins, monoclonal antibodies
- Unstable medical or psychiatric conditions

Deep White Matter Disease

YES

YES

NO



On Axial FLAIR:

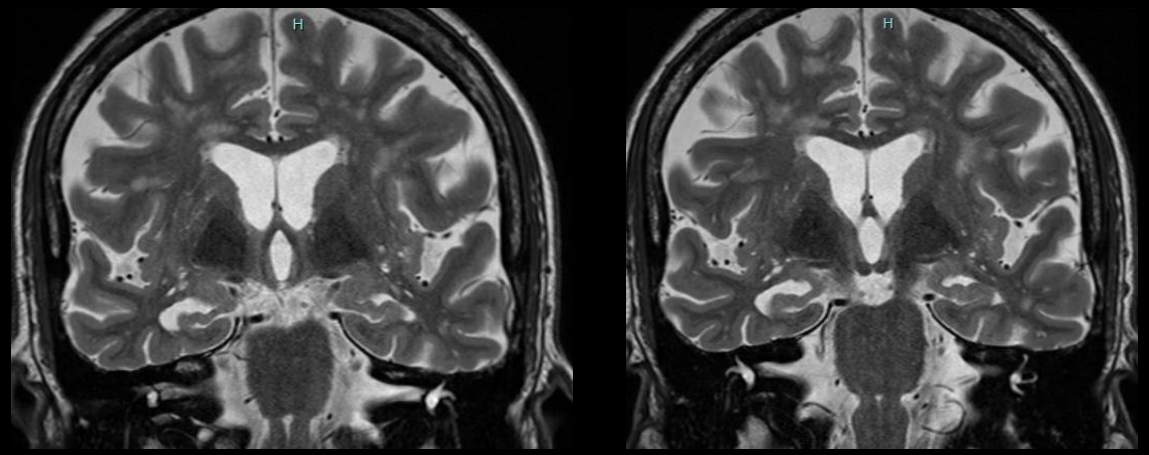
Fazekas 0:
None or a single punctate WMH lesion

Fazekas 1:
Multiple punctate lesions

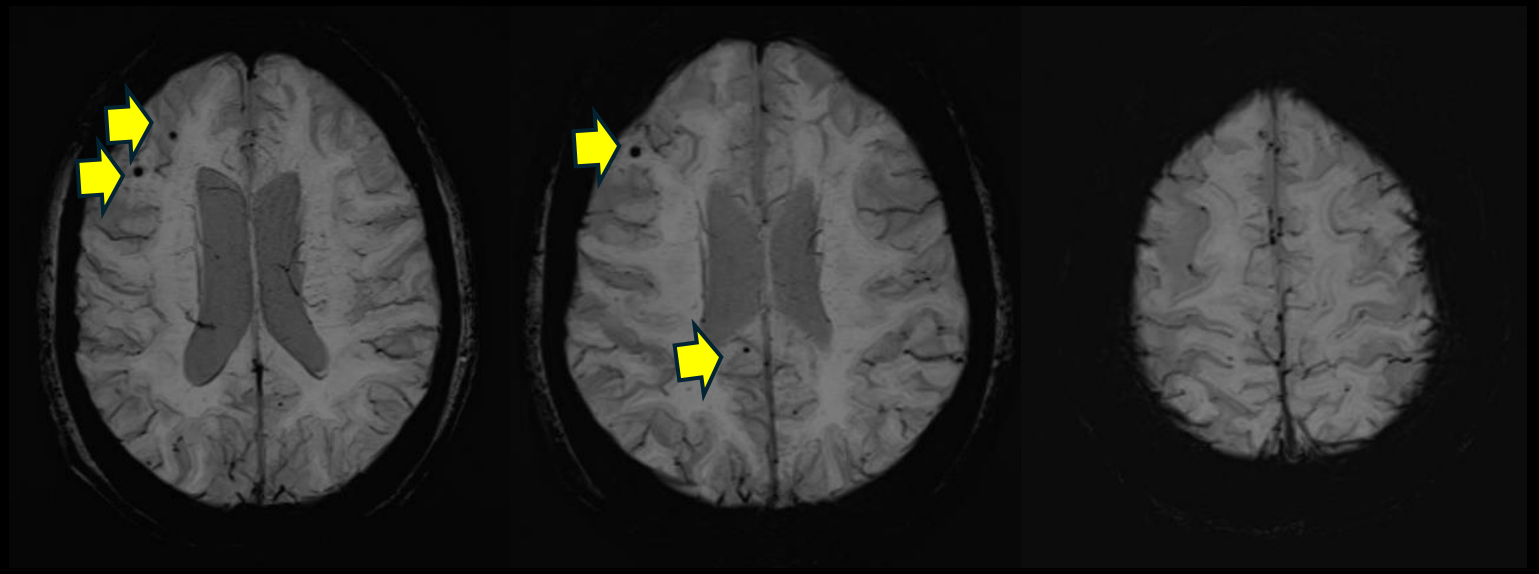
Fazekas 2:
Beginning confluency of lesions (bridging)

Fazekas 3:
Large confluent lesions

Up to 4 Microhemorhages Associated with Amyloid Angiopathy



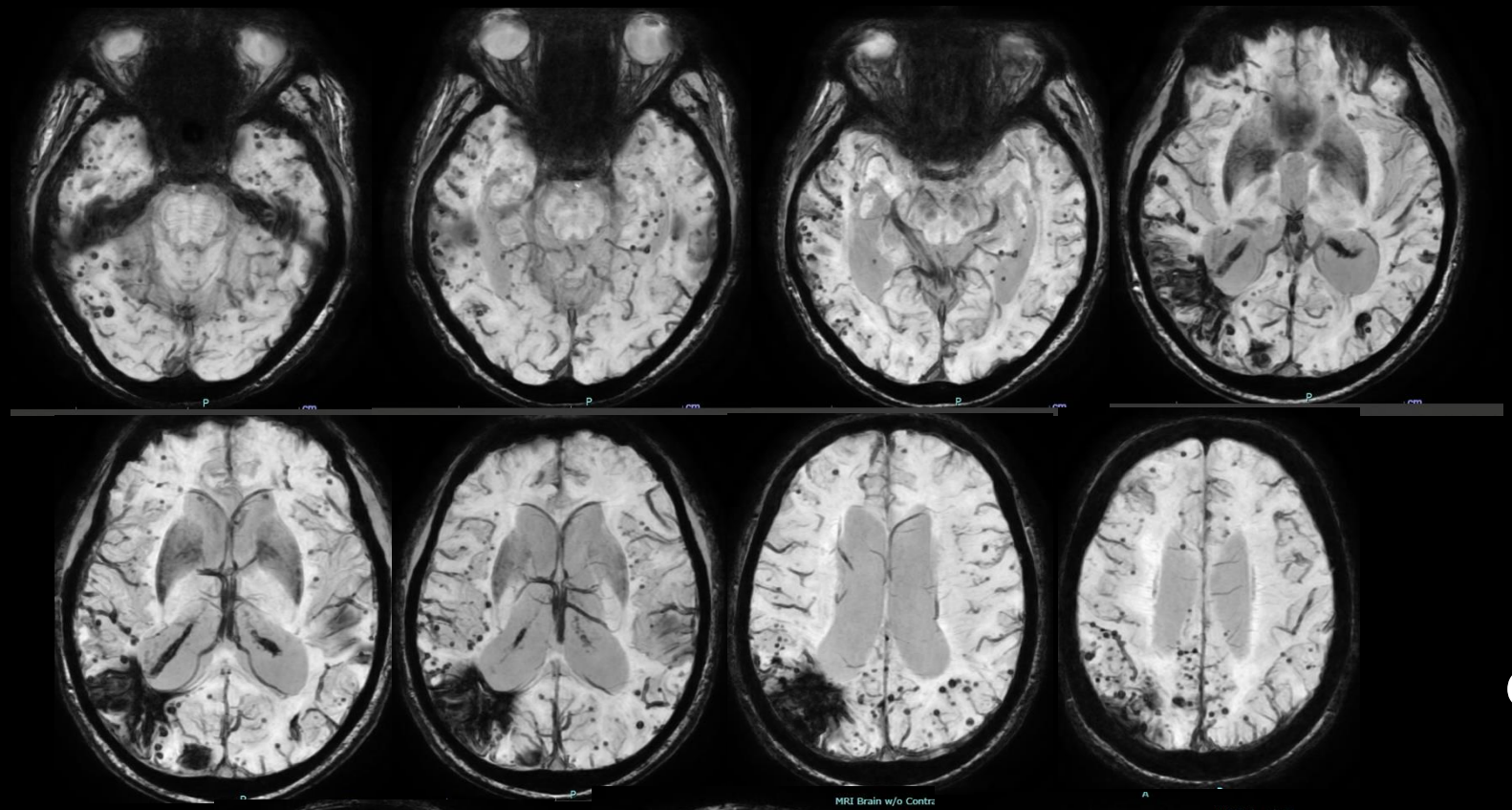
YES



GRE or SWI

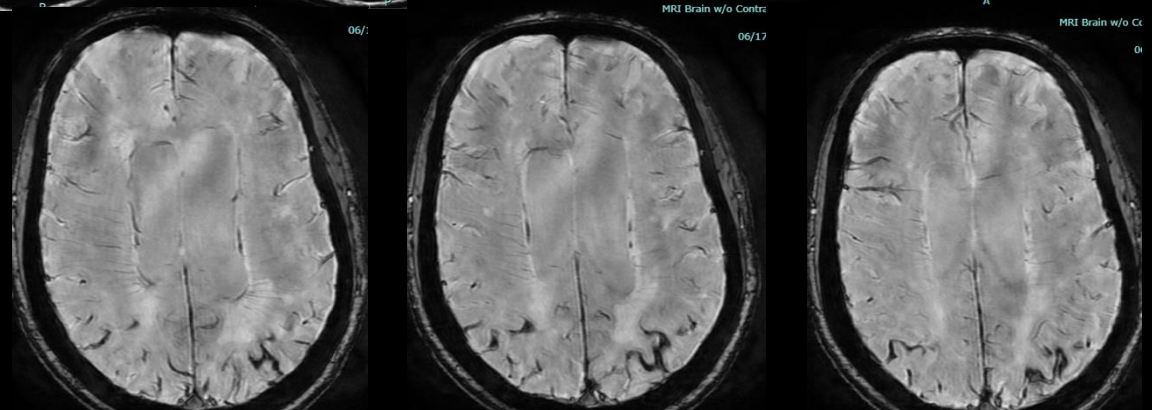
>4 Microhemorrhages, Macrohemorrhage, or Superficial Siderosis Associated with Amyloid Angiopathy

NO



GRE or SWI

NO



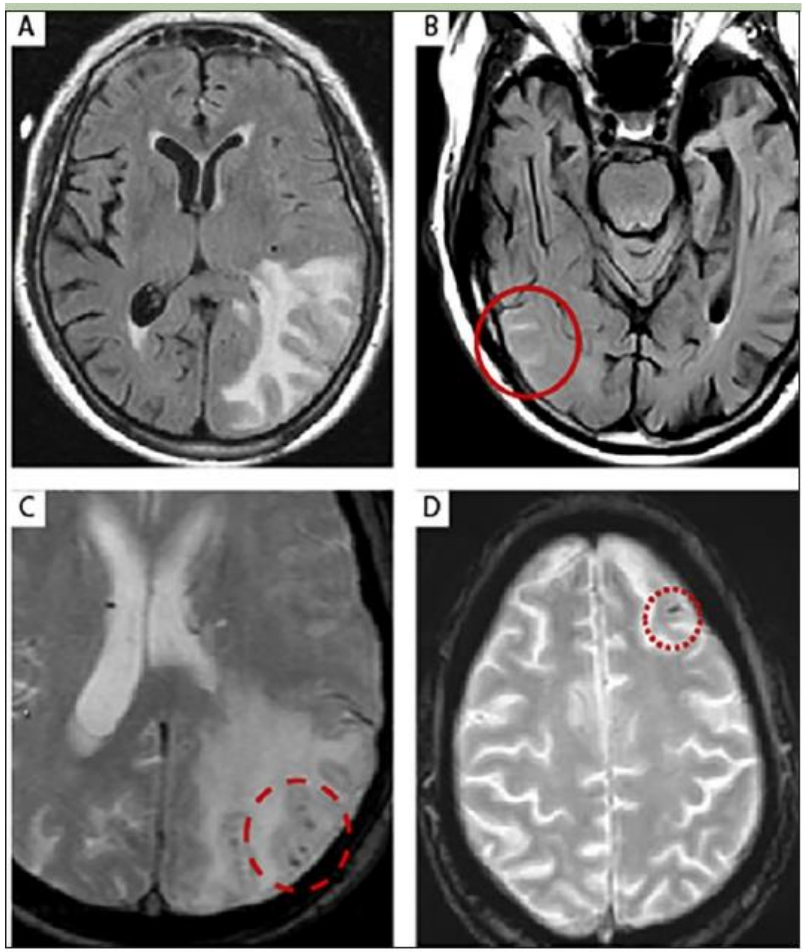
Side Effects: Amyloid Related Imaging Abnormalities (ARIA)

Observed in about 20% of cases, mostly asymptomatic

Table 4. Symptoms observed in patients who develop symptomatic ARIA

- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty
- Serious ARIA
  - o Seizures
  - o Status epilepticus
  - o Encephalopathy
  - o Stupor
  - o Focal neurological deficits

Cummings et al., 2023



ARIA-E

ARIA-H

ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema, sulcal effusions; ARIA-H, amyloid-related imaging abnormalities due to microhemorrhages, superficial siderosis; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo

Barakos et al.2022

Table 5. ARIA rates reported for the Phase 3 (CLARITY AD) trial of lecanemab

	All Participants on Placebo (N = 897)	All Participants on Lecanemab (N = 898)	APOE4 Noncarrier : Placebo (N = 286)	APOE4 Noncarrier: Lecanemab (N = 278)	APOE4 Carrier: Placebo (N = 611)	APOE4 Carrier: Lecanemab (N = 620)	APOE4 Heterozygote: Placebo (N = 478)	APOE4 Heterozygote: Lecanemab (N = 479)	APOE4 Homozygote: Placebo (N = 133)	APOE4 Homozygote: Lecanemab (N = 141)
ARIA-E	1.7% (15/897)	12.6% (113/898)	0.3% (1/286)	5.4% (15/278)	2.3% (14/611)	15.8% (98/620)	1.9% (9/478)	10.9% (52/479)	3.8% (5/133)	32.6% (46/141)
Symptomatic ARIA-E	0	2.8% (25/898)	0	(1.4%) 4/278	0	3.4% (21/620)	0	1.7% (8/479)	0	9.2% (13/141)
Serious event with ARIA-E	0	0.8% (7/898)	0	0.7% (2/278)	0	0.8% (5/620)	0	0.4% (2/479)	0	2.1% (3/141)
Total ARIA-H (Concurrent & Isolated)	9.0% (81/897)	17.3% (155/898)	4.2% (12/286)	11.9% (33/278)	11.3% (69/611)	19.7% (122/620)	8.6% (41/478)	14.0% (67/479)	22.1% (28/133)	39.0% (55/141)
Symptomatic ARIA-H	0.2% (2/897)	0.7% (6/898)	0	0.4% (1/278)	0.3% (2/611)	0.8% (5/620)	0.2% (1/478)	1.0% (5/479)	0.8% (1/133)	0
Serious event with ARIA-H	0.1% (1/897)	0.6% (5/898)	0.3% (1/286)	0.7% (2/278)	0	0.5% (3/620)	0	0.2% (1/479)	0	1.4% (2/141)
Microhemorrhage	7.6% (68/897)	14.0% (126/898)	3.1% (9/286)	7.2% (20/278)	9.7% (59/611)	17.1% (106/620)	7.1% (34/478)	12.1% (58/479)	18.8% (25/133)	34.0% (48/141)
Superficial siderosis	2.3% (21/897)	5.6% (50/898)	0.7% (2/286)	4.7% (13/278)	3.1% (19/611)	6.0% (37/620)	2.7% (13/478)	4.0% (19/479)	4.5% (6/133)	12.8% (18/141)
ICH[2] (Including non-TEAE)	0.2% (2/897)[1]	0.7% (6/898)1	0.3% (1/286)	0.4% (1/278)	0.2% (1/611)1	0.8% (5/620)1	0.2% (1/478)1	0.6% (3/479)1	0	1.4% (2/141)
Isolated ARIA-H[3]	7.8% (70/897)	8.9% (80/898)	3.8% (11/286)	8.3% (23/278)	9.7% (59/611)	9.2% (57/620)	7.3% (35/478)	8.4% (40/479)	18.0% (24/133)	12.1% (17/141)
Symptomatic Isolated ARIA-H	0.2% (2/897)	0.4% (4/898)	0	0.4% (1/278)	0.3% (2/611)	0.5% (3/620)	0.2% (1/478)	0.6% (3/479)	0.8% (1/133)	0

Cummings et al., 2023

Featured Article

Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States

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Abstract

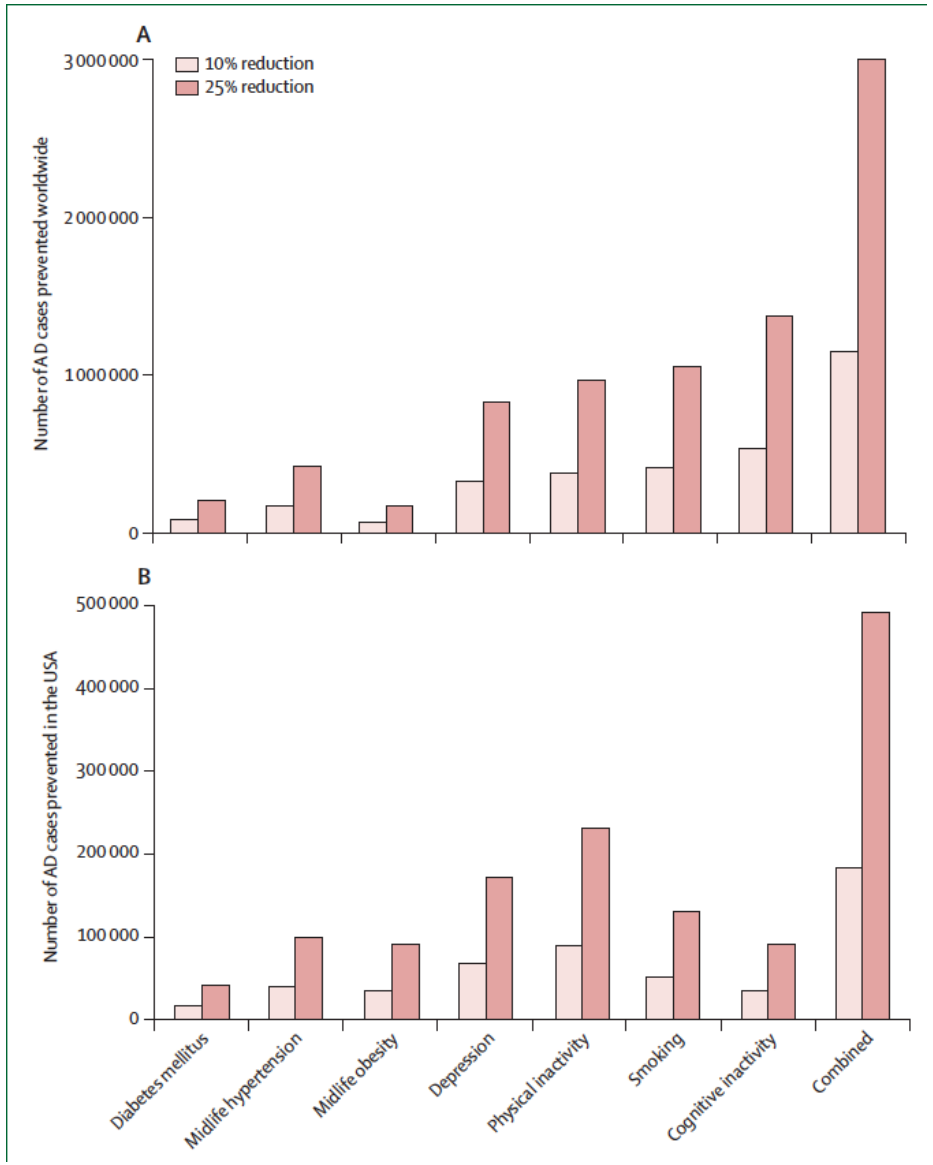
Introduction: We forecast the prevalence of preclinical and clinical Alzheimer's disease (AD) and evaluated potential impacts of primary and secondary preventions in the United States.

Methods: We used a multistate model incorporating biomarkers for preclinical AD with US population projections.

Results: Approximately 6.08 million Americans had either clinical AD or mild cognitive impairment due to AD in 2017 and that will grow to 15.0 million by 2060. In 2017, 46.7 million Americans had preclinical AD (amyloidosis, neurodegeneration, or both), although many may not progress to clinical disease during their lifetimes. Primary and secondary preventions have differential impact on future disease burden.

Discussion: Because large numbers of persons are living with preclinical AD, our results underscore the need for secondary preventions for persons with existing AD brain pathology who are likely to develop clinical disease during their lifetimes as well as primary preventions for persons without preclinical disease.

Treatment of Modifiable Risk Factors



Barnes & Yaffe, 2011

Together, up to half of AD cases worldwide (17·2 million) and in the USA (2·9 million) are potentially attributable to these factors. A 10–25% reduction in all seven risk factors could potentially prevent as many as 1·1–3·0 million AD cases worldwide and 184 000–492 000 cases in the USA.

Treatment of Modifiable Risk Factors

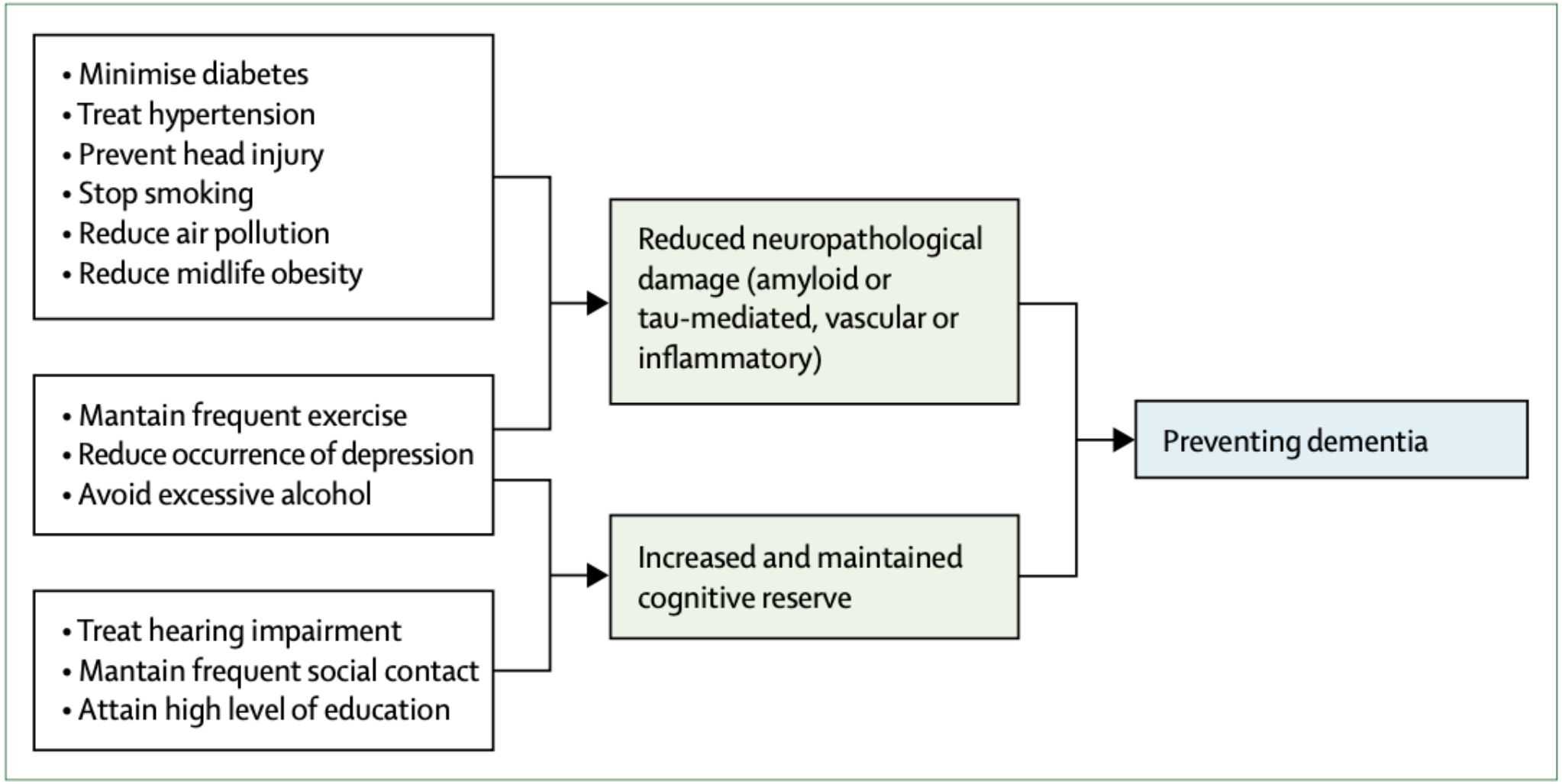


Figure 2: **Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia**

Livingston, 2020

Conclusions

Diagnosis/Prognosis:

- AD is a clinico-pathological continuum characterized by transition from the preclinical to the clinical phase of the illness

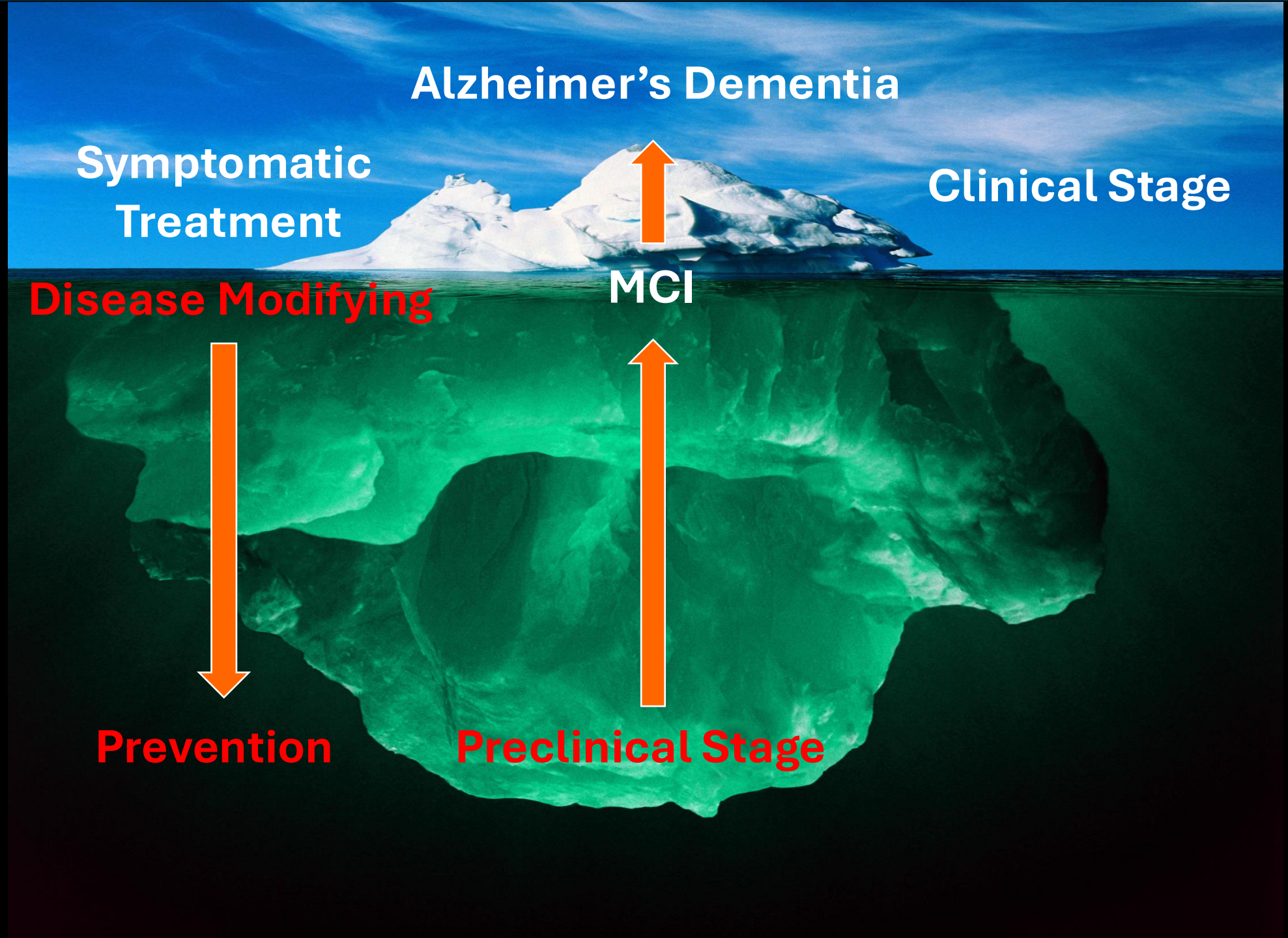
- Biomarkers have transformed our approach to diagnosis by allowing early detection of AD pathology and the prediction of risk for conversion to dementia in cognitively normal individuals, in addition to confirming AD in clinically impaired populations

Treatment: Disease-Modifying Drugs

- Several anti-amyloid drugs are available for prevention in the preclinical phase and treatment of MCI/mild AD, dramatic reduction of brain amyloid but clinically meaningful benefits still limited, side effects/ARIA

- Treatment may require a multi-drug approach targeting both amyloid and tau

- Approach to treatment should incorporate reduction of modifiable risk factors (cardiovascular, depression, lifestyle)


Alzheimer's Dementia
Symptomatic Treatment
Clinical Stage
MCI
Disease Modifying
Prevention
Preclinical Stage

Banner Health

Banner Alzheimer's Institute

The University of Arizona

Thank You for Your Attention