Center for Alzheimer Research & Treatment

HARVARD AGING BRAIN

Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital

Preclinical Alzheimer's Disease
Can we detect and treat Alzheimer's disease a decade before dementia? (And why we must!)

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BWH VE RI TAS MGH 1811

Disclosures and Funding

R. Sperling Consultant (over past 3 years, all below NIH guidelines of $5k):

Abbvie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol-Myers Squibb, Roche, Ionis, Janssen, Merck, Oligomerix, Prothena, Vaxxinity

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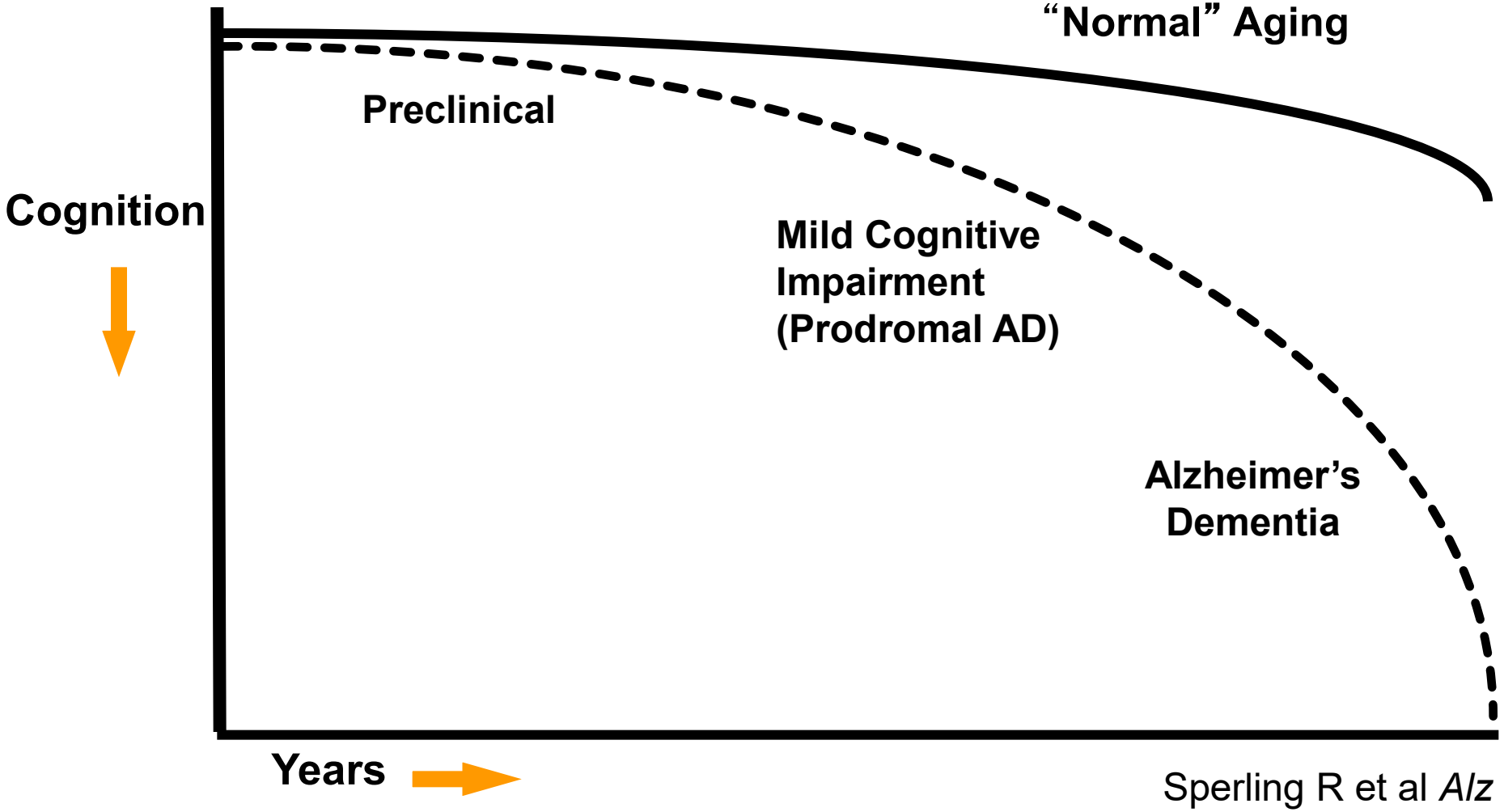
Alzheimer's Association
GHR Foundation, Fidelity Biosciences, Gates Ventures,
Accelerating Medicines Partnership FNIH

Eli Lilly, Eisai – Public Private Partnership Trials Funding to Sites

The continuum of Alzheimer's disease

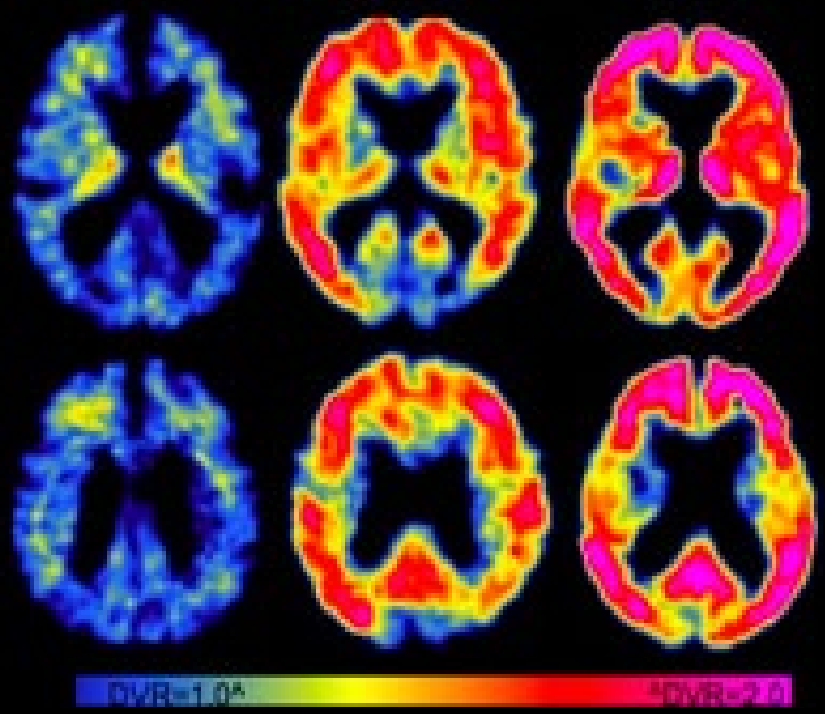


Sperling R et al *Alz & Dem* 2011
NIA-AA Preclinical Workgroup
Jack C et al *Alz & Dem* 2019, 2024

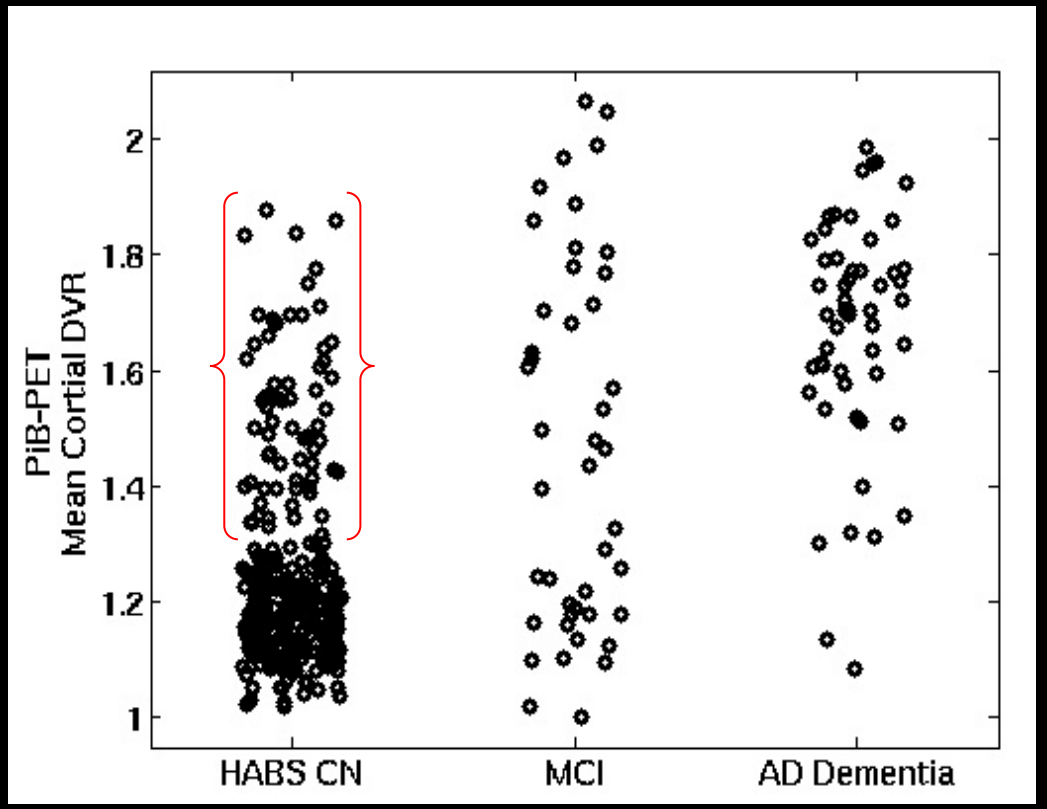
Preclinical Alzheimer's Disease

- Clear evidence that AD begins >decade before impairment
  - More amyloid associated with more tau, faster cognitive decline
  - Additional factors that increase risk of decline
- Clinical trial learnings
  - "Earlier is Better" (low pathology groups) early symptomatic trials
  - Substantial amyloid removal may be required even in preclinical
- Looking forward
  - Ongoing trials in preclinical AD with amyloid reducing antibodies
  - Plasma biomarkers to predict and track "pre-preclinical" AD
- Getting closer to primary prevention of AD

PET Amyloid Imaging Across the Spectrum of AD



CN Aβ– CN Aβ+ AD Aβ+

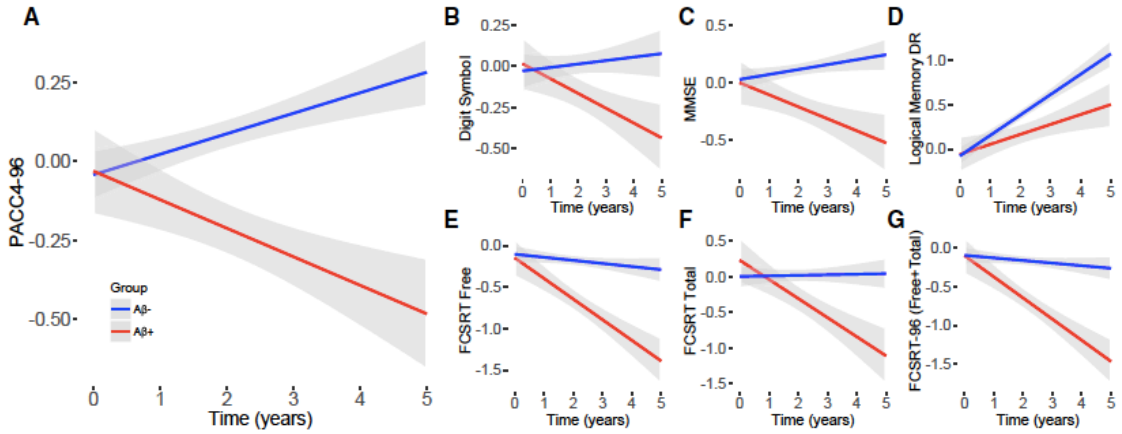


Harvard Aging Brain Sudy

Sperling, Mormino, Johnson *Neuron* 2014

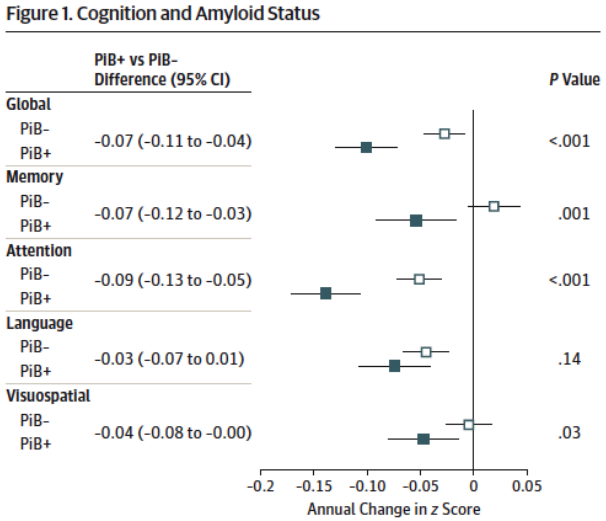
High Risk of Cognitive Decline in Amyloid+ Cognitively Unimpaired

Harvard Aging Brain Study



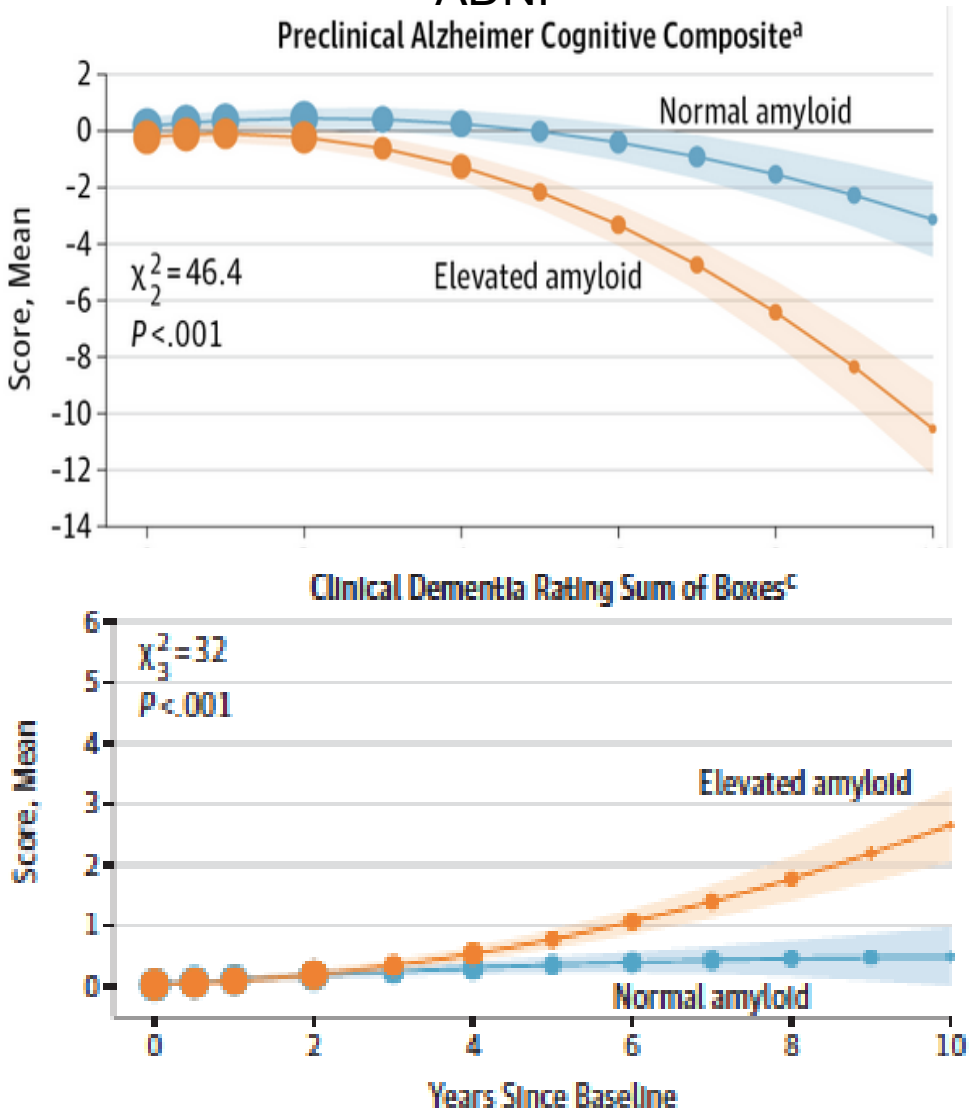
Mormino E et al. *Alz & Dementia* 2017

Mayo Clinic Study of Aging



Petersen R et al. *JAMA Neurology* 2015

ADNI

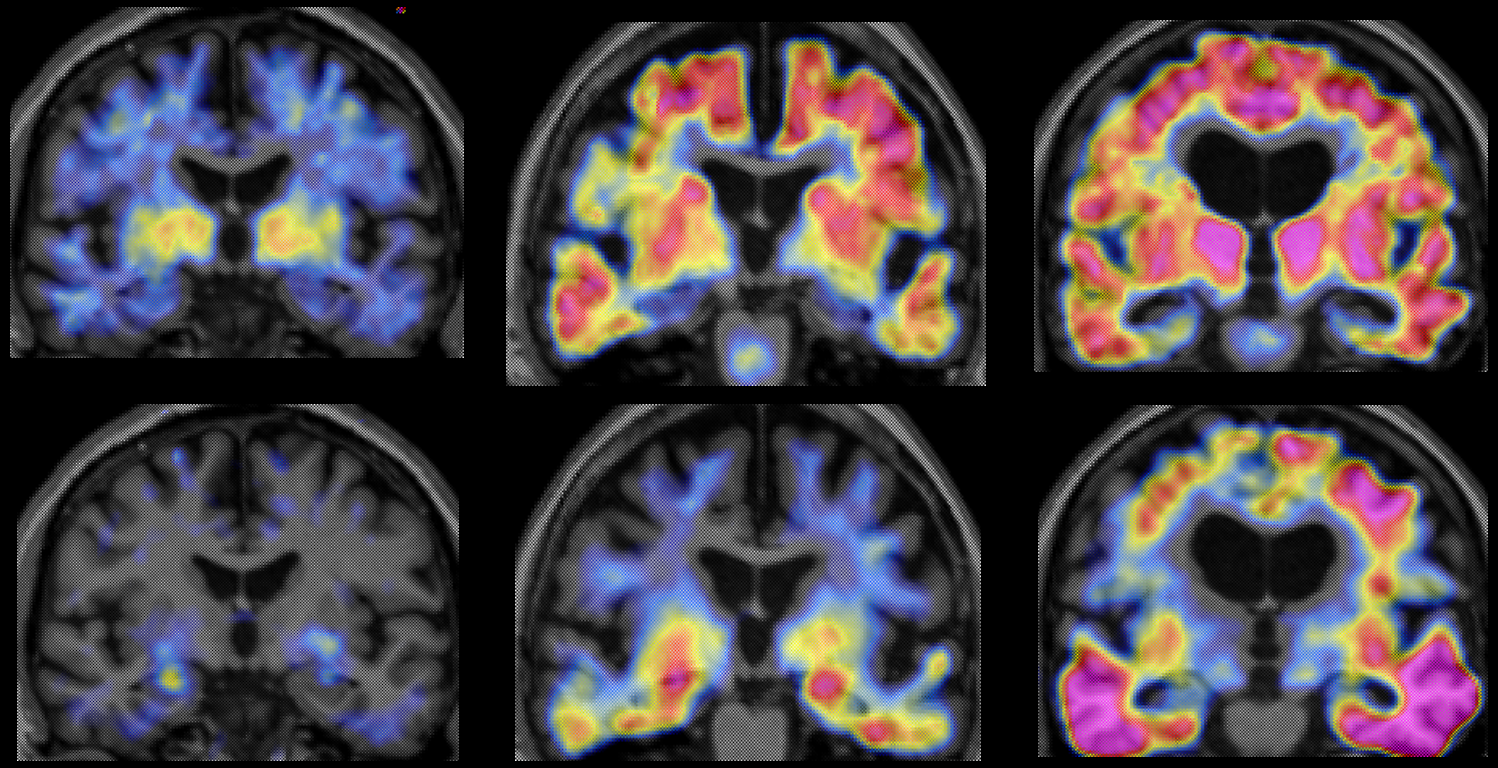


Donohue M, Sperling R et al. *JAMA* 2017

Detecting Alzheimer's Disease During Life
Amyloid and Tau PET Imaging

Amyloid β

Tau



Amyloid Negative Cognitively Unimpaired

Amyloid Positive Cognitively Unimpaired

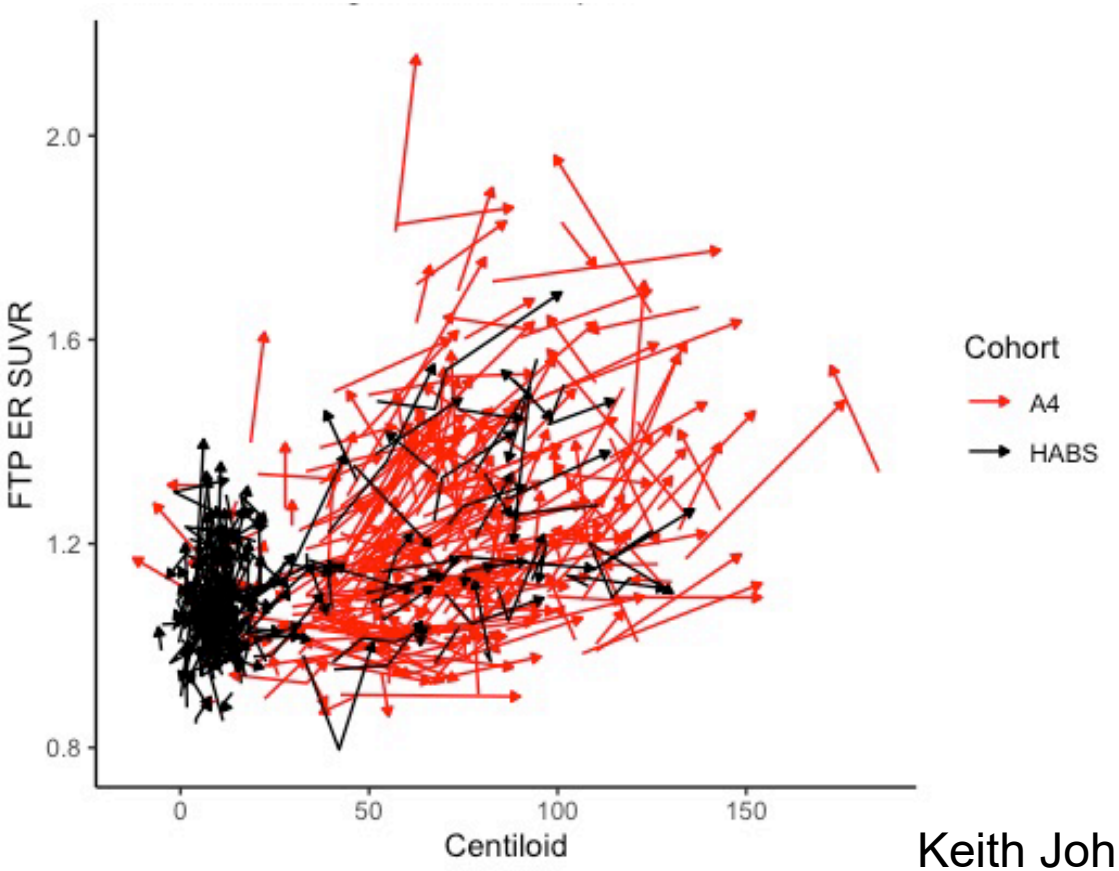
Amyloid Positive Alzheimer's Dementia

Sperling, Mormino, Johnson *Neuron* 2014

Predicting the “Ca-TAU-strophe”
Baseline Amyloid Levels vs. Longitudinal Tau PET

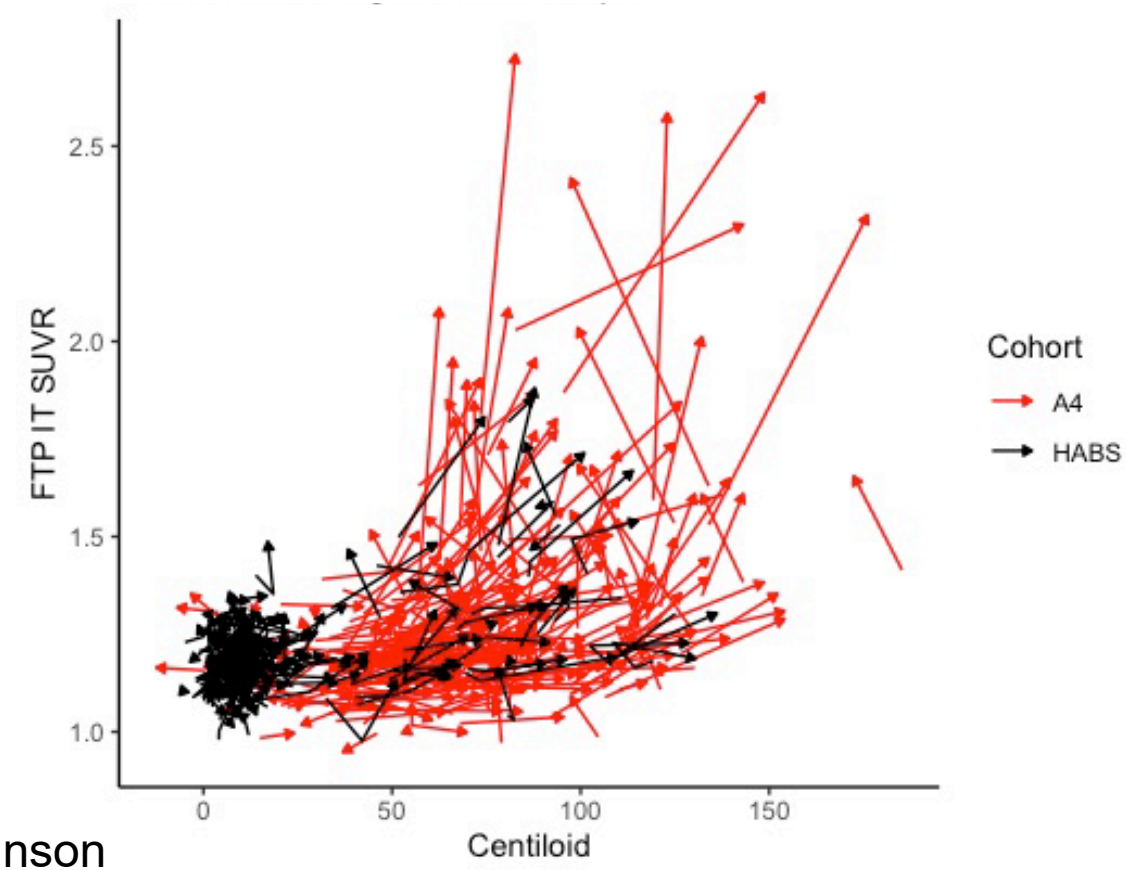
Harvard Aging Brain and A4 Study

Entorhinal Cortex



Baseline Amyloid PET

Inferior Temporal Cortex

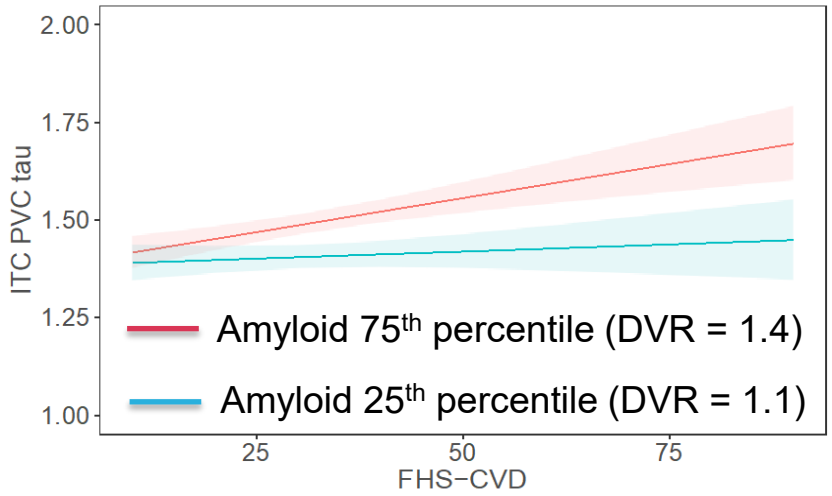


Baseline Amyloid PET

Keith Johnson

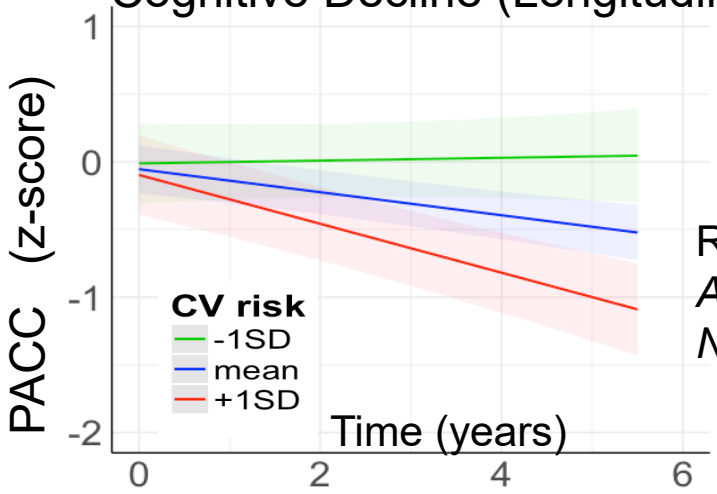
Synergy of Vascular Risk and Amyloid on Tau Deposition and Cognitive Decline in Preclinical AD

Tau PET (Cross-sectional)

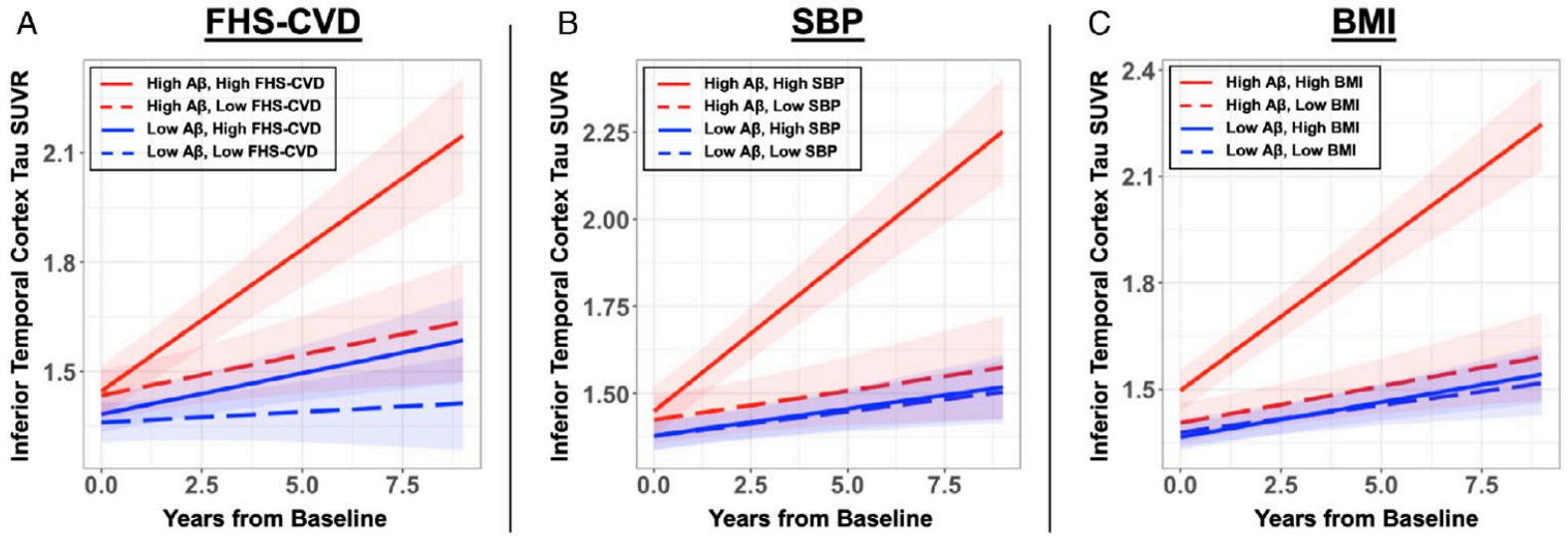


Rabin J et al
JAMA Neurology 2018

Cognitive Decline (Longitudinal)



Rabin J et al
Annals of Neurology 2019



Components of Vascular Risk on Tau PET (Longitudinal)

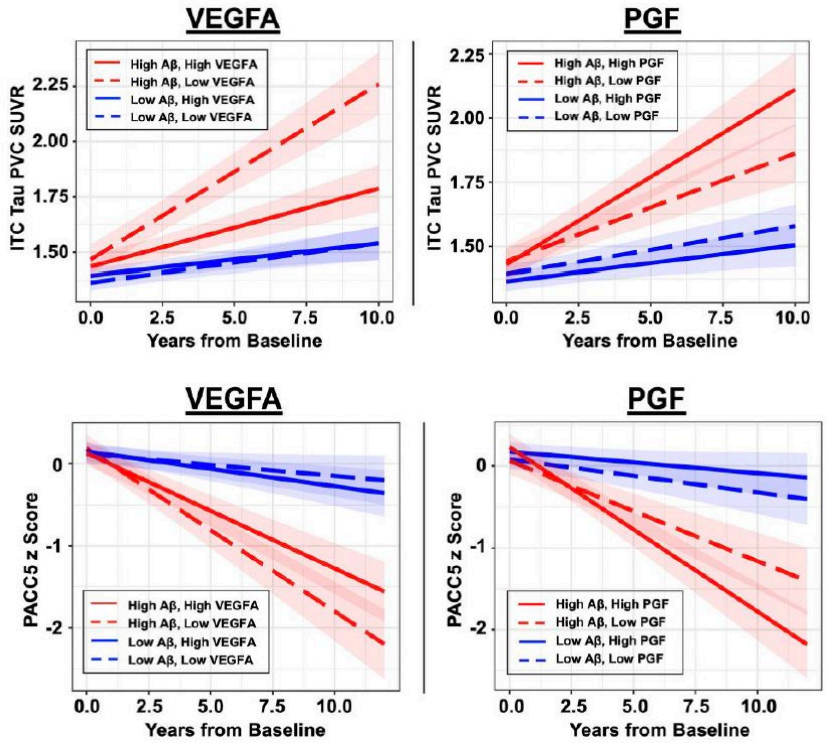
Yau W et al
Annals of Neurology 2022

Plasma Markers and Imaging Markers of Vascular Integrity Predict Tau and Cognitive Decline in Preclinical AD

BRAIN
ORIGINAL ARTICLE

Plasma VEGFA and PGF impact longitudinal tau and cognition in preclinical Alzheimer's disease

Hyun-Sik Yang,[1,2,3,†] Wai-Ying Wendy Yau,[1,2,3,†] Becky C. Carlyle,[3,4,5] Bianca A. Trombetta,[4] Can Zhang,[3,4,6] Zahra Shirzadi,[1,3] Aaron P. Schultz,[1,3,7] Jeremy J. Pruzin,[1,2,3,8] Colleen D. Fitzpatrick,[1] Dylan R. Kirn,[1,2] Jennifer S. Rabin,[9,10] Rachel F. Buckley,[1,2,3] Timothy J. Hohman,[11,12] Dorene M. Rentz,[1,2,3] Rudolph E. Tanzi,[3,6] Keith A. Johnson,[1,2,3,7] Reisa A. Sperling,[1,2,3,7] Steven E. Arnold[3,4] and Jasmeer P. Chhatwal[1,2,3]



Original Article

JCBFM

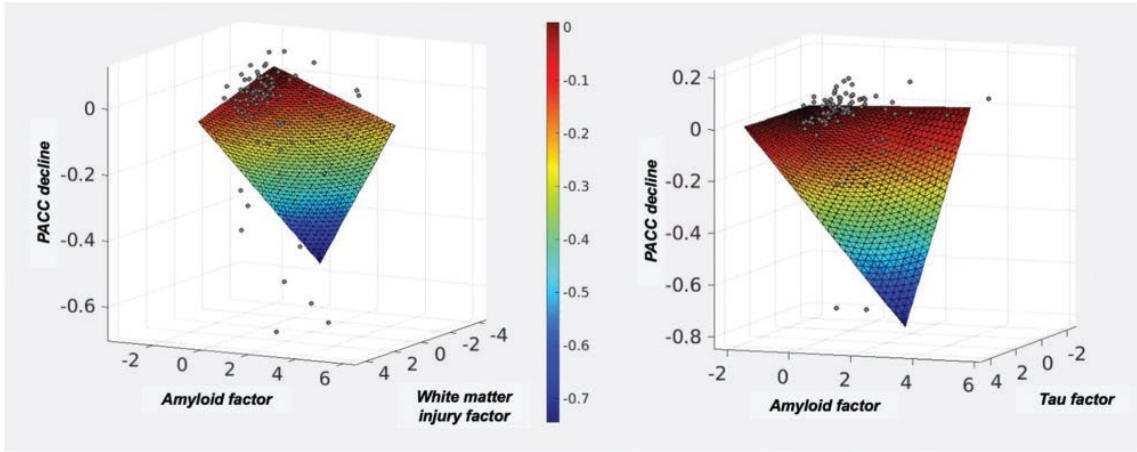
Journal of Cerebral Blood Flow & Metabolism
2024, Vol. 44(8) 1319–1328

DOI: 10.1177/0271678X241237624
journals.sagepub.com/home/jcbfm
Sage

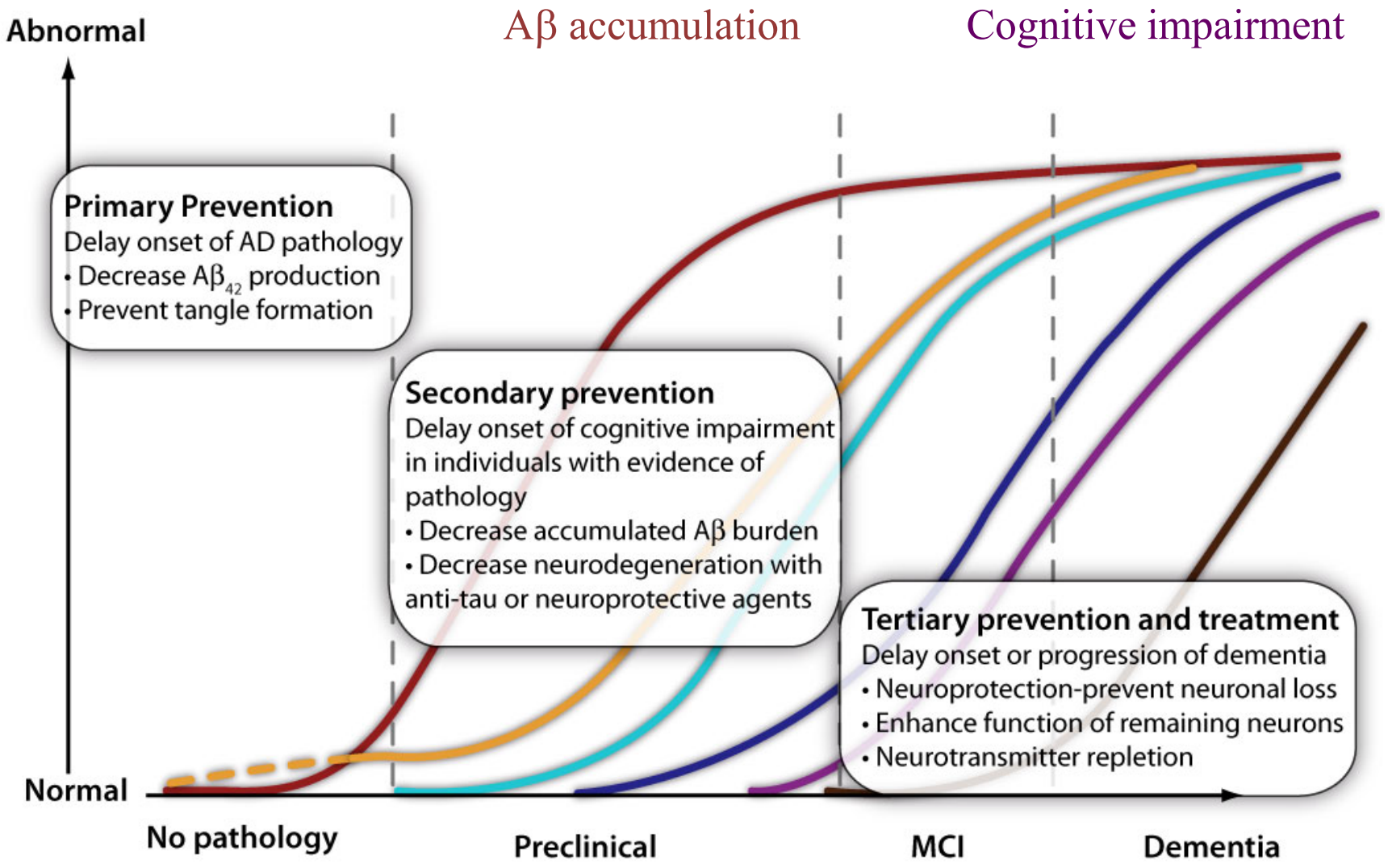
Vascular contributions to cognitive decline: Beyond amyloid and tau in the Harvard Aging Brain Study

Zahra Shirzadi[1], Rory Boyle[1], Wai-Ying W Yau[1], Gillian Coughlan[1], Jessie Fanglu Fu[2], Michael J Properzi[1], Rachel F Buckley[1], Hyun-Sik Yang[3], Catherine E Scanlon[1], Stephanie Hsieh[1], Rebecca E Amariglio[3], Kathryn Papp[3], Dorene Rentz[3], Julie C Price[2], Keith A Johnson[2], Reisa A Sperling[1,3], Jasmeer P Chhatwal[1] and Aaron P Schultz[1]

Interactive Effects of Vascular, Amyloid and Tau



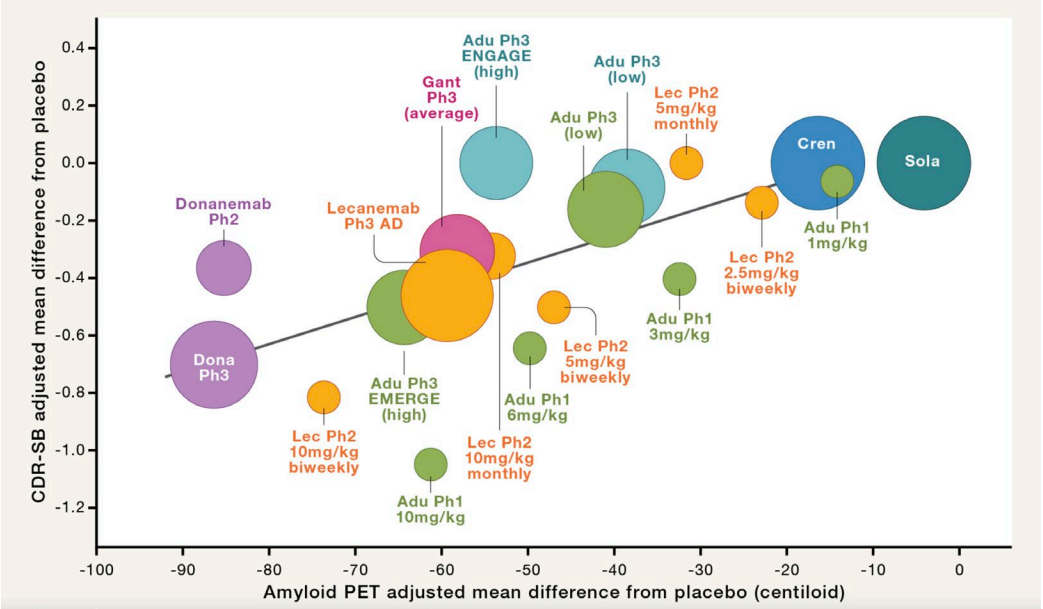
Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



Sperling, Jack, Aisen *Science Trans Med* 2011

Why have we finally succeeded (somewhat) in AD disease modifying therapeutic trials?

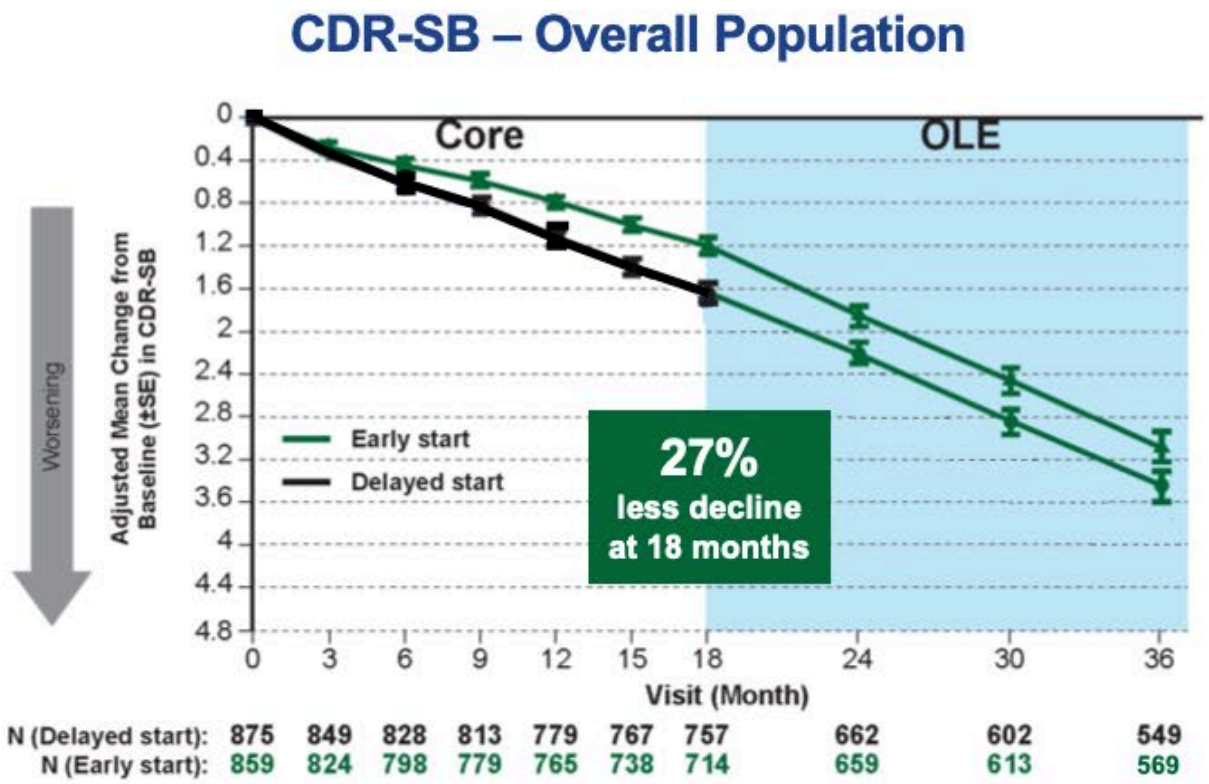
- Defining population with target pathology
- Aggressive reduction of amyloid PET below baseline down into “amyloid negative” range
- Moving earlier in the clinical spectrum to MCI/mild dementia
- Greater clinical benefit observed in subgroups with lower levels of AD pathology

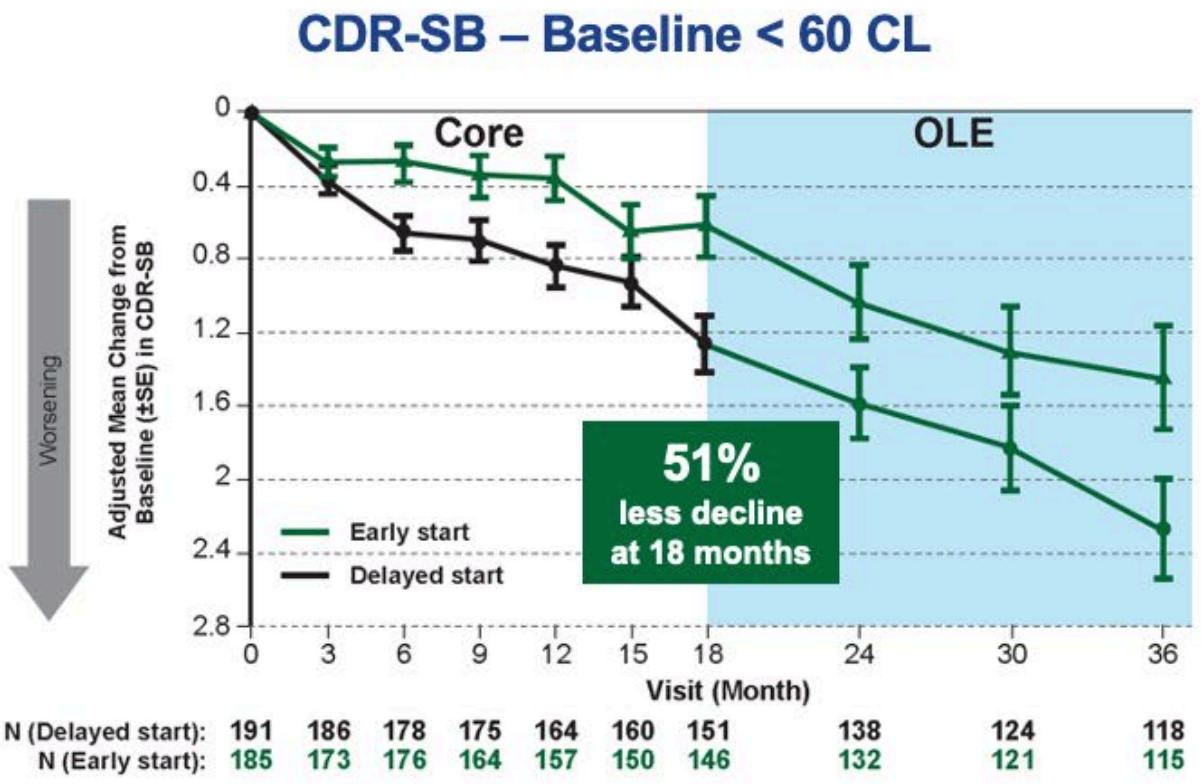


Boxer A and Sperling R *Cell* 2023

Phase 3 Lecanemab Clinical Outcomes Through 36 Month OLE

Lower Baseline Amyloid Group Shows Greater Continued Benefit





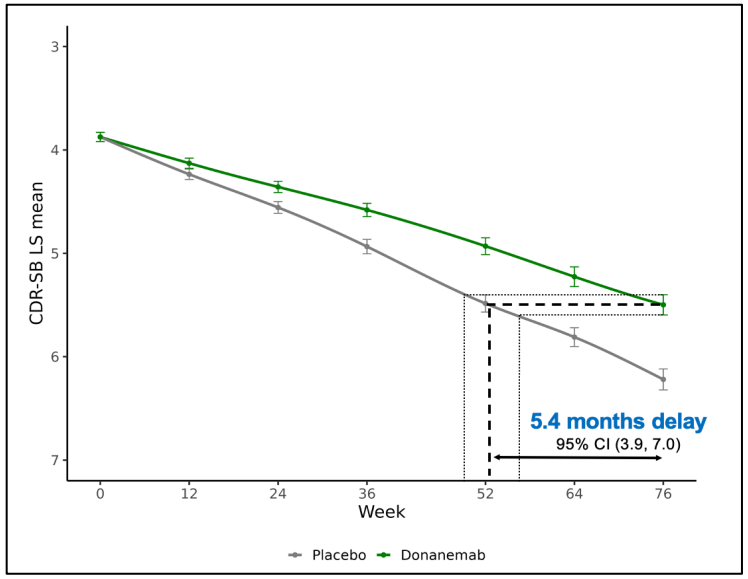
Presented at CTAD 2024

OLE includes those participants on subcutaneous and intravenous formulations.

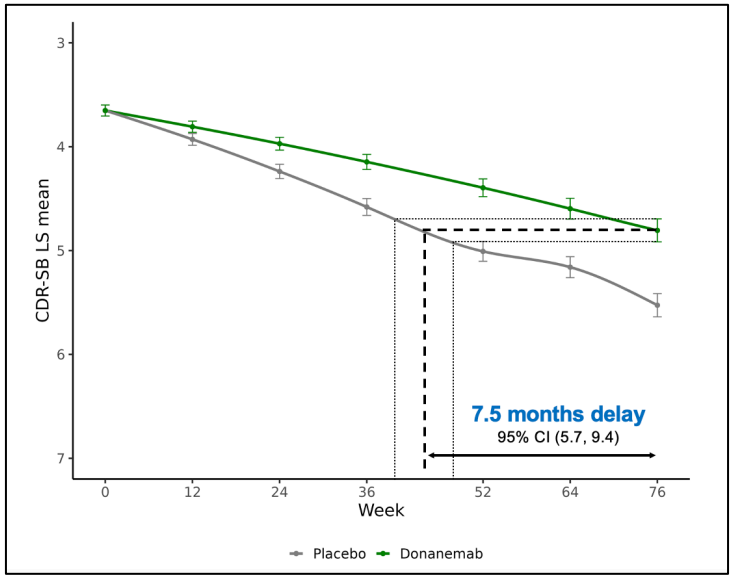
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. CL, Centiloid. OLE, open-label extension. SE, standard error.

Phase 3 Donanemab -
Lower Baseline Tau Associated with Greater Clinical Benefit

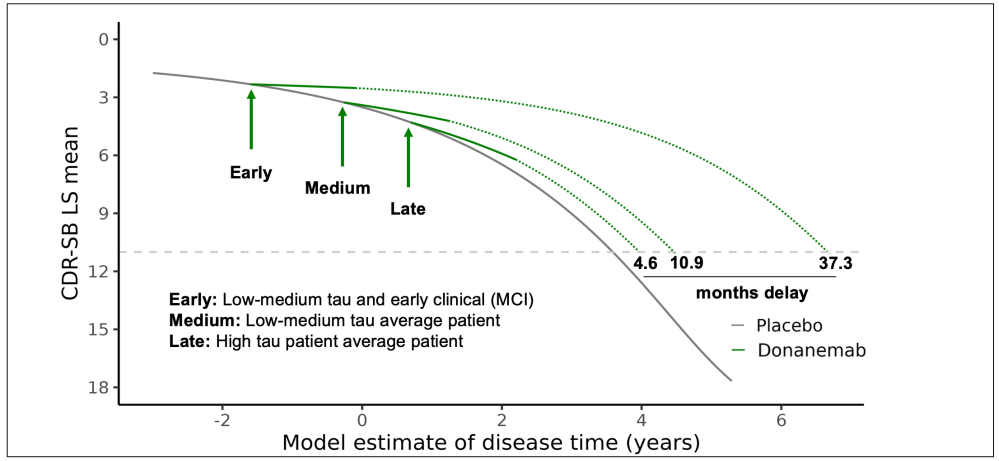
CDR-SB
Overall Population



CDR-SB
Low-Med Tau Population



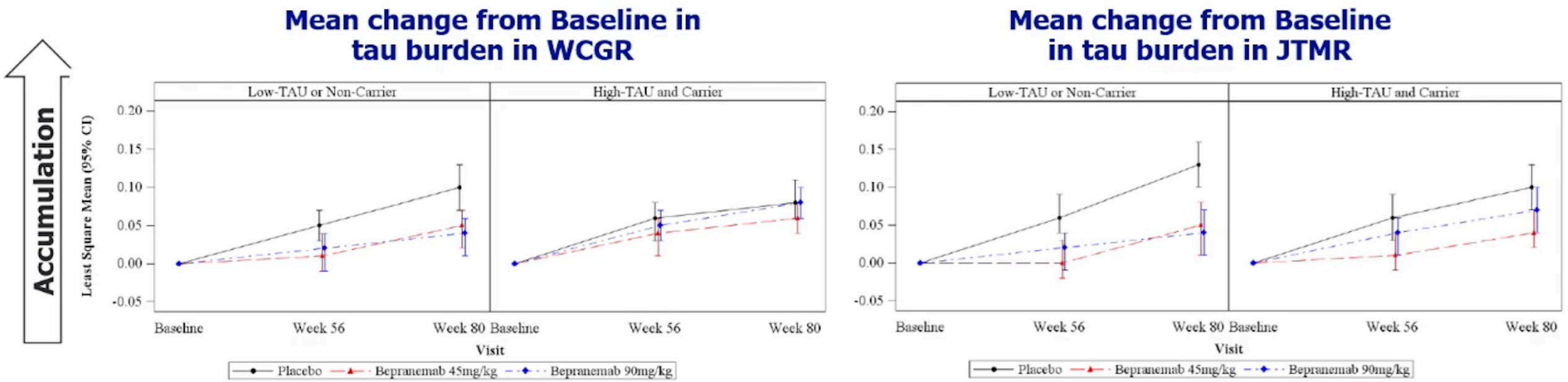
CDR-SB
Earlier Intervention
Extrapolation Model

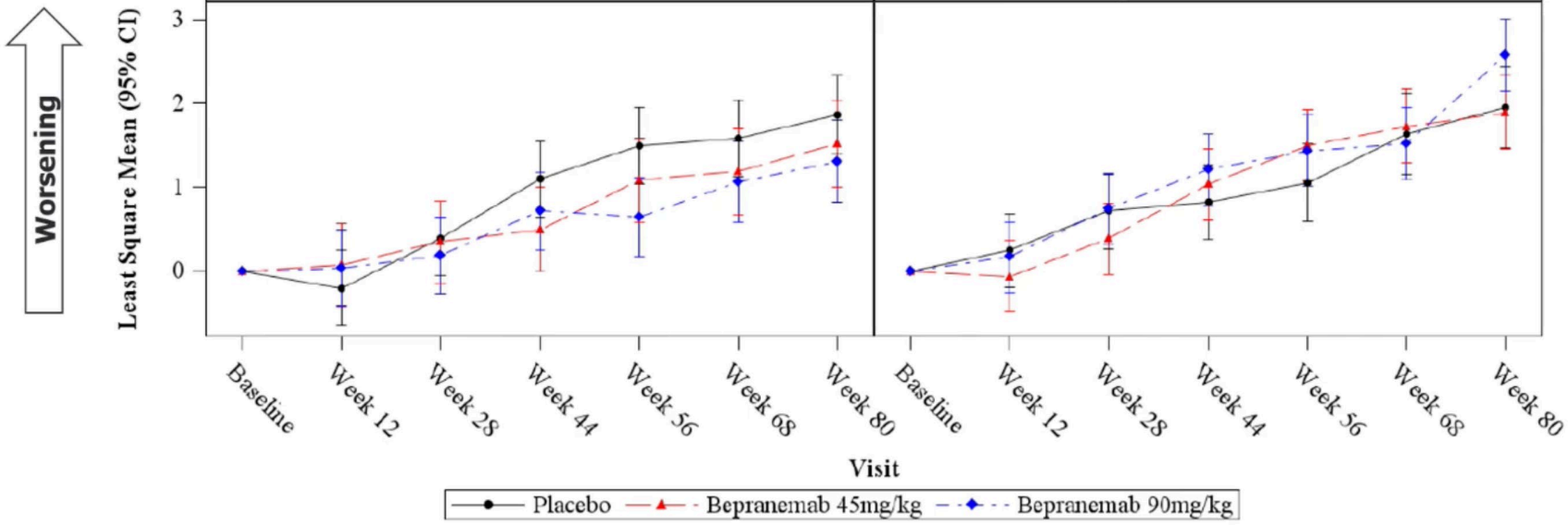


Proportional time slowing PMRM analysis
Error bars indicate +/- 1 standard error
PMRM = Progression Model for Repeated Measures, CI = Confidence Interval

Sperling R Presented at FDA Advisory Meeting June 2024

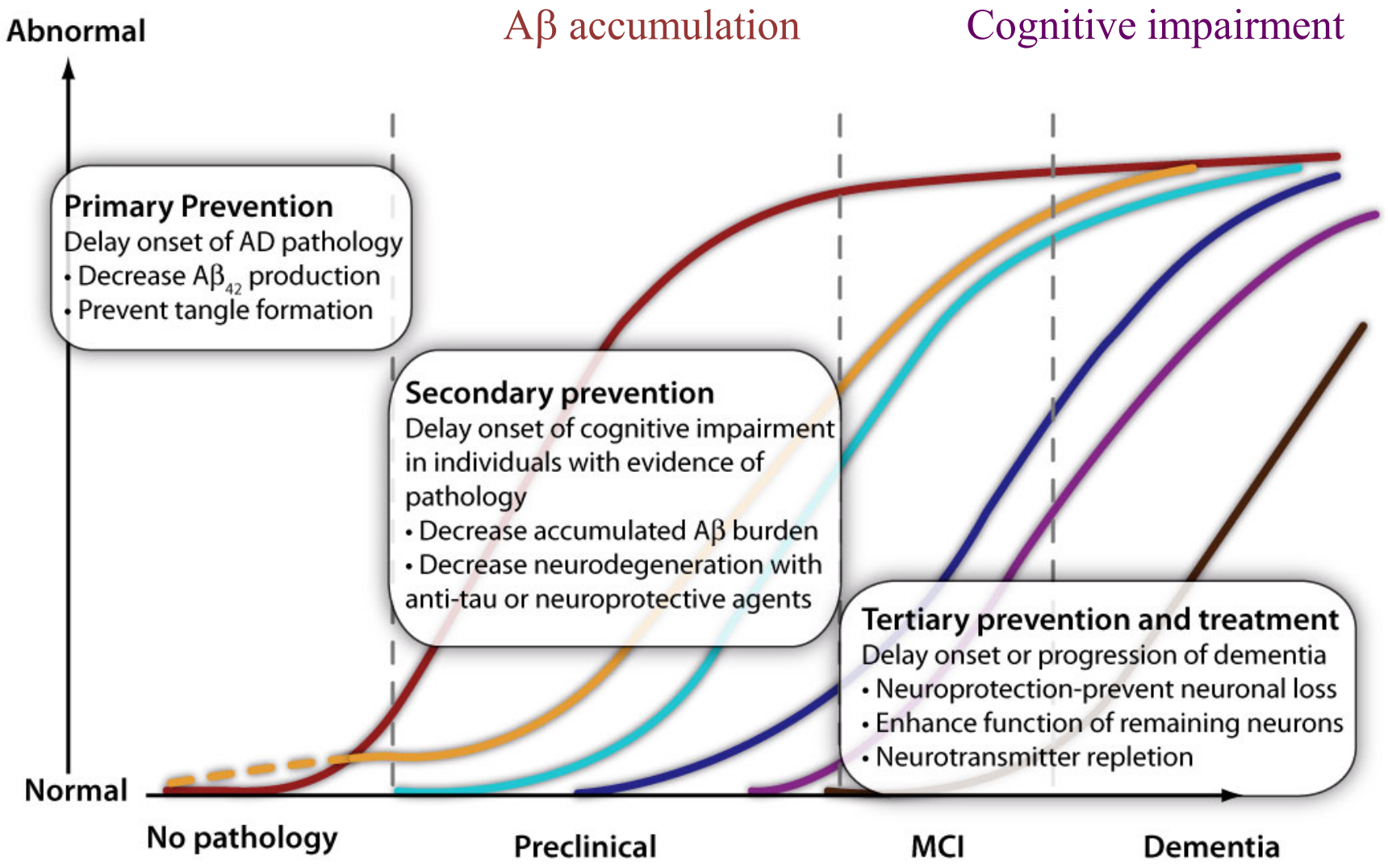
Bepranemab (anti-Tau Antibody) Phase 2





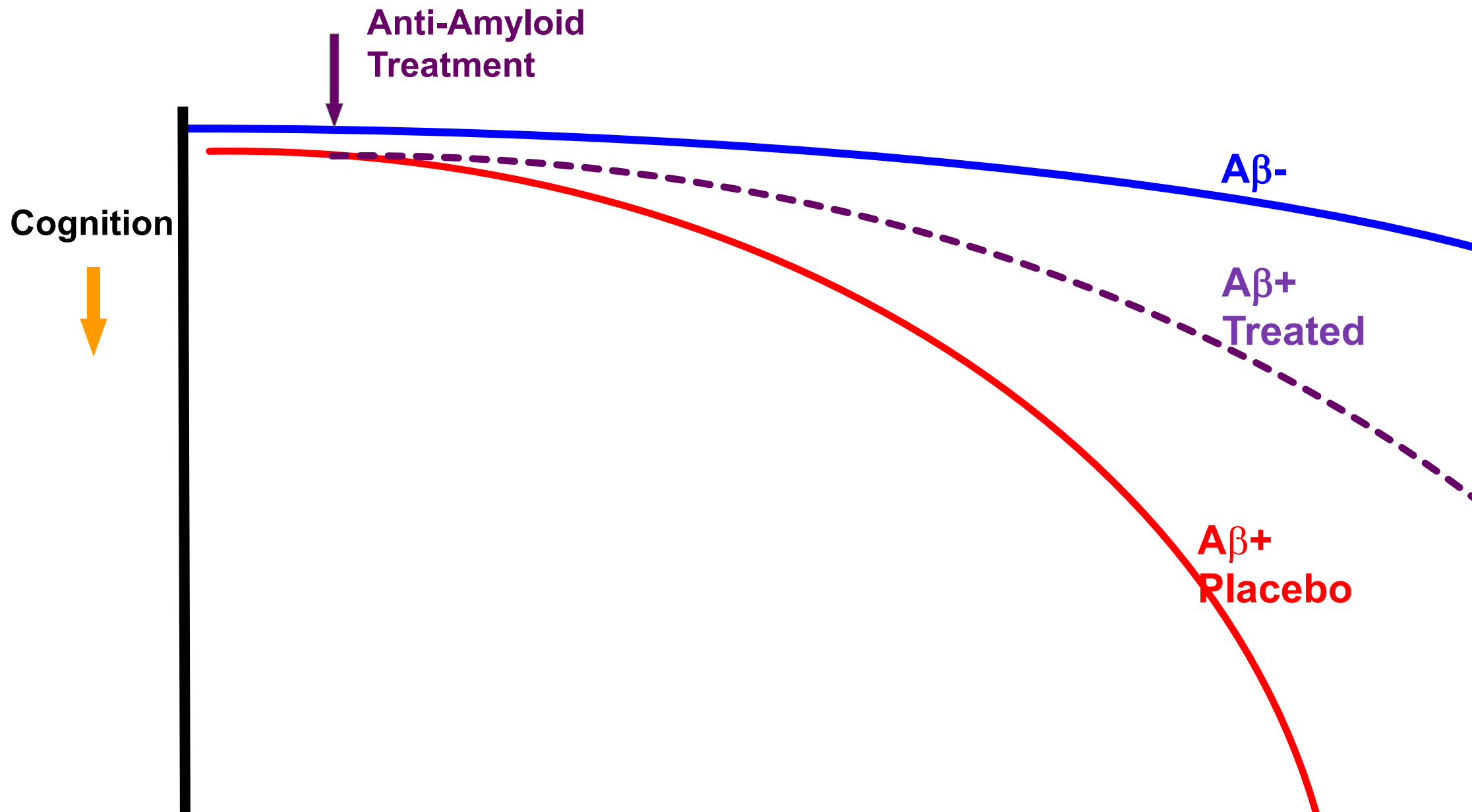
UCB Presented at CTAD 2024

Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease

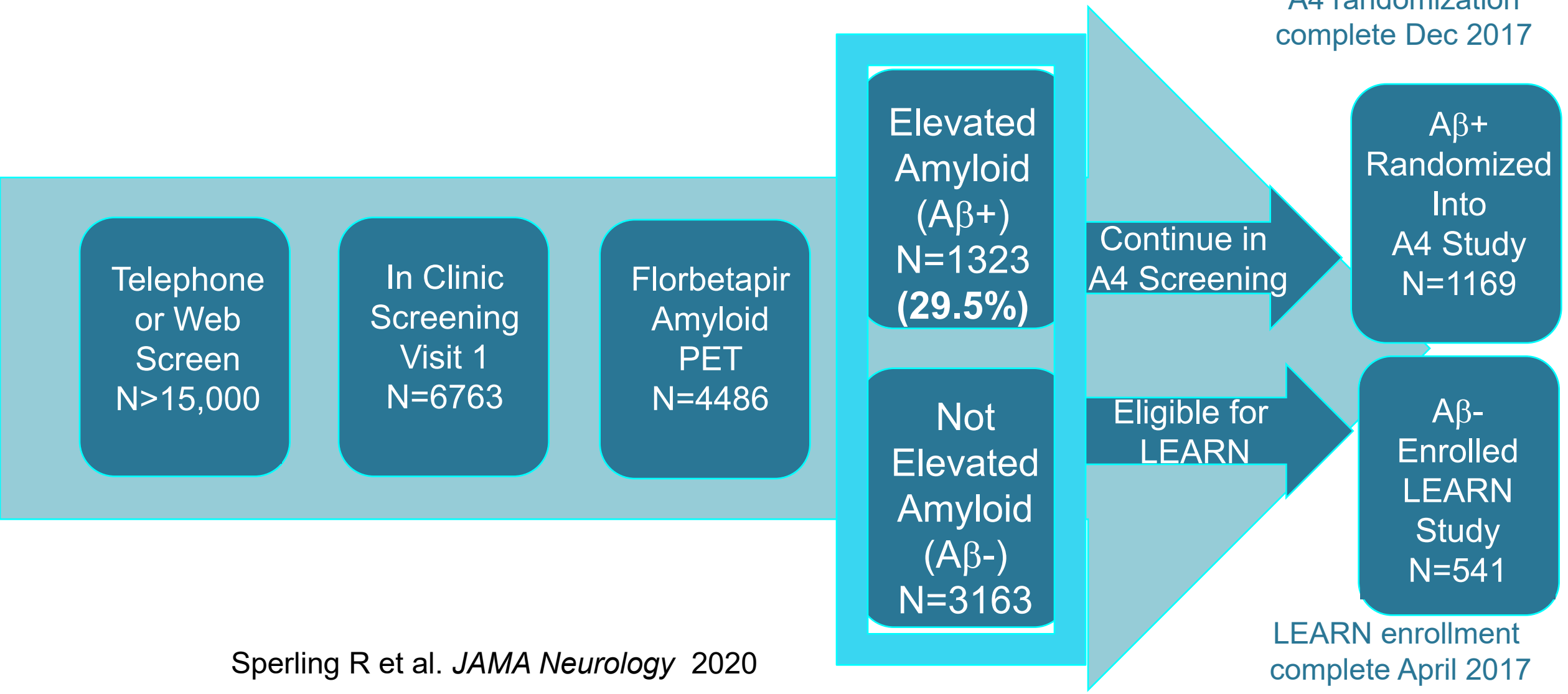


Sperling, Jack, Aisen *Science Trans Med* 2011

Secondary Prevention Trials in Preclinical AD



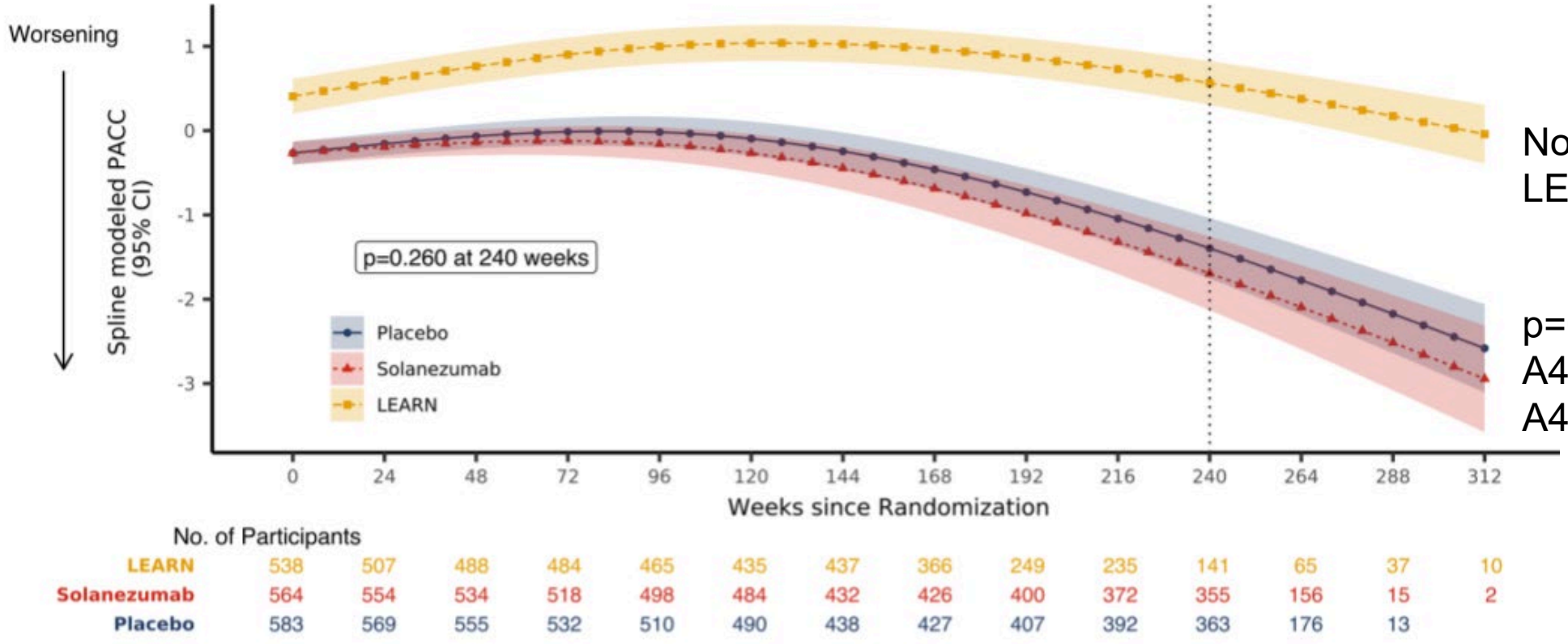
A4 Screening Results



Sperling R et al. *JAMA Neurology* 2020

No treatment difference on cognitive decline in A4
No cognitive decline observed in LEARN (Amyloid negative)

Preclinical Alzheimer Cognitive Composite (PACC)



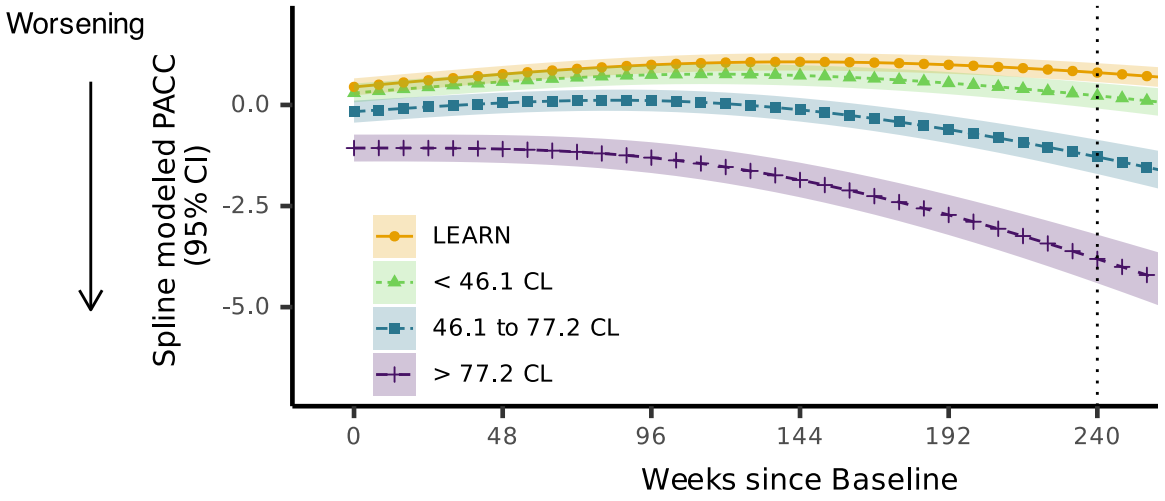
Nominal p<0.001
LEARN vs. A4 Placebo

p=0.26
A4 Solanezumab vs.
A4 Placebo

Mean (95% CI) derived from spline model of Preclinical Alzheimer's Cognitive Composite (PACC).

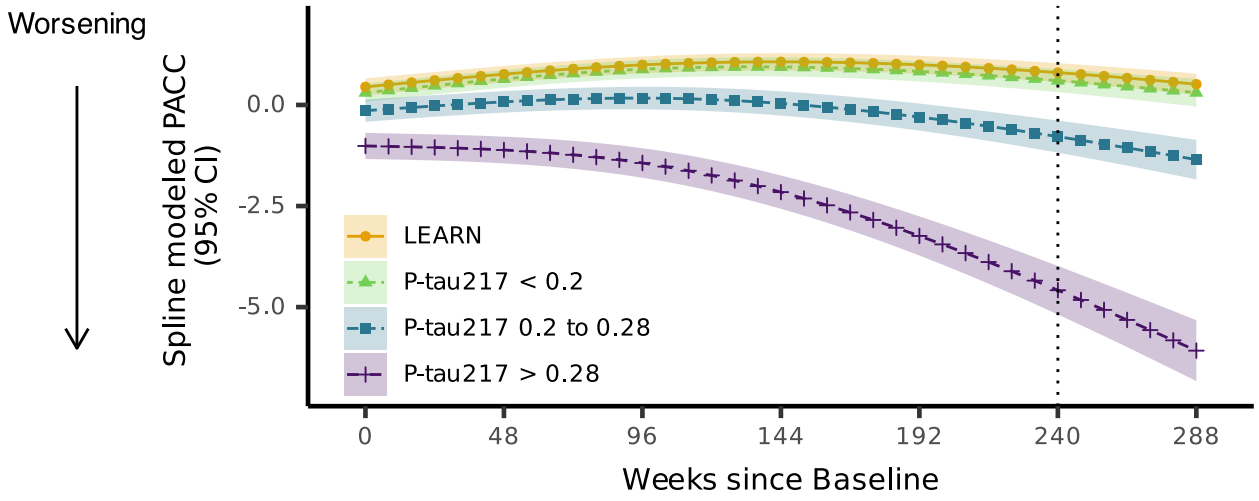
Sperling R et al *New England Journal of Medicine* 2023

Impact of Baseline Amyloid and Plasma P-tau217 on Cognition (PACC) Across LEARN and A4 Study



No. of Participants

> 77.2 CL	366	346	319	301	279	258
46.1 to 77.2 CL	405	392	363	336	318	299
< 46.1 CL	394	374	357	325	302	283
LEARN	553	511	489	458	342	313



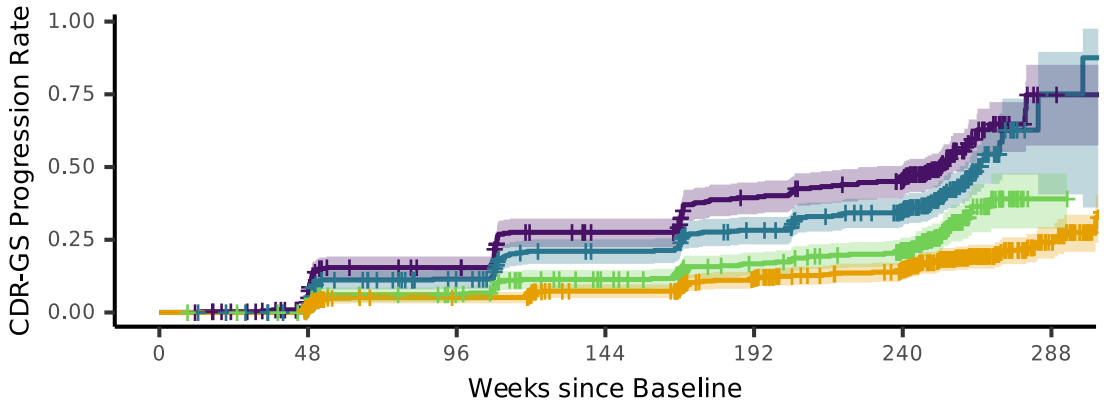
No. of Participants

P-tau217 > 0.28	372	358	337	316	291	264	35
P-tau217 0.2 to 0.28	374	359	332	306	287	271	39
P-tau217 < 0.2	373	360	337	308	292	277	40
LEARN	553	511	489	458	342	313	206

Mean (95% CI) derived from spline model of Preclinical Alzheimer's Cognitive Composite (PACC).

Higher CDR-Global Progression Rate Predicted by Higher Baseline Amyloid PET or Plasma P-tau217

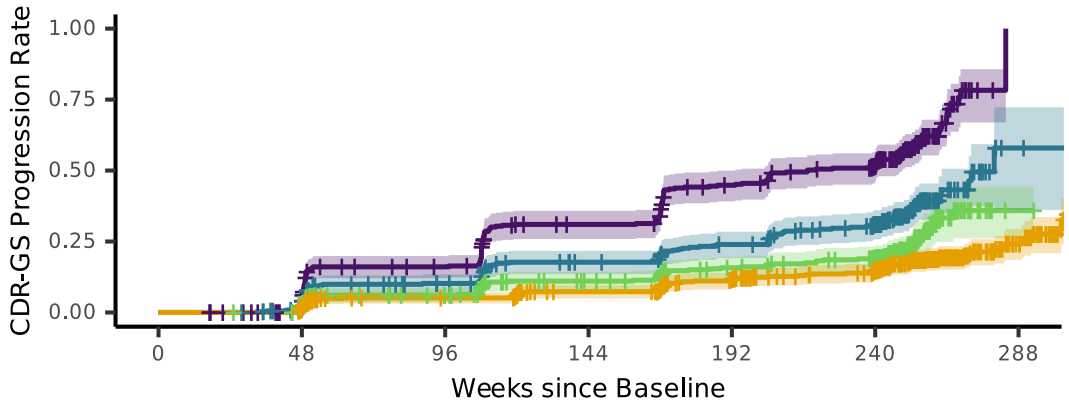
Baseline Amyloid PET



Number at risk

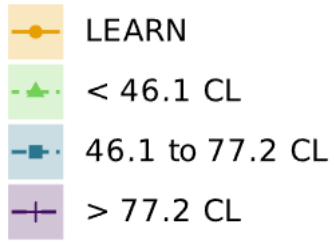
>77.2 CL	348	320	269	218	175	147	2
46.1 to 77.2 CL	389	376	313	264	233	184	2
<46.1 CL	369	358	325	291	256	204	1
LEARN	506	492	442	399	334	282	72

Baseline Plasma P-tau 217

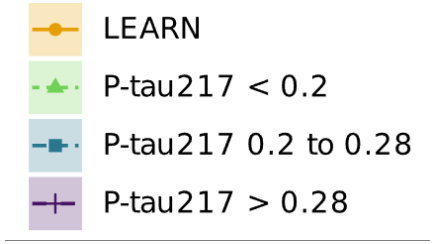


Number at risk

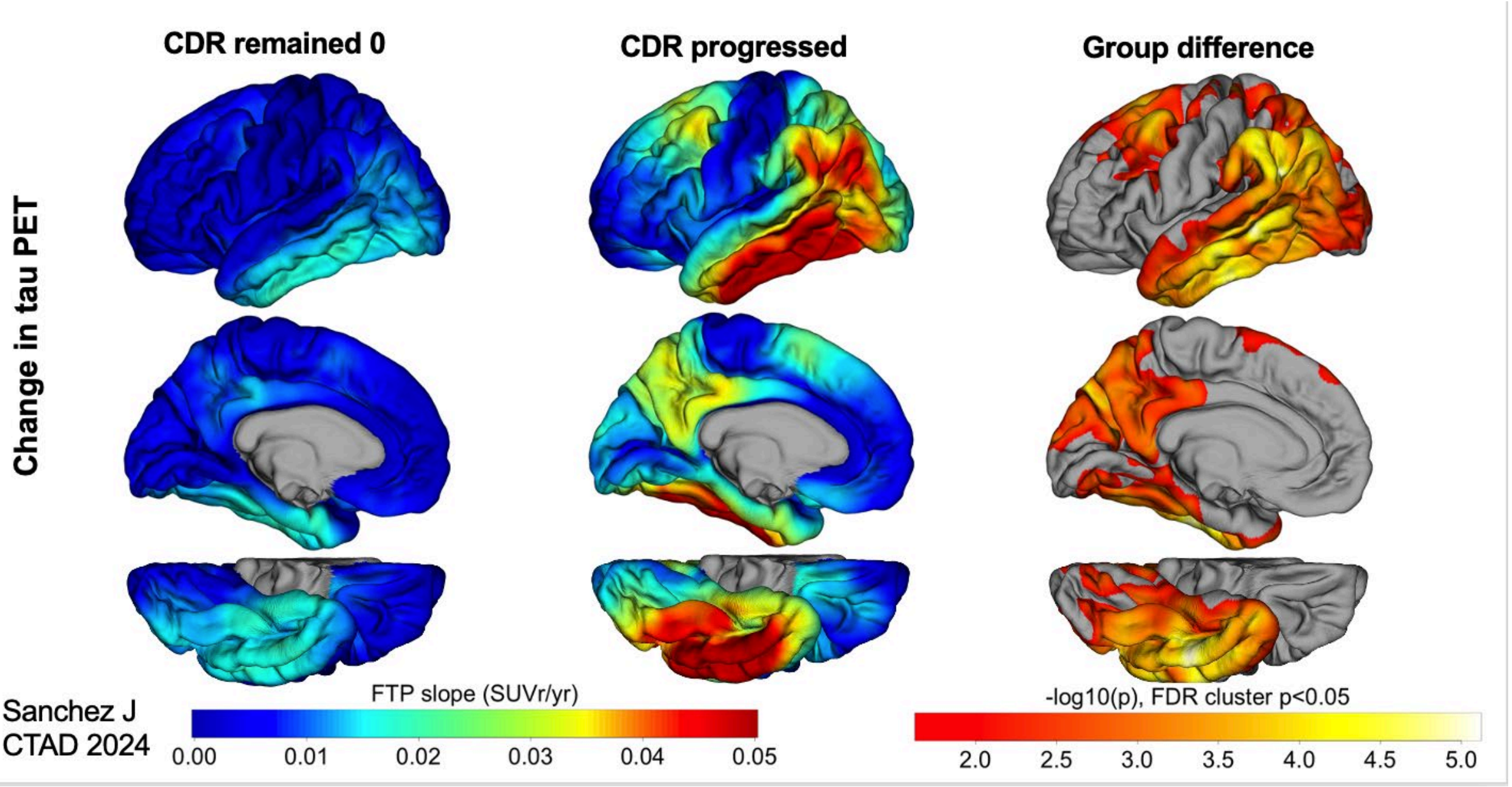
P-tau217 > 0.28	357	337	278	219	167	131	0
P-tau217 0.2 to 0.28	354	340	292	254	229	181	2
P-tau217 < 0.2	354	343	308	273	243	202	1
LEARN	506	492	442	399	334	282	72



More than 50% of people in highest levels of AD biomarker progressed to MCI or dementia within 5 years

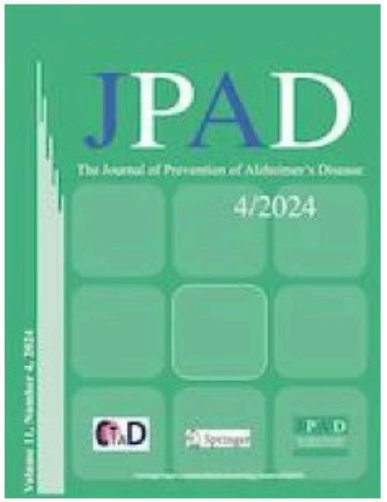


A4 Study – Increase in Tau PET with CDR Progression



Sanchez J
CTAD 2024

A4/LEARN Study
Full Longitudinal Dataset Available



Volume 11, Issue 4

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A4STUDYDATA.org

Introduction to the Special Issue on the A4 Study

Paul Aisen & R. Sperling

Data available via GRIP, Synapse, GAAIN and more

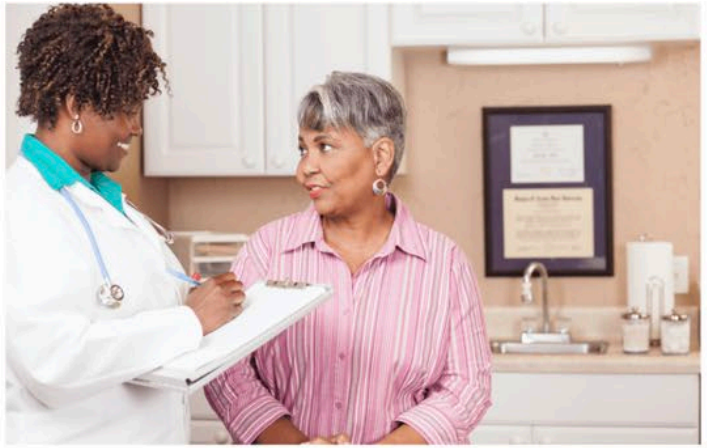
AHEAD STUDY

www.aheadstudy.org

The AHEAD Study

The AHEAD Study is testing whether an investigational treatment can lower people's risk of memory loss due to Alzheimer's disease.

View Participation Requirements



We are looking for people ages 55-80 who do not yet have symptoms of Alzheimer's disease, but who are interested in participating in clinical trials aiming to help prevent memory problems in the future. You can answer a few short questions to learn if you may be eligible to participate in the AHEAD Study.

Join the Study

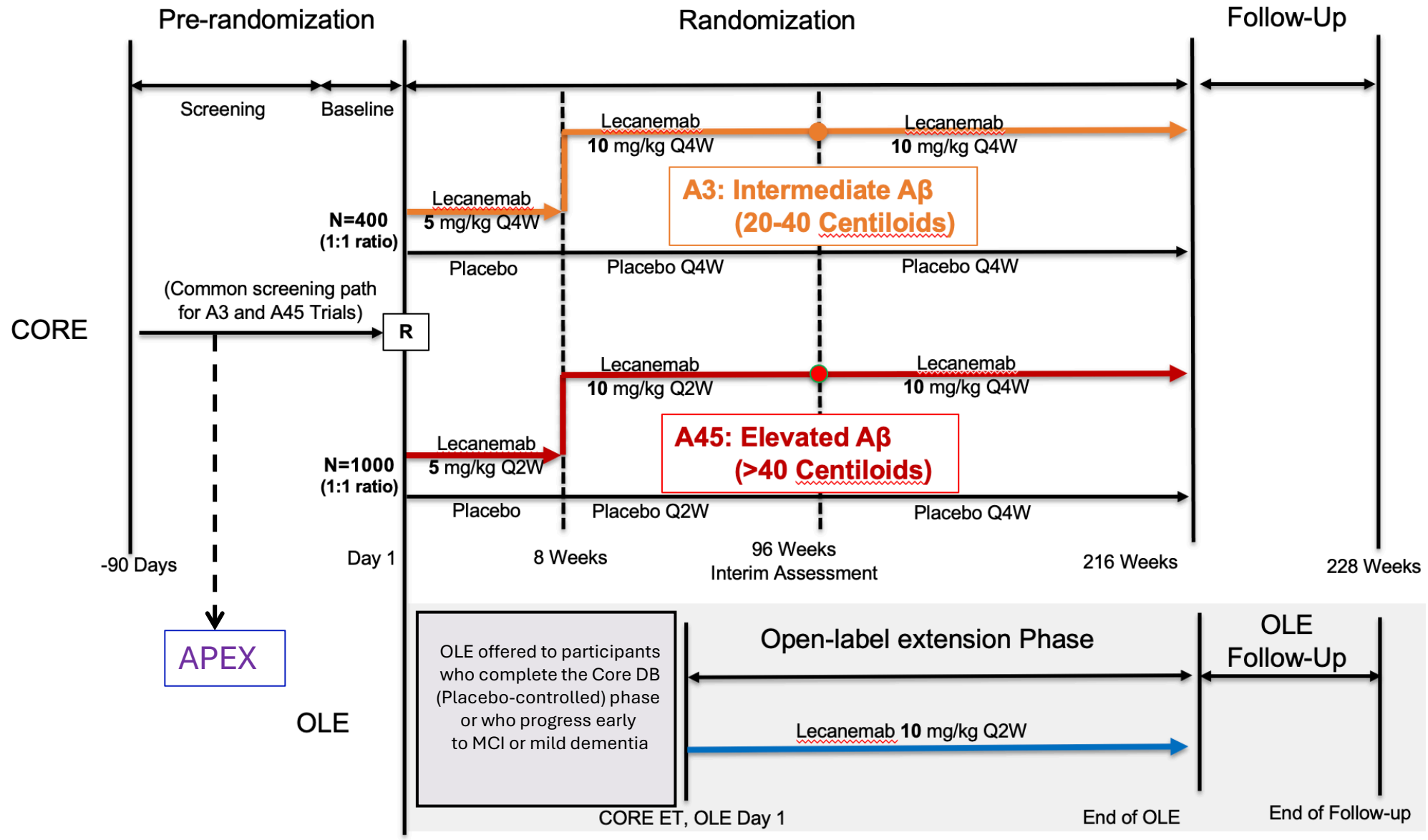
AHEAD 3-45 Design Overview

- AHEAD 3-45 Study is composed of two sister trials spanning the continuum of early-late preclinical AD
- AHEAD Study testing targeted dosing of lecanemab, a monoclonal antibody targeting protofibrillar forms of Aβ, on the basis of screening amyloid PET level

- **A3 – Intermediate amyloid (20-40 centiloids) aimed at slowing Aβ accumulation (N=448)**
  - 4 year Phase 2 trial – 10mg/kg monthly lecanemab (n=200/arm)
  - Amyloid PET primary outcome – Tau PET key secondary
  - Cognition exploratory (PACC-5 and C3)

- **A45 – Elevated amyloid (>40 centiloids) aimed at preventing cognitive decline (N=1173)**
  - 4 year Phase 3 trial – 10mg/kg lecanemab biweekly then monthly maintenance (n=500/arm)
  - Cognitive primary outcome (PACC-5)
  - Amyloid and Tau PET key secondary (potential interim for accelerated approval)
  - Additional cognitive, participant reported, plasma and CSF biomarker outcomes

AHEAD 3-45 Study Design

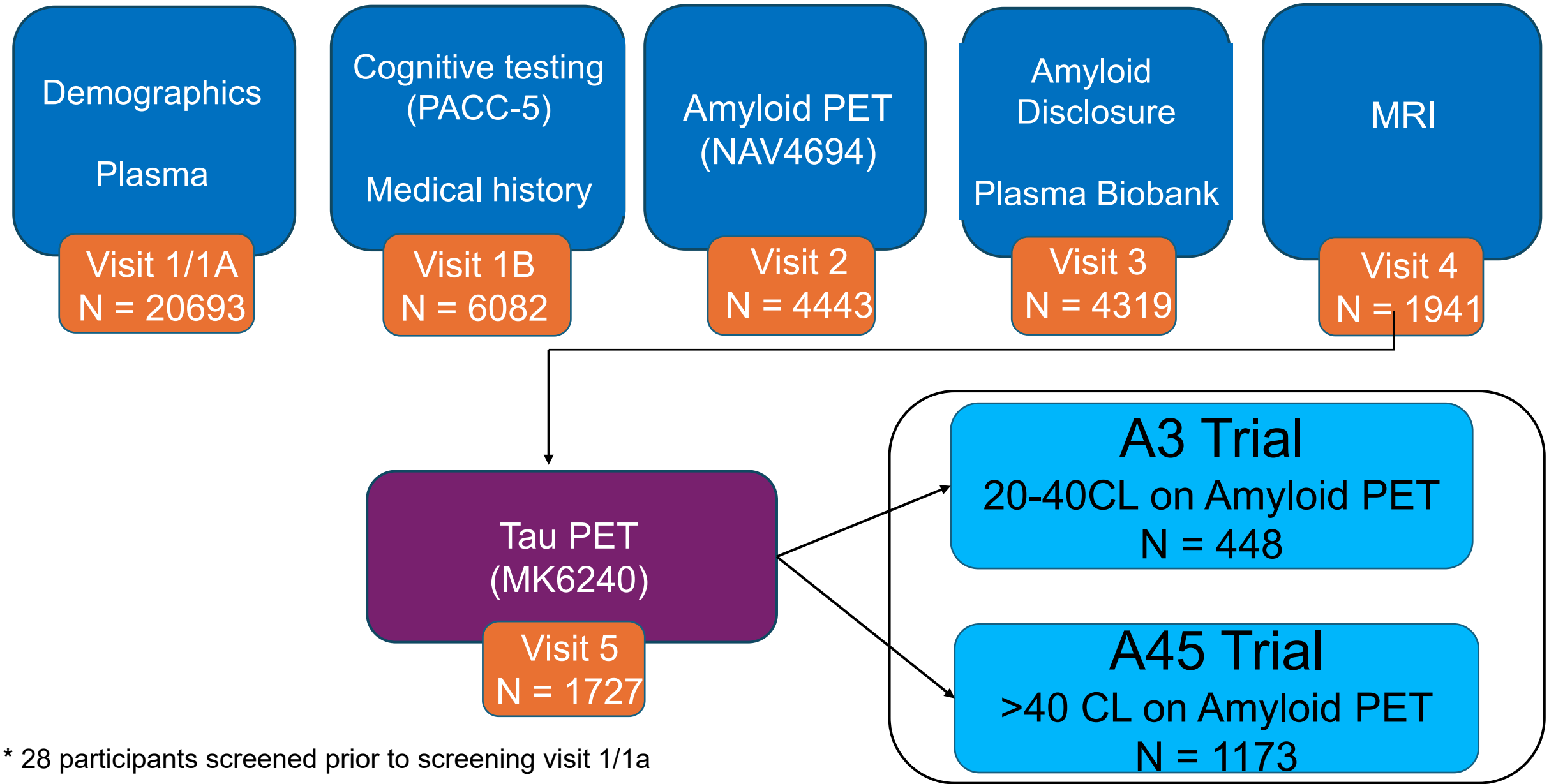


AHEAD 3-45 Participant Characteristics

Characteristics	Screened Participants (N=20721)	Randomized Participants	
		A3 (N=448)	A45 (N=1173)
Age in years, Mean (SD)	68.3 (6.3)	68.3 (5.4)	70.6 (5.3)
Female Sex, n (%)	13007 (62.9%)	293 (65.5%)	752 (64.1%)
Education in years, Mean (SD)	15.8 (3.1)	16.1 (2.9)	16.3 (2.9)
Family history of dementia, n (%)	4524/6021 (75.1%)	361 (80.9%)	946 (81.3%)
APOE ε4 carriers, n (%)	7335/20130 (36.4%)	322 (71.9%)	862 (73.5%)
MMSE	28.4 (1.7)	29.0 (1.1)	28.6 (1.6)
Race and Ethnic Underrepresented Groups (URG - North America only)	4534 (26.9%)	57 (15.2%)	108 (11.0%)

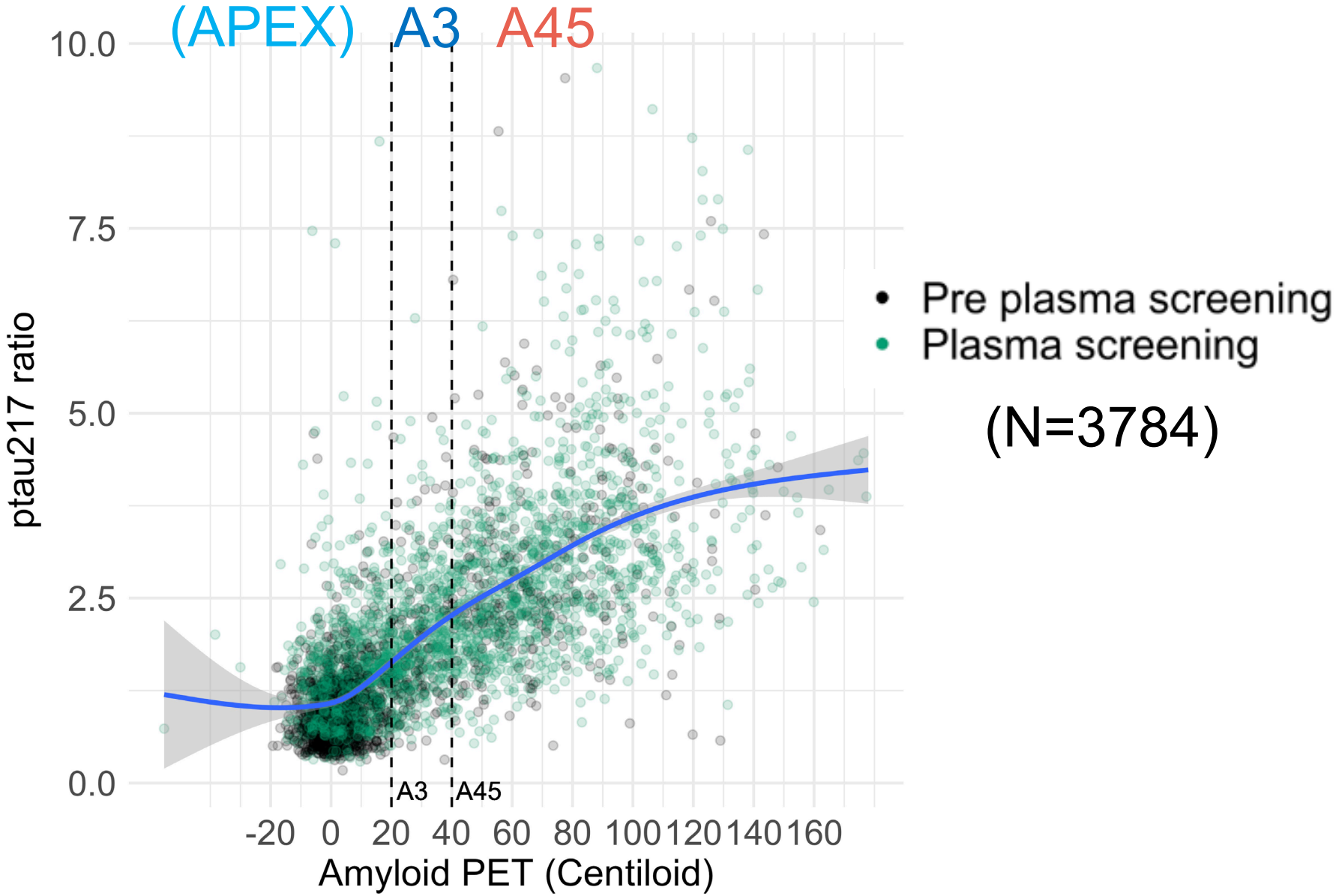
AHEAD 3-45 Study: Shared screening platform

Total consent N = 20721*



* 28 participants screened prior to screening visit 1/1a

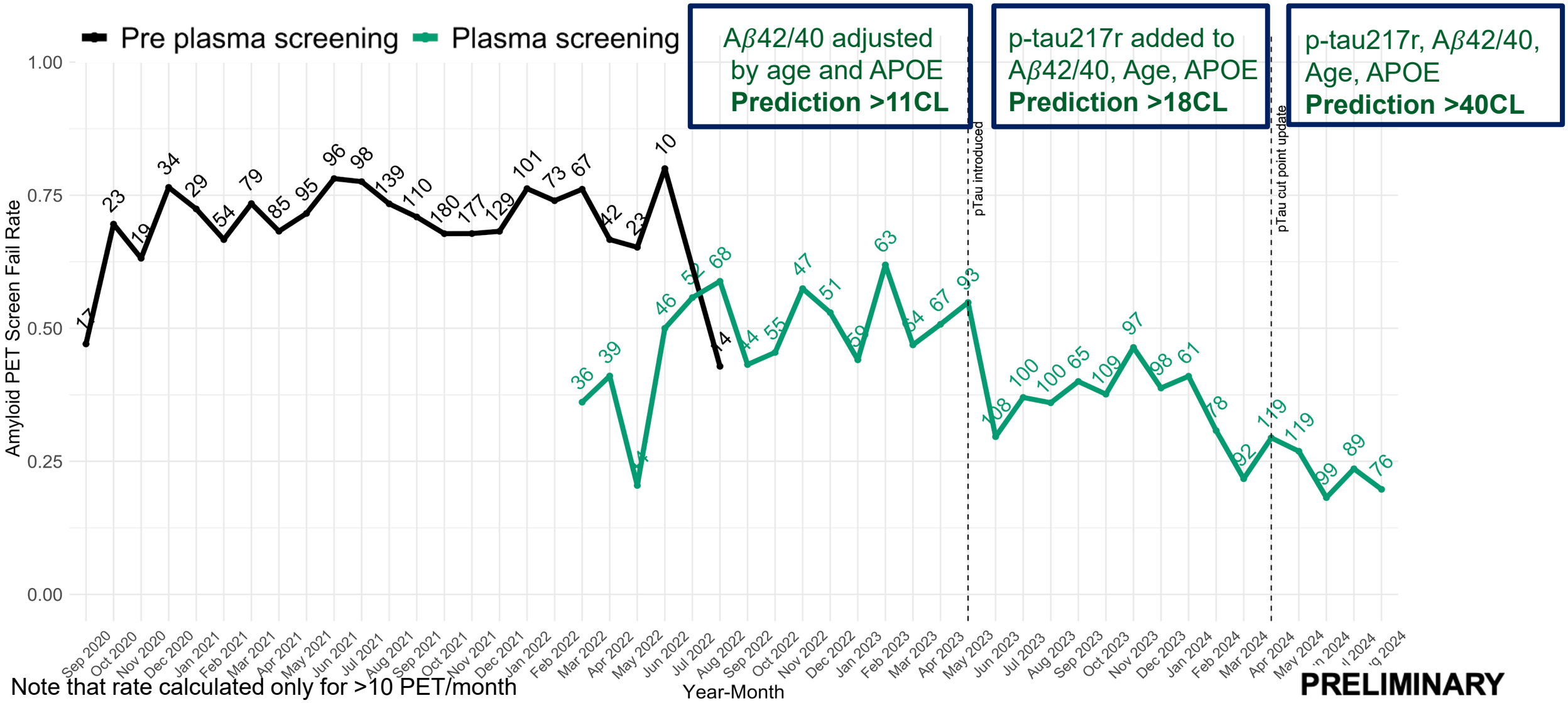
Plasma Screening vs. Amyloid PET in AHEAD 3-45 Study



ACTC Biostats-Oliver Langford

PRELIMINARY

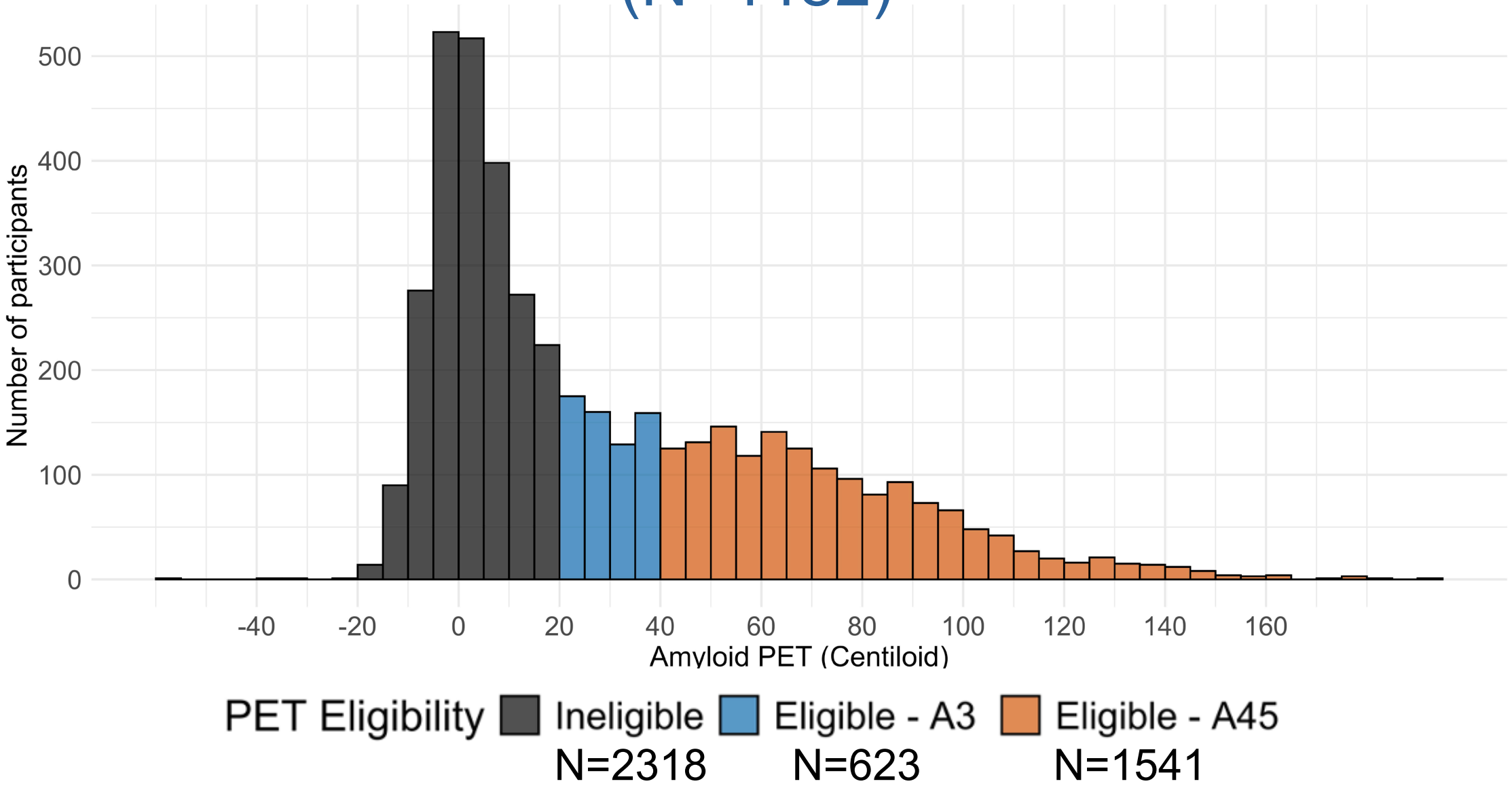
Minimizing screening ineligibility on PET – Introduction of plasma algorithms in AHEAD



Note that rate calculated only for >10 PET/month

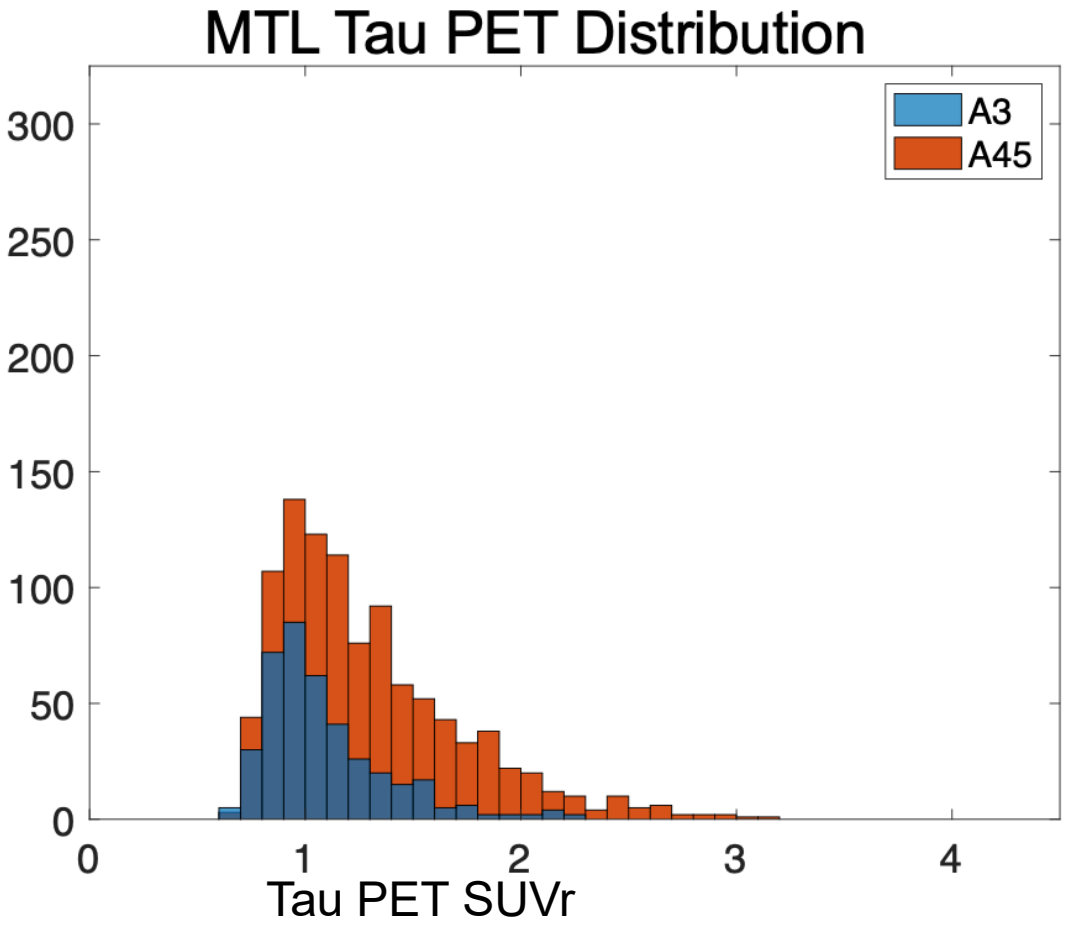
PRELIMINARY

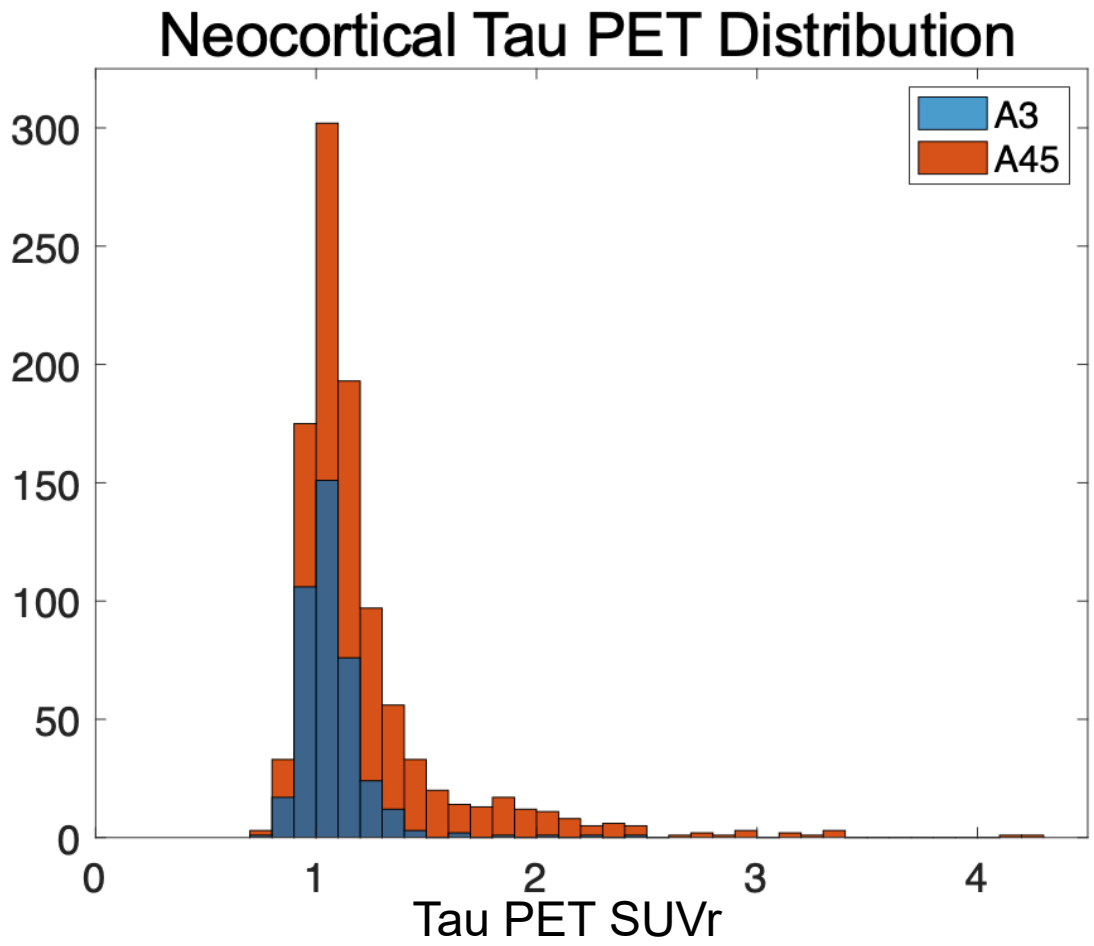
Frequency Distribution of Amyloid CL by PET Eligibility (N=4482)



PRELIMINARY

Tau PET Pre-Randomization Data in A3 and A45 MTL and Neocortical SUVr Distribution

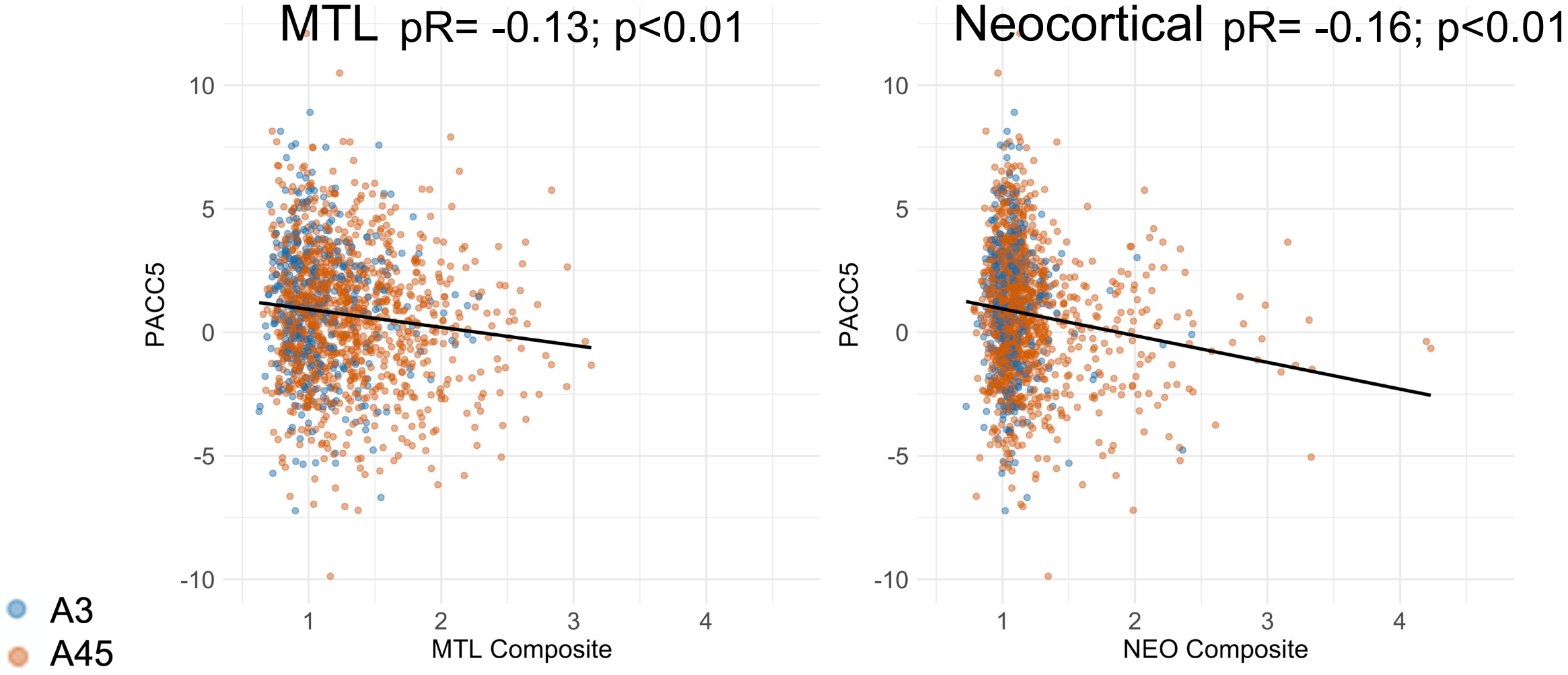




A3 N=429
A45 N=1106

PRELIMINARY

MTL and Neocortical Tau PET Associated with Cross-Sectional Screening Cognition (PACC-5)

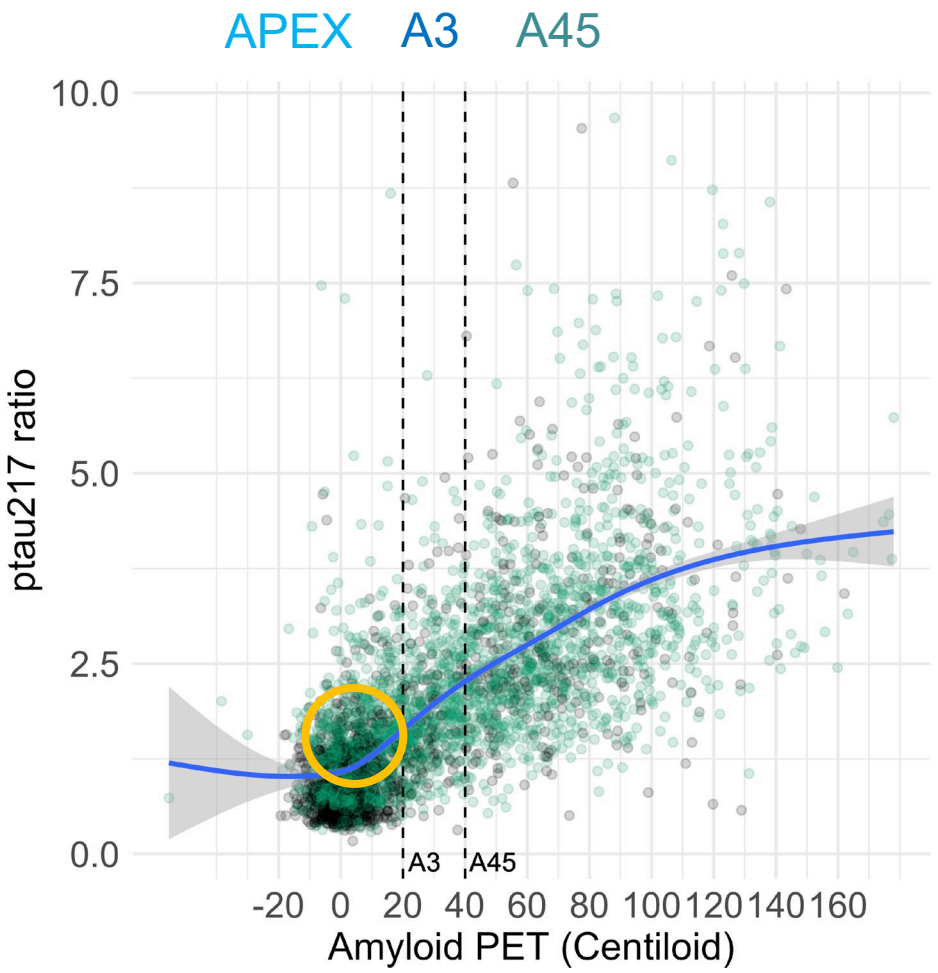


N=1531 pR: partial correlation adjusting for Age, Sex and Education **PRELIMINARY**

Where do we go from here?
Getting Closer to Primary Prevention – "A2…A1"

- Validate algorithms for predicting risk of future Aβ accumulation
  - Age x APOE x plasma p-tau217 levels
- Build large trial ready cohorts
  - Plasma AD biomarkers, remote cognitive testing, digital monitoring
  - Measure proteomics (vascular integrity, co-pathologies, synaptic markers)
- Design trials for active immunization (vaccines), intermittent passive immunization (antibodies) and/or oral agents
  - Primary outcome - ? Longitudinal amyloid PET vs. blood tests alone?
  - Smart phone cognitive testing - assess earliest changes in learning/memory
- Design combination trials that will simultaneously decrease amyloid accumulation, reduce vascular risk and build brain resilience

How early do blood tests begin to change in preclinical AD?



AHEAD 3-45 Screens (N=3748)

- Blood test abnormalities detectable prior to intermediate levels (<20CL) on amyloid PET

- The Alzheimer Plasma EXtension (APEX) Study is enrolling people who screen-failed for AHEAD to predict who will become amyloid + and validate longitudinal plasma outcomes for future prevention trials

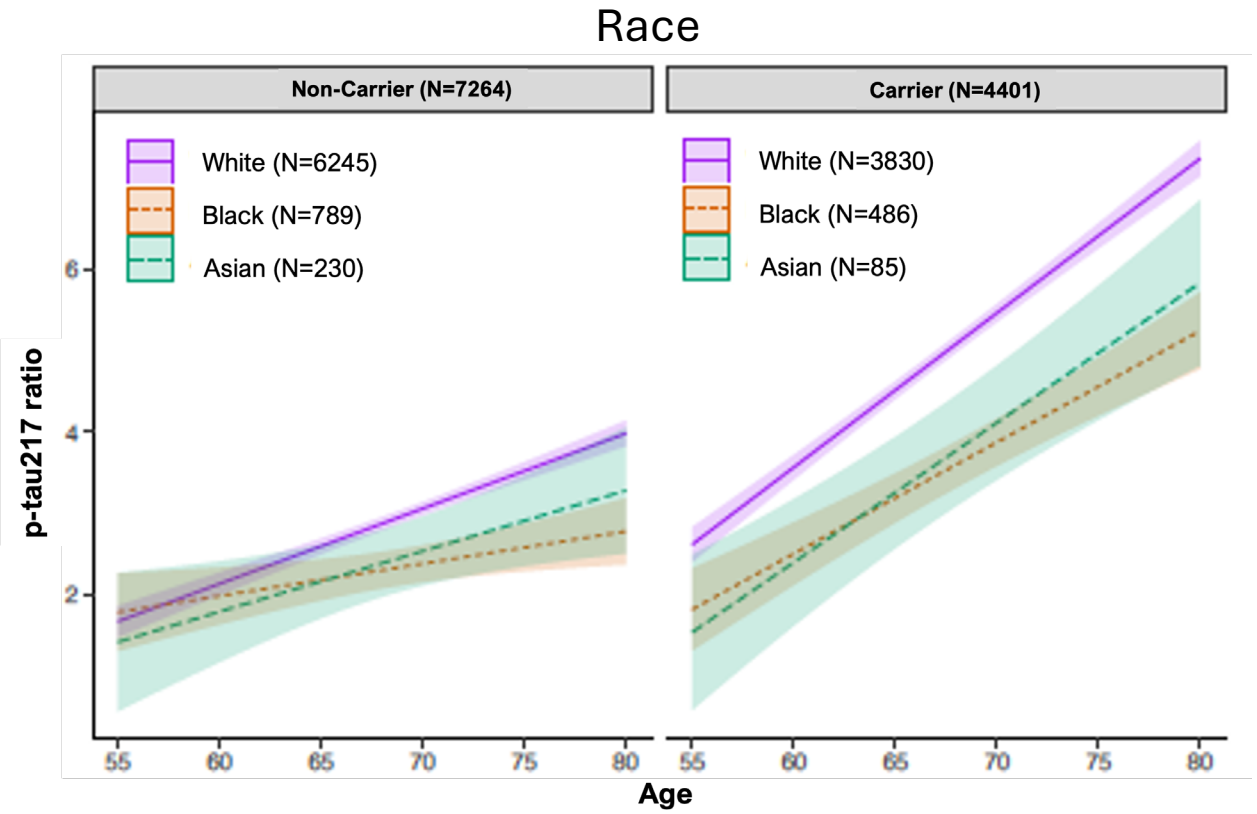
- APEX will run as a comparison arm in parallel with the A3 and A45 treatment and placebo arms of the AHEAD Study

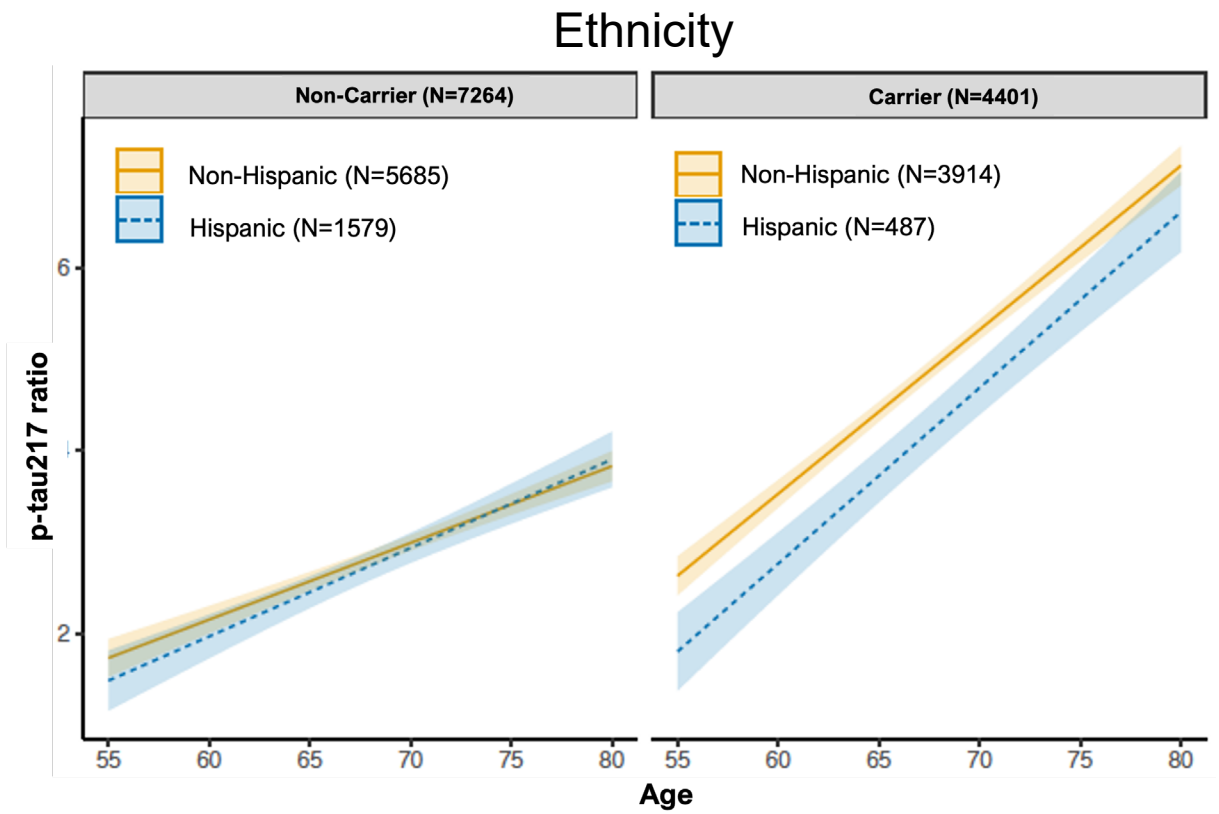
- APEX sets the stage for “A2…A1” prevention trials to ultimately prevent people from becoming amyloid positive altogether

Gaps in Knowledge

- Need more data in representative cohorts
  - Thus far, biomarker thresholds operate consistently across groups to predict amyloid PET (Molina-Henry Alz & Dem 2024; JPAD 2024)
  - Consistent evidence of lower prevalence of amyloid across plasma, CSF, PET and autopsy in Black/AA, Asians. Less clear among Latina/Hispanics.
- "Apparent paradox" of lower biomarker prevalence with increased risk of cognitive decline and dementia in URG
  - Potential explanations include higher inflammatory state that might favor amyloid clearance but increase future synaptic vulnerability
- Likely that multiple processes contribute to cognitive decline in diverse communities
  - Need to understand contributions of social determinants of health, comorbidities (e.g. vascular), continuing biases in testing and diagnoses

AD Biomarkers Across Race and Ethnicity by Age by APOE (N=11,665)



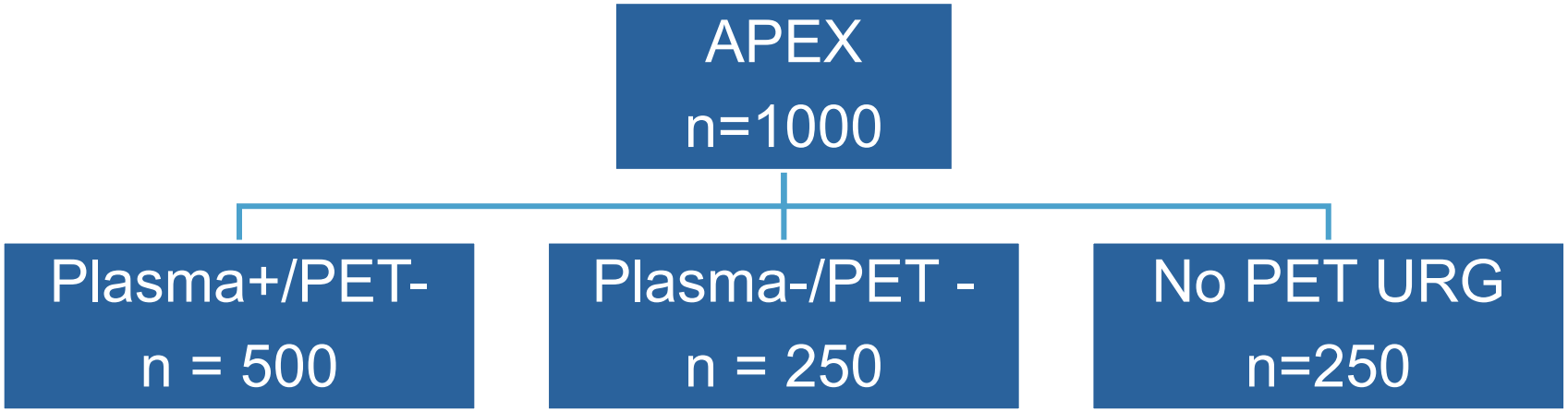


Doris Molina-Henry HAI 2025

AD biomarkers increase with age, particularly among APOE4 carriers. Black/AA, Asian, and Hispanic/Latina participants show later age increases in AD biomarkers

APEX Study Design – Phase I

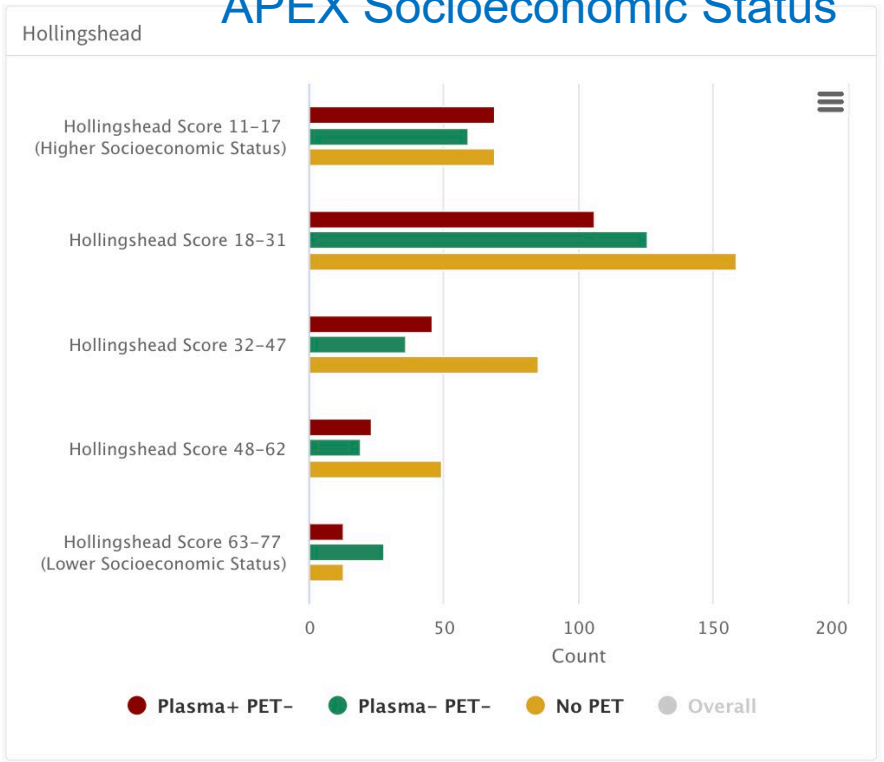
- Enrolling 1000 cognitively unimpaired individuals who were found to be amyloid ineligible (<20CL) screening for the AHEAD 3-45 Study
- 55 sites across US (hoping to expand internationally!)
- Annual plasma samples, cognitive and functional assessments
- Amyloid PET and MRI at 4 years

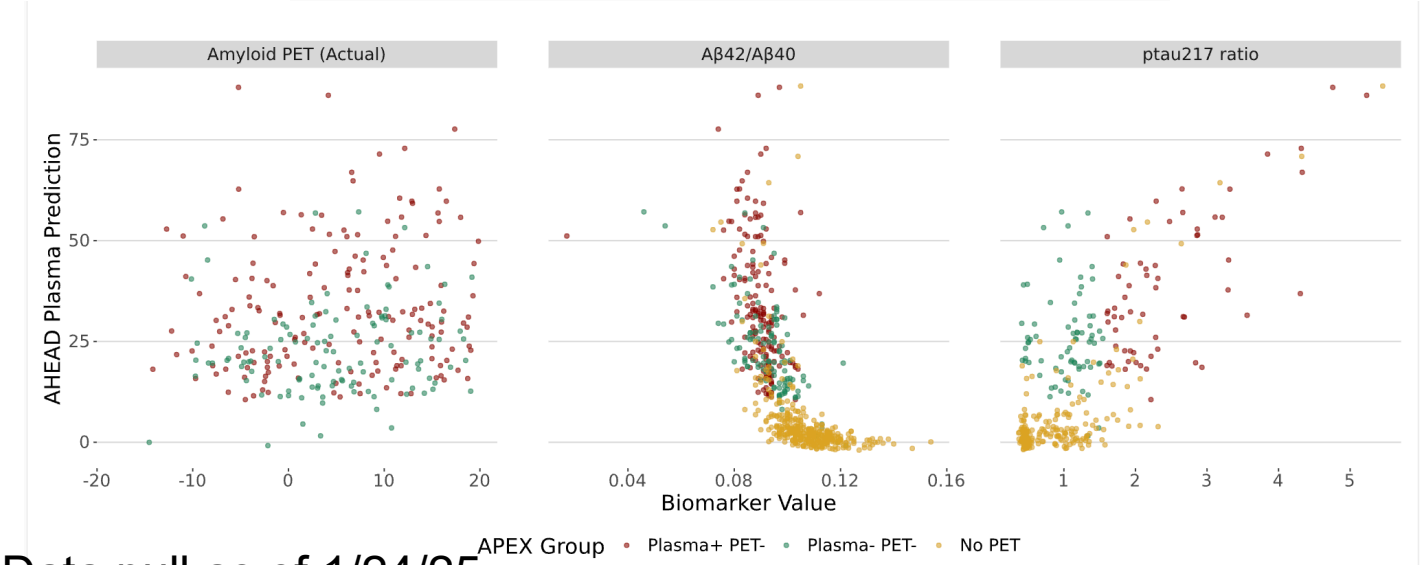


- Oversampling from race-ethnic underrepresented groups (URG) in AD research, including URG who screen-failed prior to PET (Baseline PET for these participants being funded by GHR and Alz Assoc)

	APEX (N=901)
Age	
-Mean (SD)	68.2 (6.2)
Sex	
-Female	583 (64.7%)
Education (years)	
Mean (SD)	16.1 (3.1)
Race	
American Indian or Alaska Native	3 (0.3%)
Asian	64 (7.1%)
Black or African American	173 (19.2%)
More than one race	50 (5.6%)
Native Hawaiian or Other Pacific Islander	4 (0.4%)
Other	24 (2.7%)
Unknown or Not Reported	7 (0.8%)
White	576 (63.9%)
Ethnic group	
Hispanic or Latino	221 (24.5%)
Not Hispanic or Latino	680 (75.5%)
RE-URG	
- Non-URG	349 (38.7%)
- URG	516 (57.3%)

APEX Socioeconomic Status



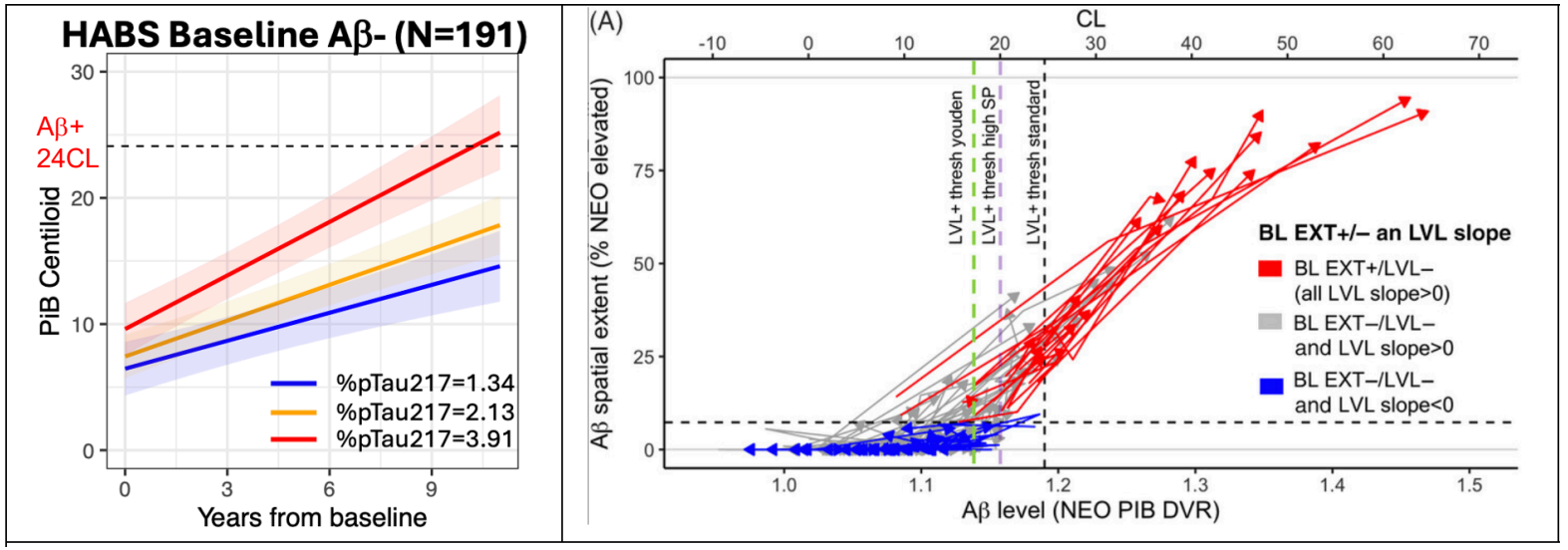


Race and/or Ethnic URG Enrollment =(56.3%) Data pull as of 1/24/25

Predicting Future "Amyloid Positivity"
Preliminary Data from Harvard Aging Brain Study and LEARN Study

HARVARD AGING BRAIN

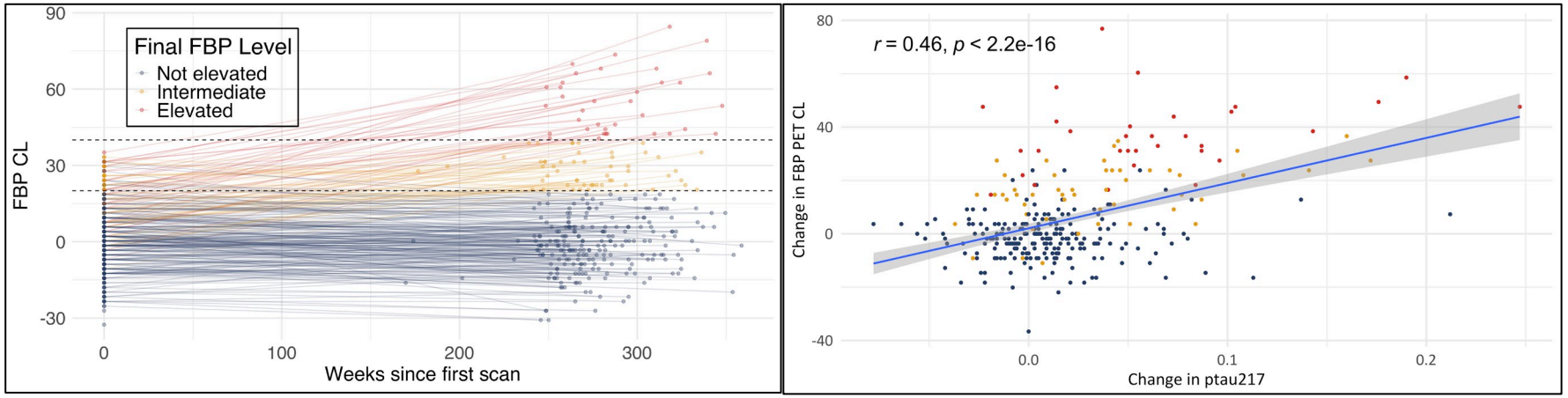
Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital



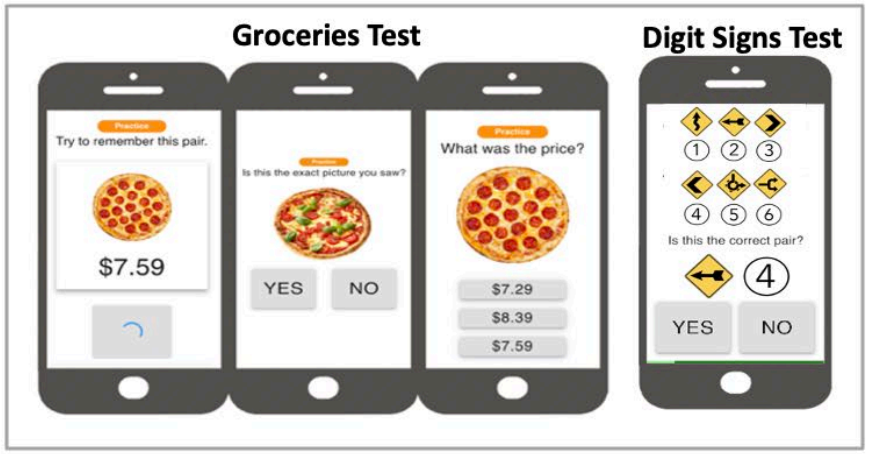
Yang HS et al (in prep)

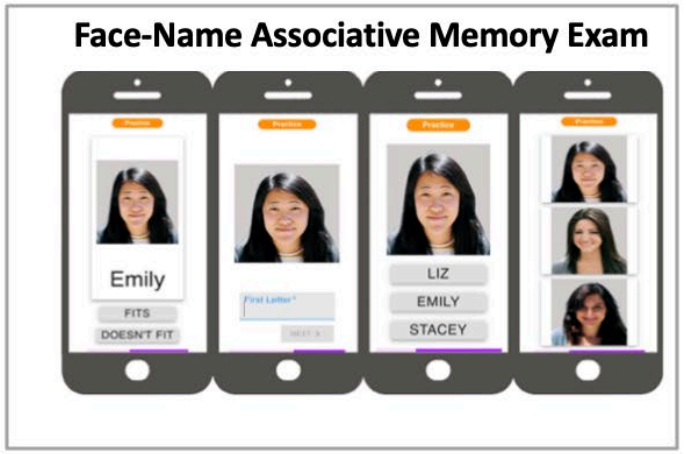
Farrell M et al *Alz & Dementia* 2024

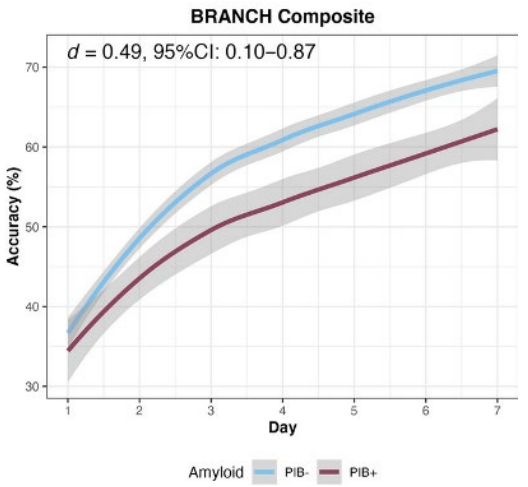
LEARN



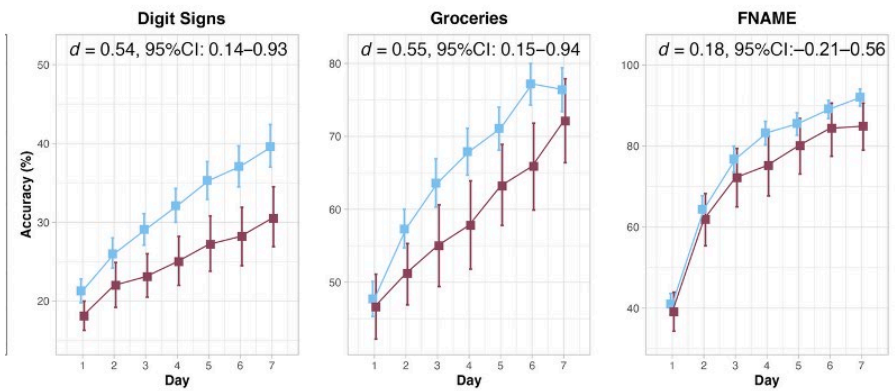
Digital Multi-Day BRANCH Learning Curves Diminished Learning in Preclinical AD





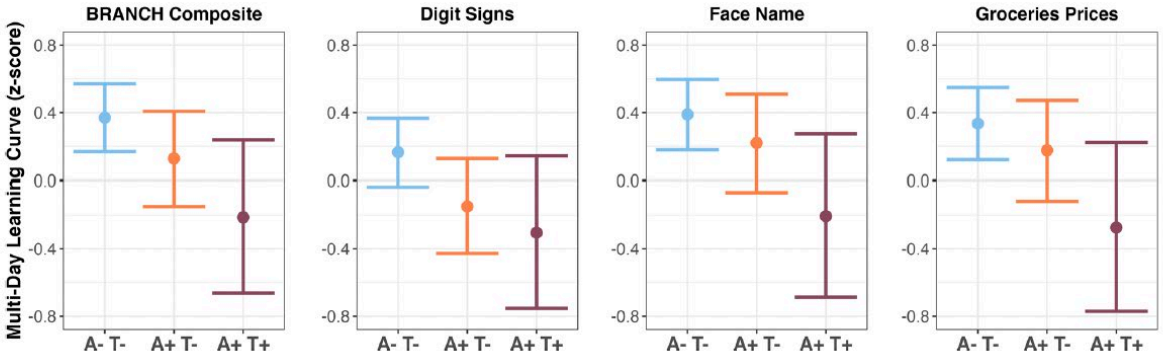


Amyloid Status



Papp K et al *Annals of Neurology* 2024

Amyloid and Tau Status

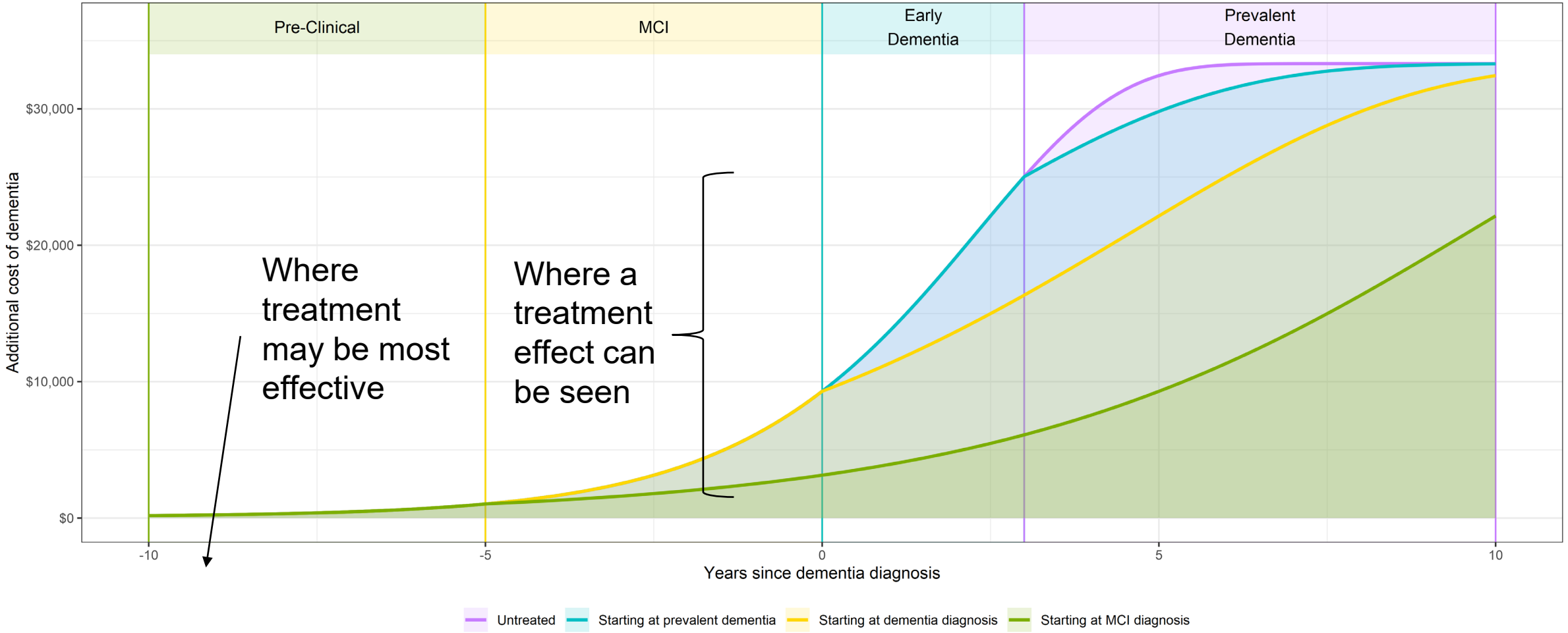


Jutten R et al *npj Digital Medicine* (In Press)

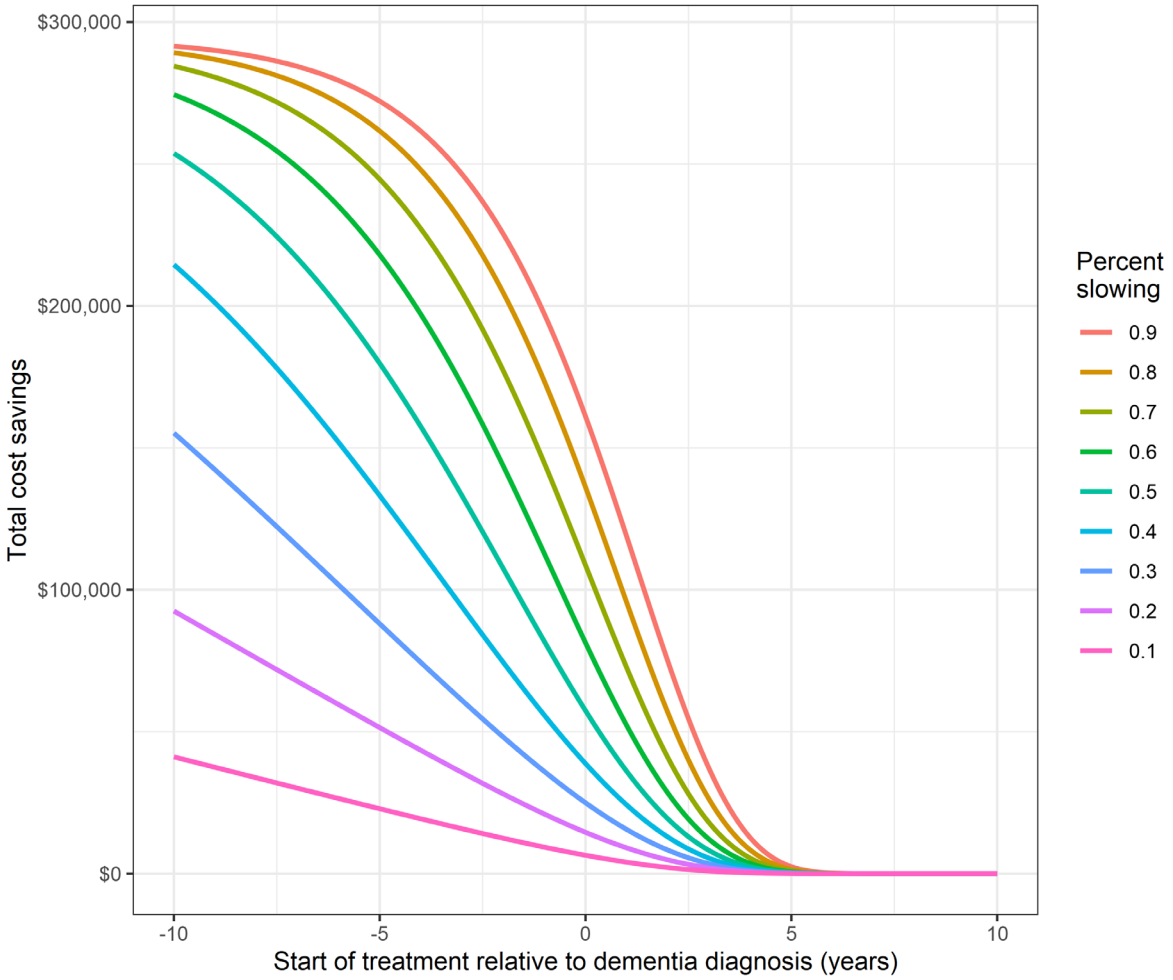
The Paradox of Clinical Development in AD

To show an effect the disease must progress, but…

The disease may be most treatable before it begins progressing



Total cost savings over expected disease course by treatment start



Percent slowing	Start of Treatment			
	5 years pre-MCI	MCI diagnosis	Dementia diagnosis	Start of prevalent dementia
90%	$291,000	$272,000	$161,000	$37,000
80%	$281,000	$261,000	$136,000	$26,000
70%	$284,000	$245,000	$109,000	$18,000
60%	$274,000	$218,000	$81,000	$12,000
50%	$254,000	$180,000	$57,000	$8,000
40%	$215,000	$133,000	$39,000	$5,000
30%	$155,000	$88,000	$25,000	$4,000
20%	$93,000	$51,000	$15,000	$2,000
10%	$41,000	$23,000	$6,000	$1,000

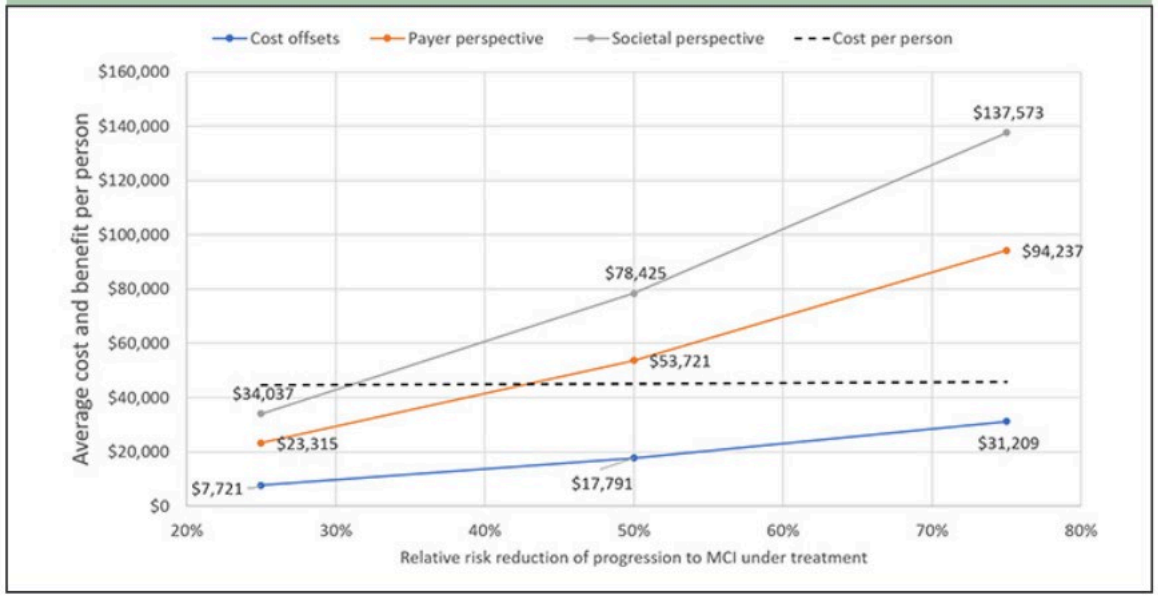
The Economic Arguments for Treating Earlier

Table 2. Attributable cost after transition to MCI

	Overall cost after reaching MCI	Average annual cost after reaching MCI
Medical care	$138,153	$15,099
Social care	$175,455	$19,175
QALY loss	$731,022	$79,893
Caregiver medical care	$75,198	$8,218
Caregiver time loss	$205,500	$22,459
Caregiver QALY loss	$154,763	$16,914
Total	$1,480,092	$161,759

Note: Estimates were derived from the projection of the impact of the natural history of MCI due to AD by Prados et al. (4) and inflated to US$20231

Figure 5. Breakeven analysis for different assumptions for size of treatment effect



Mattke S et al *JPAD* 2024

Why is Preclinical AD So Controversial?

Stigma around the "A" Word

- We used to be afraid to say the "C" word for Cancer, because cancer was thought to be an untreatable fatal illness
  - Not all carcinoma *in situ* will progress to metastatic disease, but detecting and treating cancer at the earliest possible stages has dramatically improved survival
- It is true that some people with amyloid accumulating in their brains will not develop AD dementia in their lifetime
  - High risk of cognitive decline and progression to MCI and dementia
  - Need to avoid the ca-"tau"-strophe – decrease amyloid before tau spreads into neocortex
- Important to change the perception of the "A" word - Alzheimer's disease is treatable and the earlier we detect evidence of disease, the better chance to be able to bend the curve of cognitive decline

Encouraging history from other fields

- Think about what has changed in cancer, stroke, HIV, diabetes, osteoporosis …. when we detect disease BEFORE symptoms?
- Delaying dementia by just 5 years would reduce projected Medicare costs related to dementia care by nearly 50%
- Serious diseases require aggressive treatments
  - Many older people fear Alzheimer's disease more than cancer
  - We commonly administer cancer treatments with debilitating side effects that are acceptable to gain valuable time
  - But we need to determine which people with preclinical AD need treatment and when they need it
- Alzheimer's disease is a formidable opponent – We must be even bolder! But we are getting there…

Acknowledgments

- Keith Johnson, Dorene Rentz, and many colleagues from the Harvard Aging Brain Study
- Paul Aisen and A4 and AHEAD Teams, Doris Molina-Henry and APEX Teams at ATRI/ACTC
- AHEAD Teams at Eisai, A4 Teams at Eli Lilly
- Mayo Clinic, InVicro, Cogstate, C2N
- Clinical trial site investigators and staff
- Most of all - the research participants and their study partners!
- Funding from National Institute on Aging, Alzheimer's Association, Fidelity Biosciences, GHR Foundation, Gates Ventures, Accelerating Medicines Partnership