Alzheimer's Disease: From Biomarkers to Treatment and Prevention

Wai-Ying Wendy Yau, MD

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HARVARD MEDICAL SCHOOL

Alzheimer's Disease

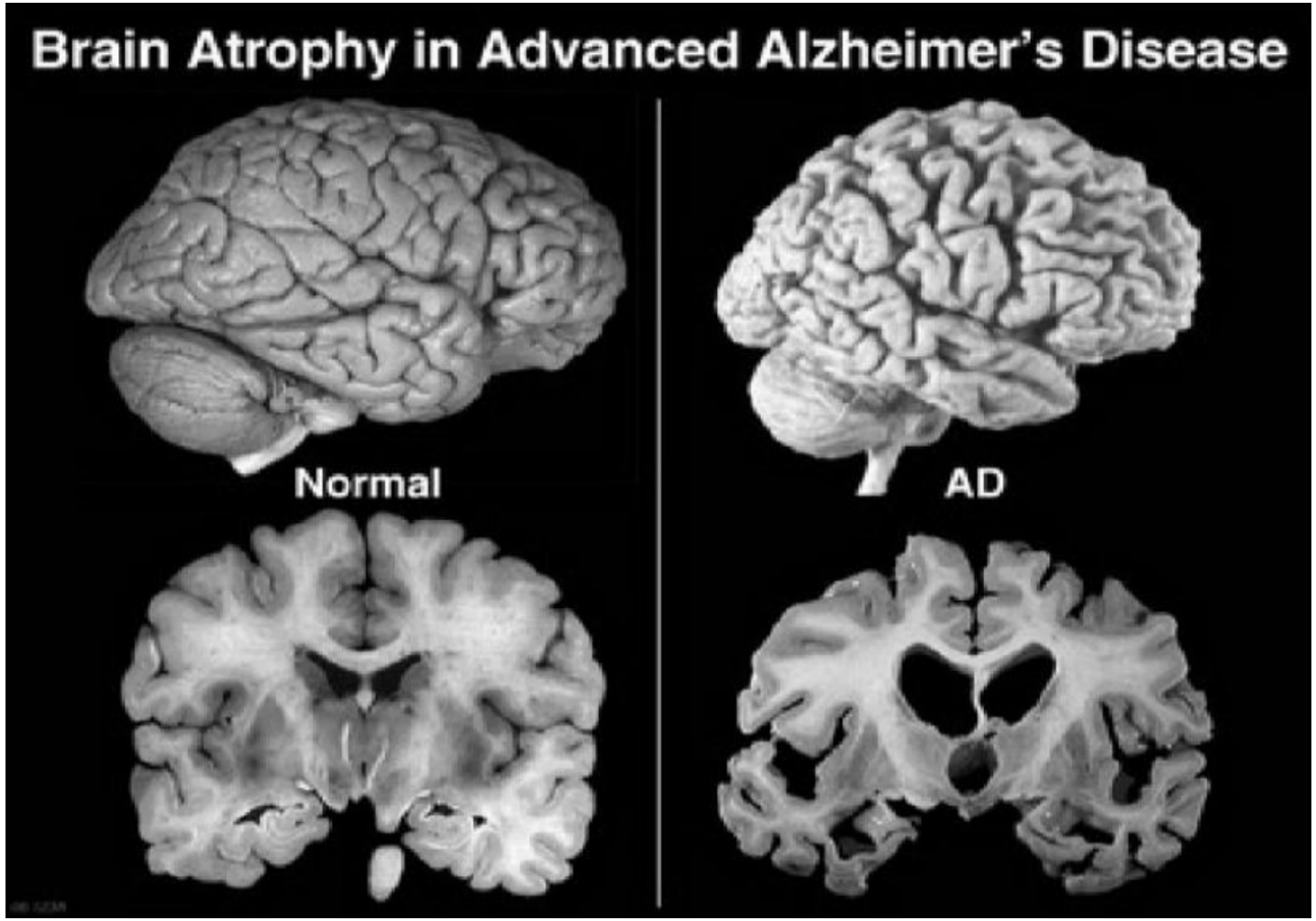


Dr. Alois Alzheimer



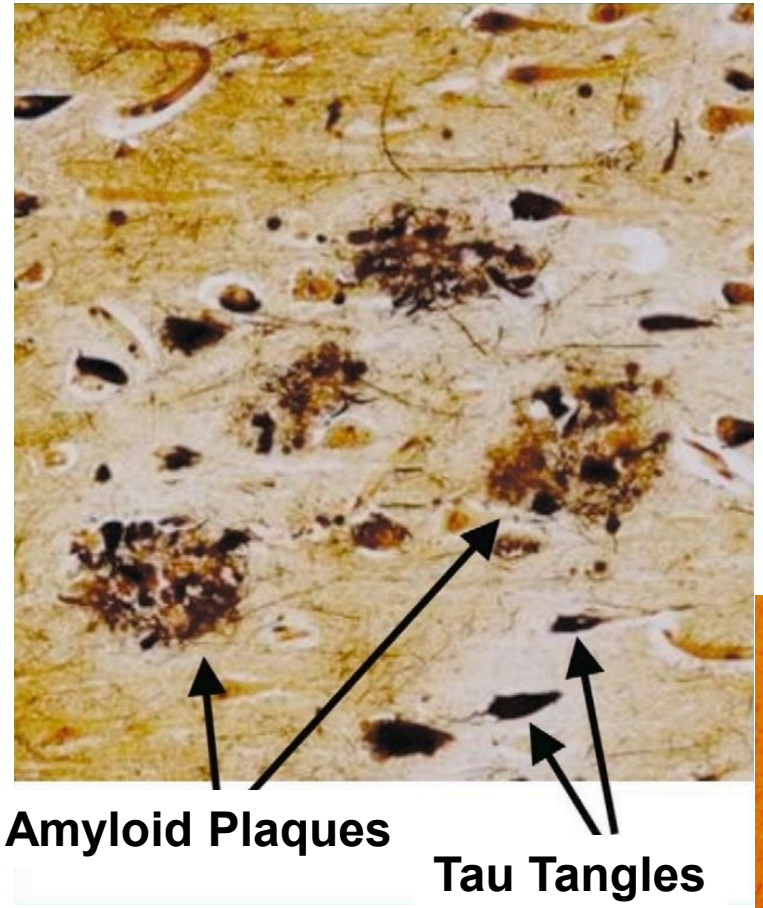
Auguste Deter
(1850-1906)

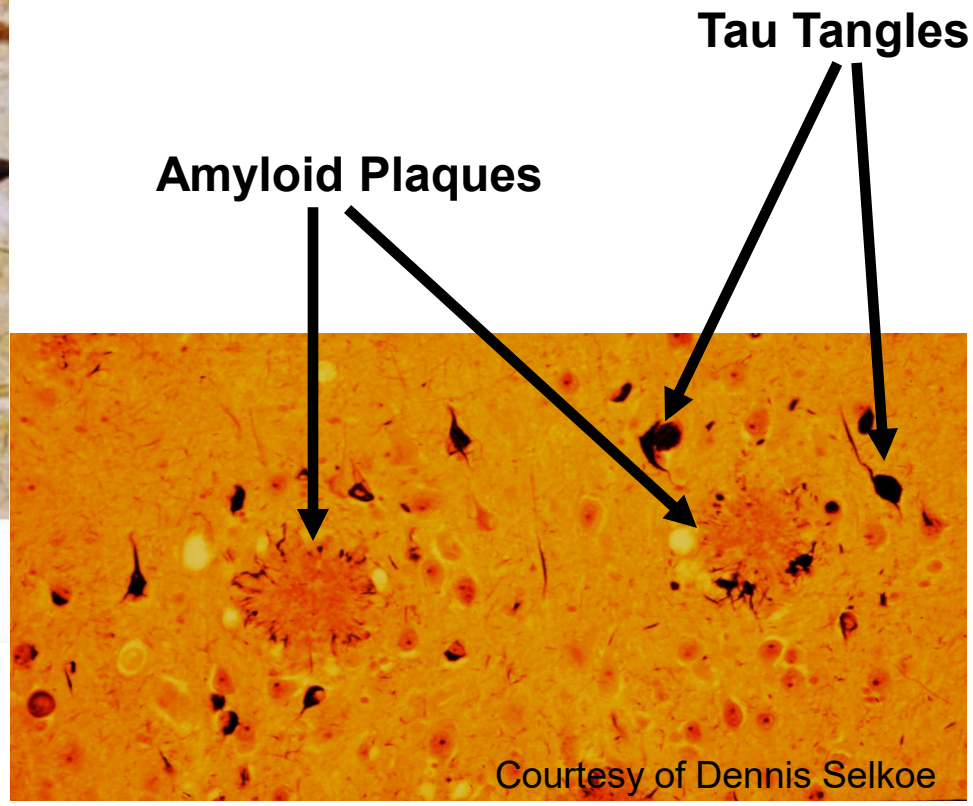
51-year-old with progressive memory loss, cognitive impairment, mood and behavioral change.

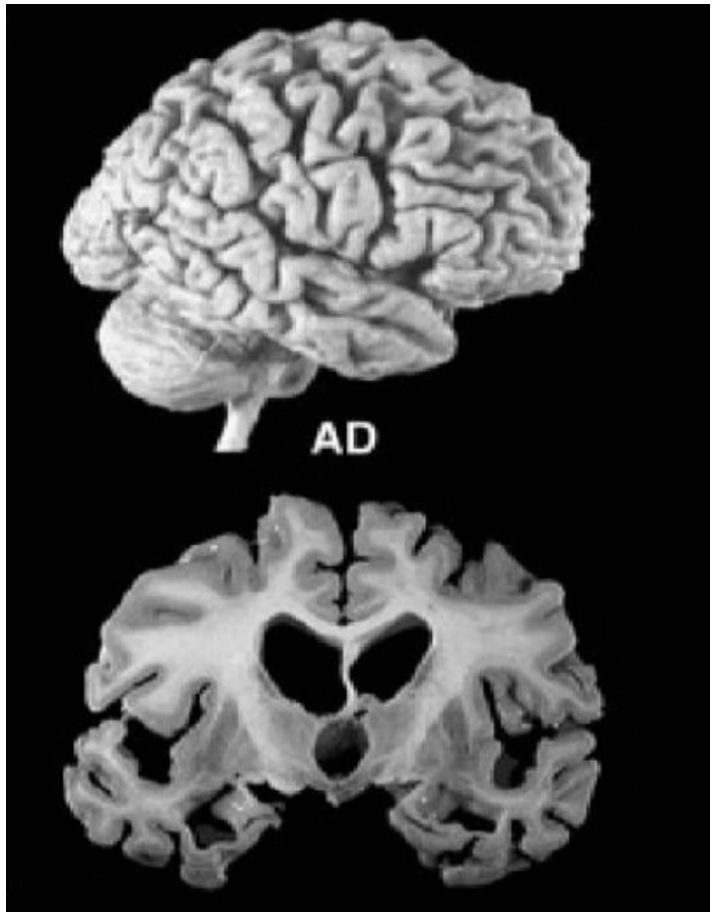


Bagad et al. (2013); Mufson et al. (2015)

AD Neuropathology: Plaques and Tangles

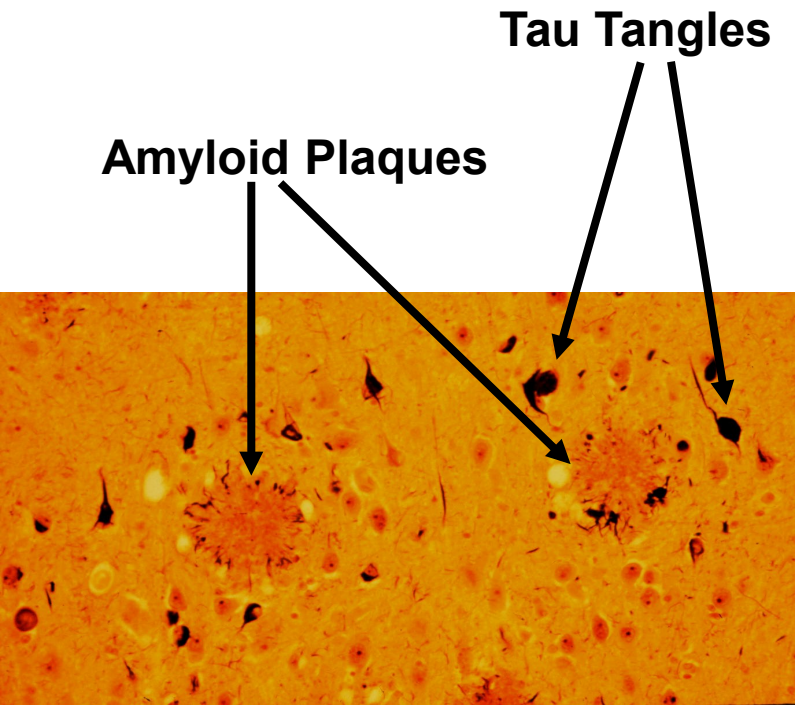






Bagad et al. (2013); Schramm (2018)

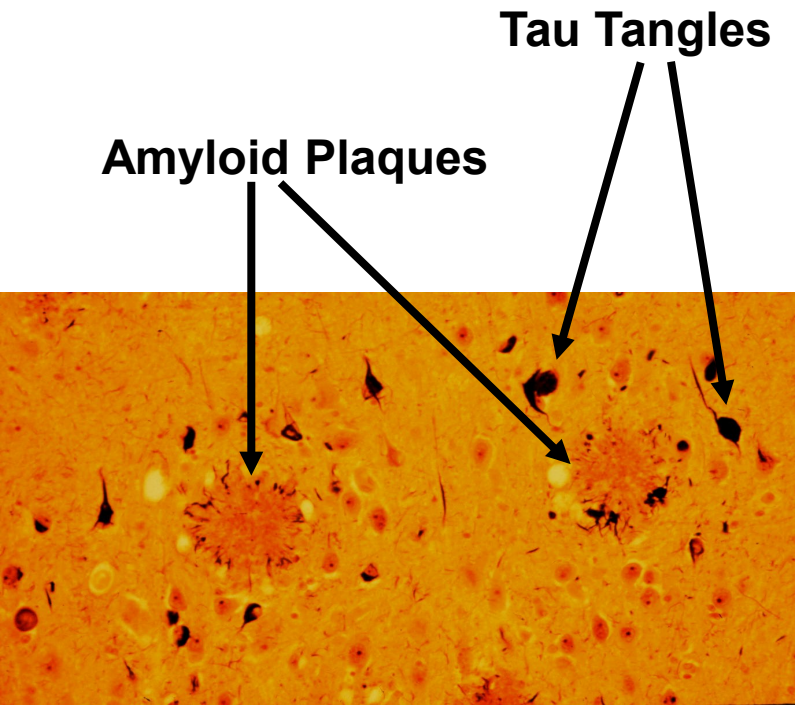
Detecting AD Pathology Non-Invasively: Amyloid and Tau PET Imaging



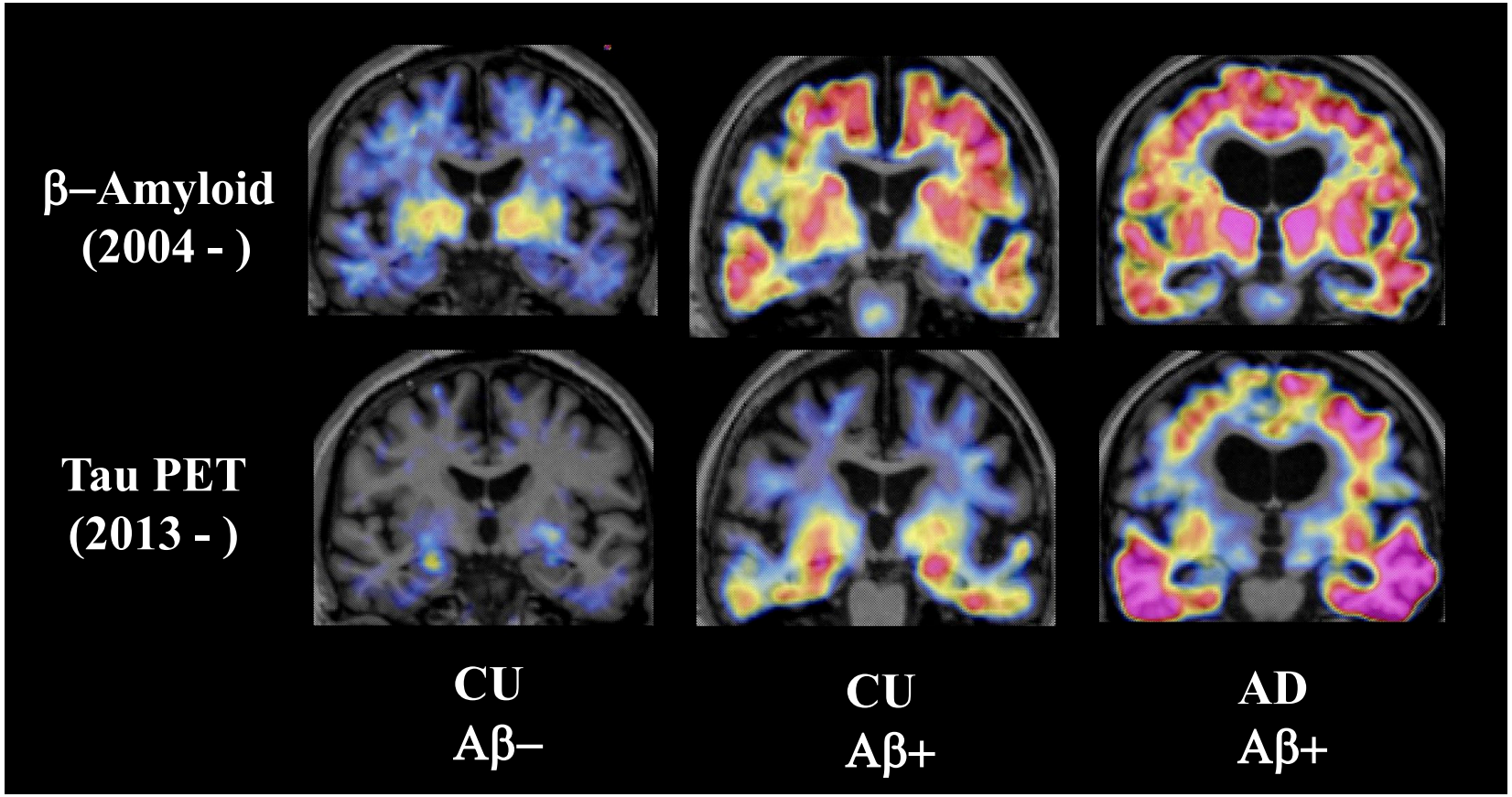
Courtesy of Dennis Selkoe

Klunk et al. (2004); Chen et al. (2013); Sperling et al. (2014)

Detecting AD Pathology Non-Invasively: Amyloid and Tau PET Imaging



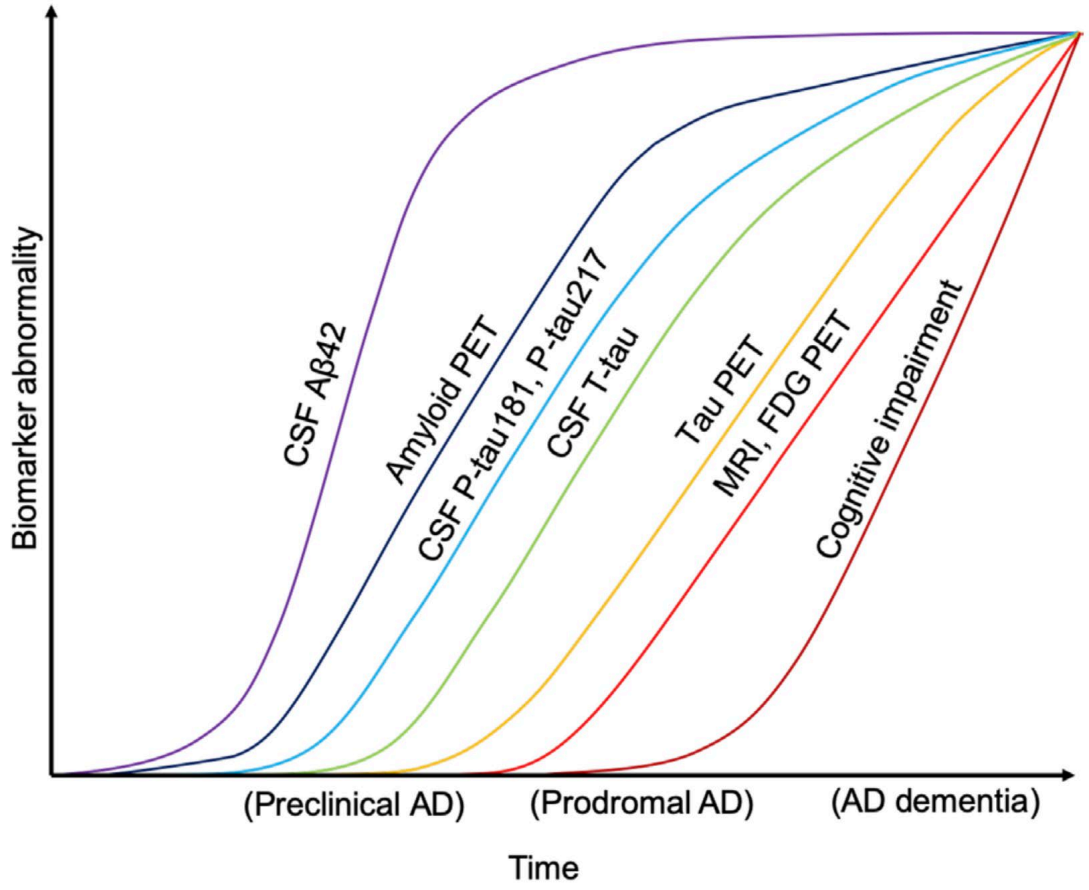
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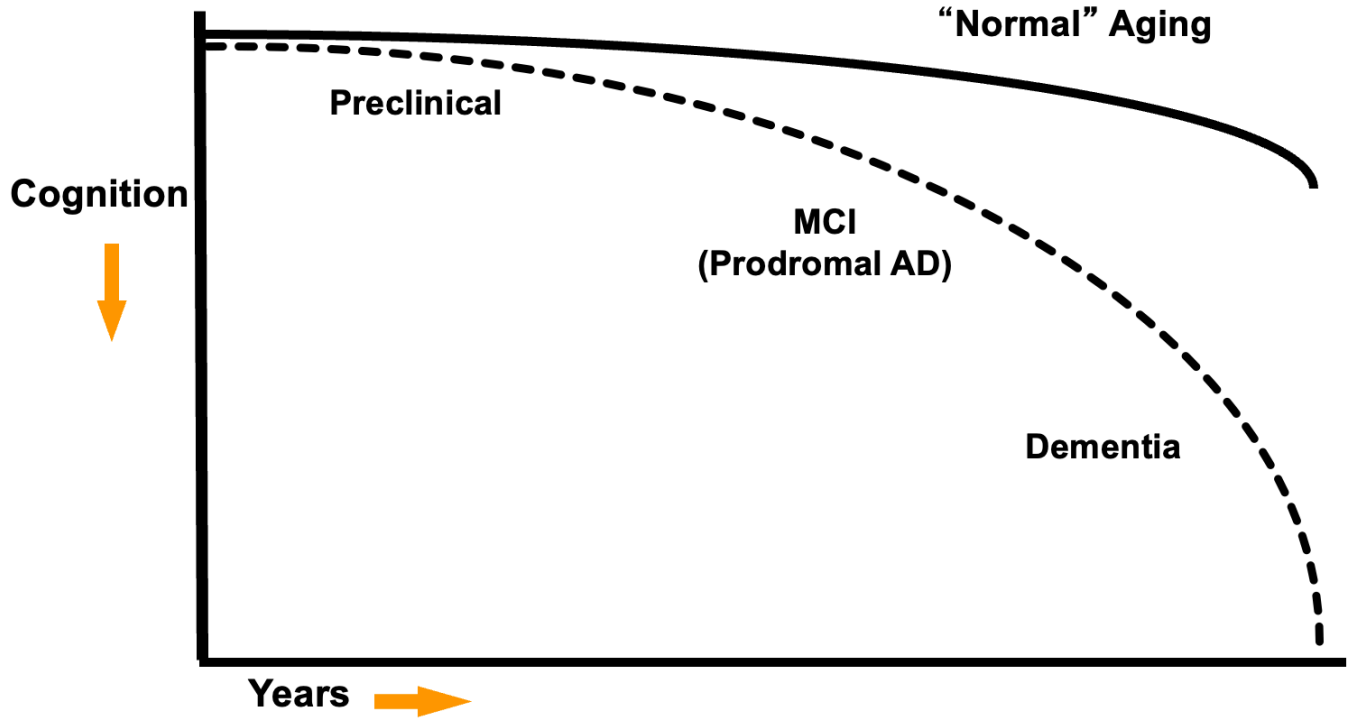


CU = Cognitively Unimpaired

Klunk et al. (2004); Chen et al. (2013); Sperling et al. (2014)

The Alzheimer's Disease Continuum: From Biomarker Changes to Cognitive Decline





Mattsson-Carlgren et al. (2020); Sperling et al. (2011)

The Next Frontier in AD Diagnosis: Blood-Based Biomarkers

- **Plasma p-tau217 identifies amyloid pathology with high accuracy**

- Three p-tau217–based blood tests are now FDA-cleared for evaluating **symptomatic individuals**:
  - **Fujirebio Lumipulse G**: p-tau217/Aβ42 ratio
  - **C2N PrecivityAD2**: %p-tau217 + Aβ42/40
  - **Roche Elecsys pTau217**: p-tau217 alone

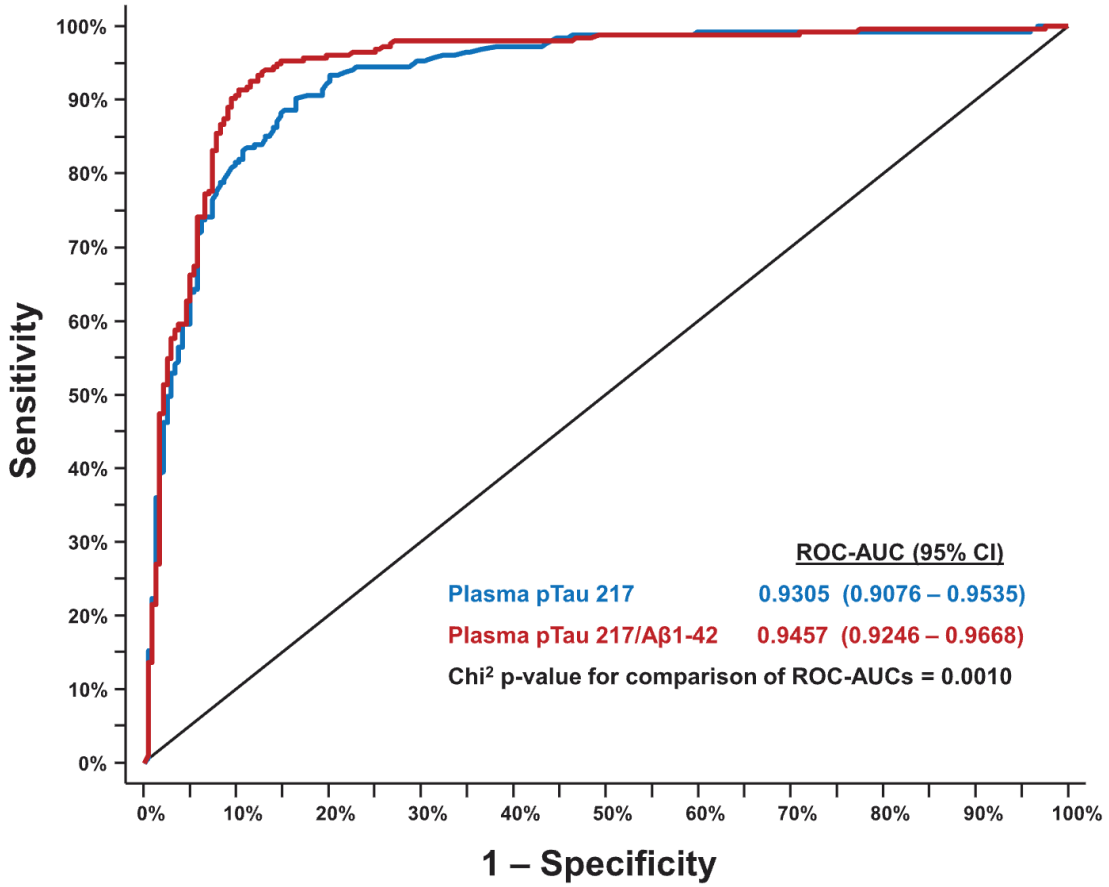
The Next Frontier in AD Diagnosis: Blood-Based Biomarkers

Multicenter Study > Alzheimers Dement. 2026 Jul;22(7):e71644. doi: 10.1002/alz.71644.

Multicenter validation of plasma p-tau217/ amyloid beta 1-42 ratio in symptomatic Alzheimer's disease

Abhay R Moghekar [1], James A Rock [2], Richard C Mohs [3], Oskar Hansson [4], Erik Stomrud [4 5], Sebastian Palmqvist [4 5], Niklas Mattsson-Carlgren [4 5 6], Sterling C Johnson [7 8], Henrik Zetterberg [7 8 9 10 11 12 13 14], Rachel R Radwan [15], Jessica Junfola [15], M Craig Miller [15], Luna Buitrago [15], Francesca I De Simone [15], Katie Martin [15], Diana Dickson [15], Natalya Benina [15], Douglas M Hawkins [16]

- Fujirebio Lumipulse G plasma p-tau217 and p-tau217/Aβ42 accurately identifies amyloid pathology defined by CSF biomarkers or amyloid PET (AUC 0.93 - 0.95)



Implications for Alzheimer's Clinical Trials: Selecting Patients with AD Biology

Clinical diagnosis only

- Probable Alzheimer's dementia by NINCDS-ADRDA or DSM-III-R criteria
- +/- CT or MRI imaging

Clinical Trial > JAMA. 2004 Jan 21;291(3):317-24. doi: 10.1001/jama.291.3.317.

Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial

Pierre N Tariot [1], Martin R Farlow, George T Grossberg, Stephen M Graham, Scott McDonald, Ivan Gergel; Memantine Study Group

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Clinical diagnosis + Biomarker Confirmation

Clinical Trial > N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29.

Lecanemab in Early Alzheimer's Disease

Amyloid PET

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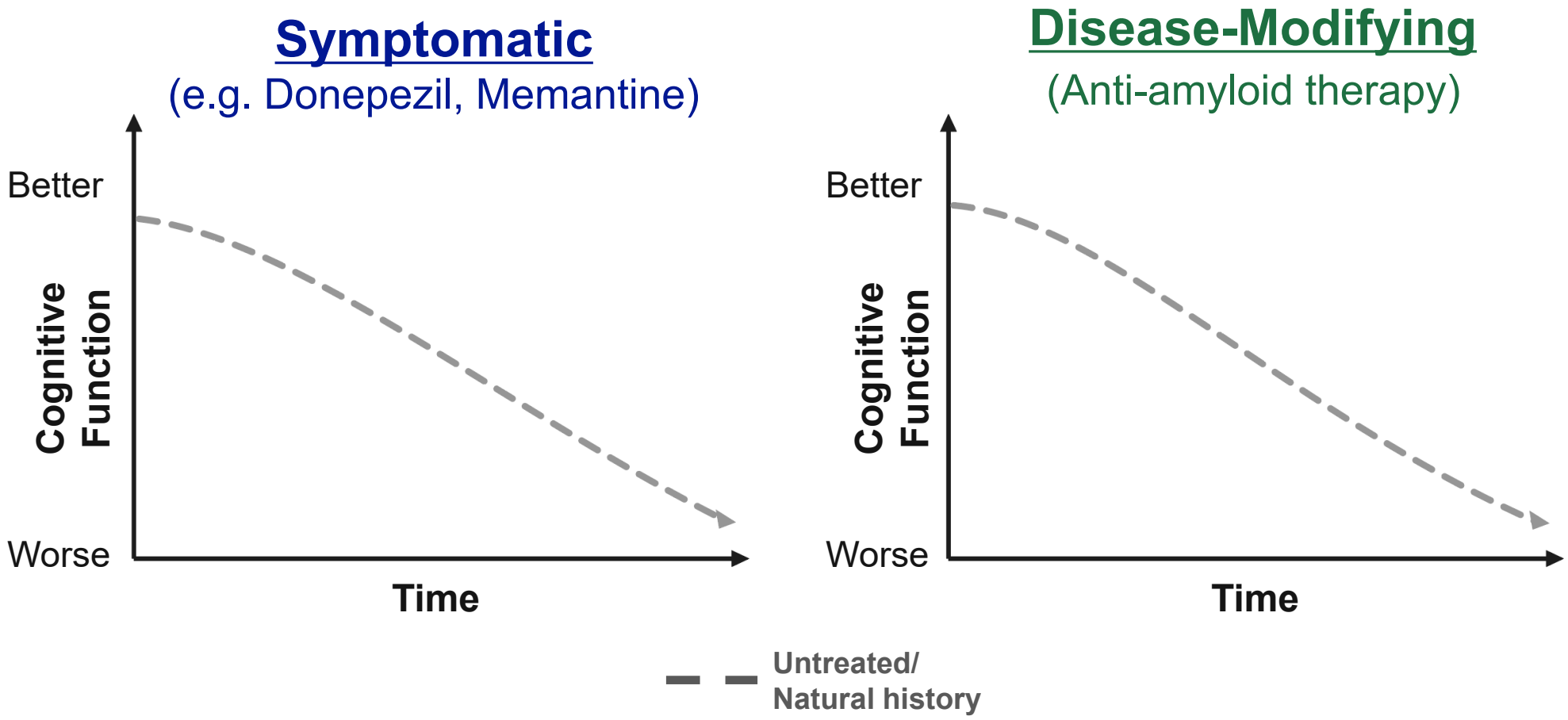
> JAMA. 2023 Aug 8;330(6):512-527. doi: 10.1001/jama.2023.13239.

Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

Amyloid PET + Tau PET

John R Sims [1], Jennifer A Zimmer [1], Cynthia D Evans [1], Ming Lu [1], Paul Ardayfio [1], JonDavid Sparks [1], Alette M Wessels [1], Sergey Shcherbinin [1], Hong Wang [1], Emel Serap Monkul Nery [1], Emily C Collins [1], Paul Solomon [2], Stephen Salloway [3 4], Liana G Apostolova [5], Oskar Hansson [6], Craig Ritchie [7], Dawn A Brooks [1], Mark Mintun [1], Daniel M Skovronsky [1]; TRAILBLAZER-ALZ 2 Investigators

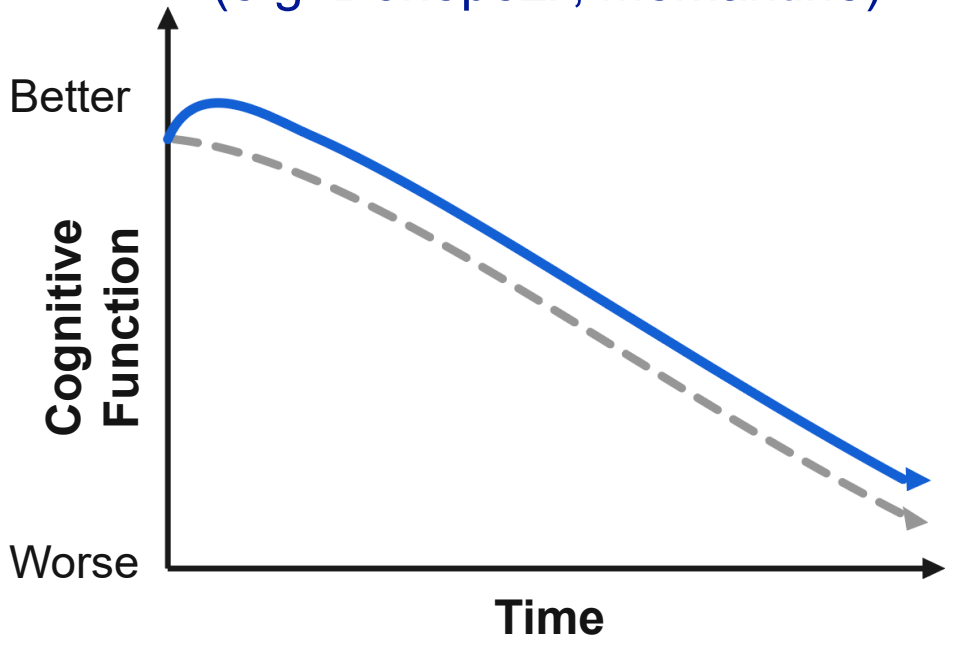
AD Treatment Distinction: Symptomatic vs Disease-Modifying



AD Treatment Distinction: Symptomatic vs Disease-Modifying

Symptomatic

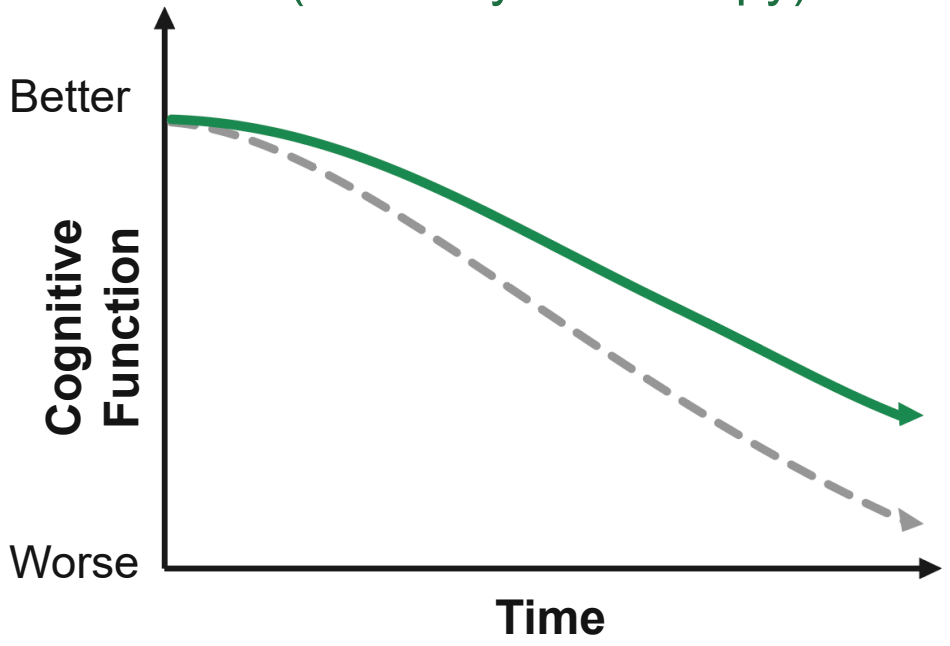
(e.g. Donepezil, Memantine)



- Unchanged rate of decline
- Benefit not sustained after treatment discontinuation

Disease-Modifying

(Anti-amyloid therapy)



- Slows rate of decline
- Alters disease trajectory

Anti-Amyloid Therapy: Early Hopes with Aducanumab

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny, Ping Chiao, Thierry Bussière, Paul H. Weinreb, Leslie Williams, Marcel Maier, Robert Dunstan, Stephen Salloway, Tianle Chen, Yan Ling, John O'Gorman, Fang Qian, Mahin Arastu, Mingwei Li, Sowmya Chollate, Melanie S. Brennan, Omar Quintero-Monzon, Robert H. Scannevin, H. Moore Arnold, Thomas Engber, Kenneth Rhodes, James Ferrero, Yaming Hang, Alvydas Mikulskis, ... Alfred Sandrock + Show authors

Nature **537**, 50–56 (2016) | Cite this article

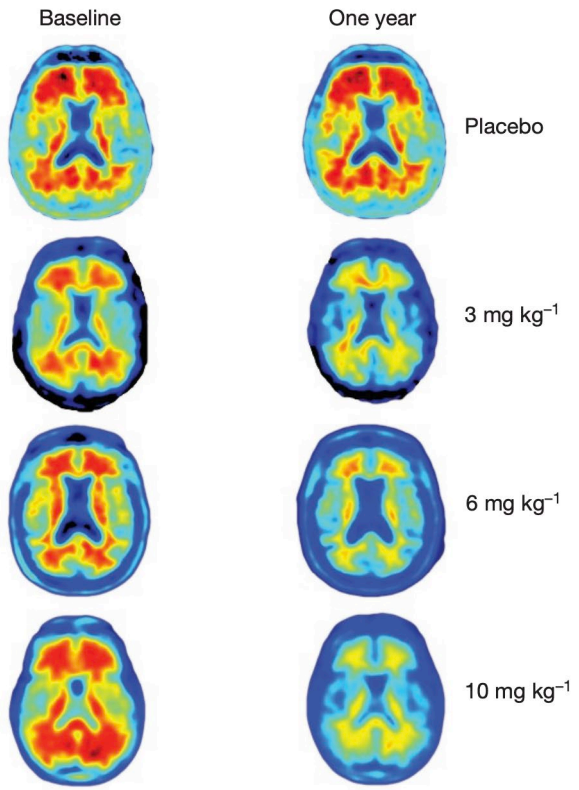


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

Current Anti-Amyloid Therapy: Lecanemab and Donanemab

Early Alzheimer's Disease
= Mild Cognitive impairment or Mild Dementia

Clinical Trial > N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948.
Epub 2022 Nov 29.

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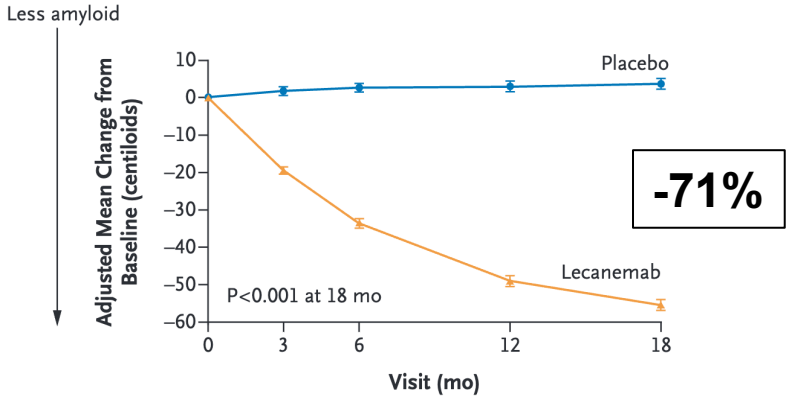
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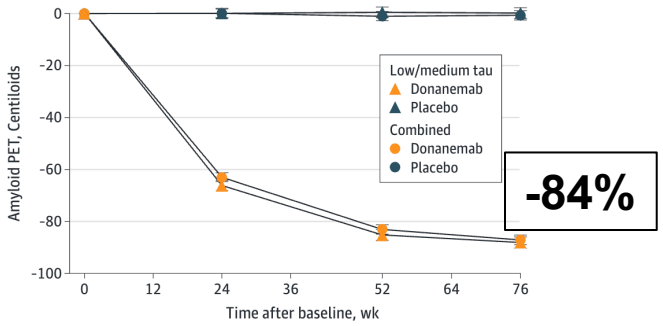


No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

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Current Anti-Amyloid Therapy: Lecanemab and Donanemab

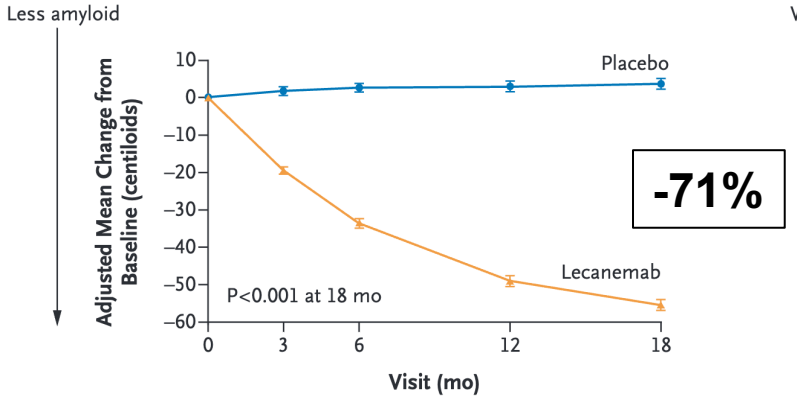
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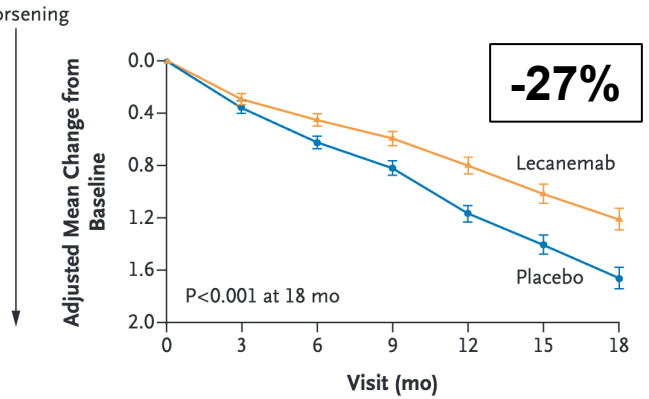
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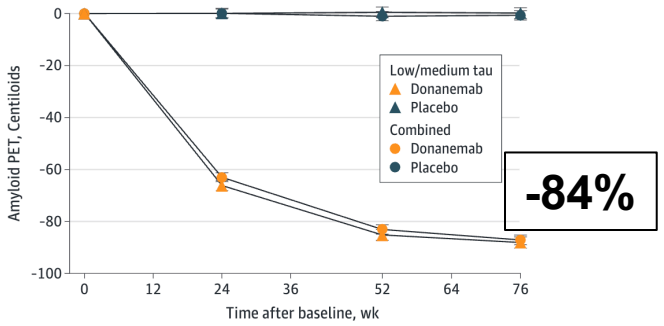


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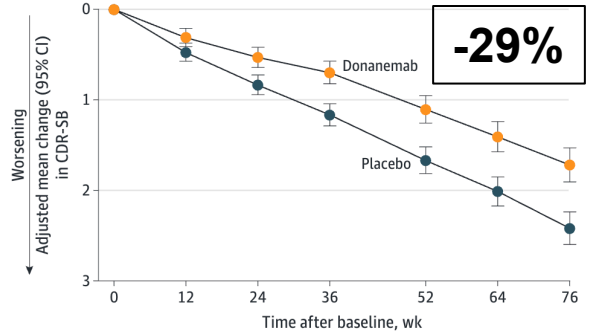
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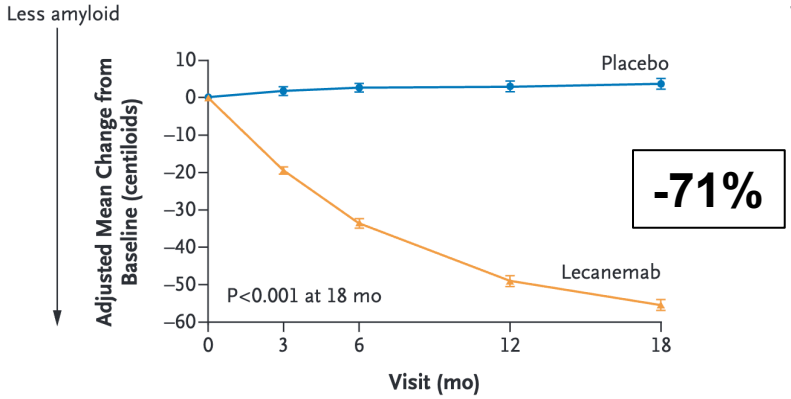
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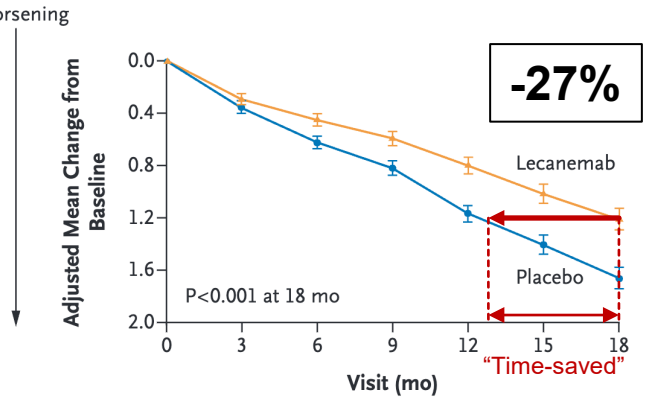
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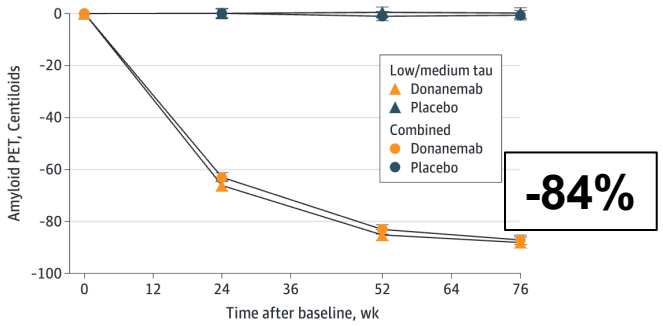


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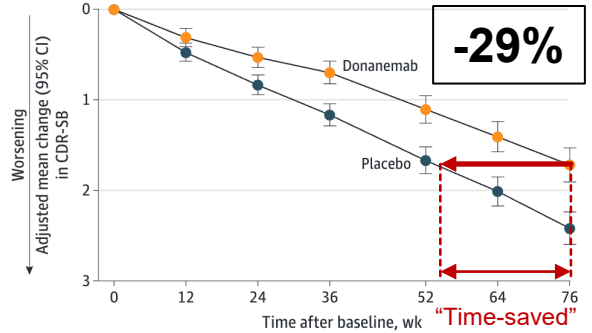
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"Time-saved": Delay of 5 to 6 months

Using Anti-Amyloid Therapy in the Real-World

J Prev Alzheimers Dis. Author manuscript; available in PMC: 2024 Jan 1.

Lecanemab: Appropriate Use Recommendations

J Cummings [1], L Apostolova [2], GD Rabinovici [3], A Atri [4], P Aisen [5], S Greenberg [6], S Hendrix [7], D Selkoe [8], M Weiner [9], RC Petersen [10], S Salloway [11]; Alzheimer's Disease and Related Disorders Therapeutics Work Group

Prev Alzheimers Dis. 2025 Mar 27;12(5):100150. doi: 10.1016/j.tjpad.2025.100150

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Key points:

- Diagnosis of MCI or mild dementia
- AD clinical syndrome (amnestic, dysexecutive, posterior cortical atrophy, logopenic-variant primary progressive aphasia)
- Positive AD biomarker (PET or CSF)
- APOE genotype testing
- Brain MRI within 1 year: Exclude >4 microhemorrhages, any superficial siderosis, any intracerebral hemorrhage greater than 1 cm

Using Anti-Amyloid Therapy in the Real-World

J Prev Alzheimers Dis. Author manuscript; available in PMC: 2024 Jan 1.

Lecanemab: Appropriate Use Recommendations

J Cummings [1], L Apostolova [2], GD Rabinovici [3], A Atri [4], P Aisen [5], S Greenberg [6], S Hendrix [7], D Selkoe [8], M Weiner [9], RC Petersen [10], S Salloway [11]; Alzheimer's Disease and Related Disorders Therapeutics Work Group

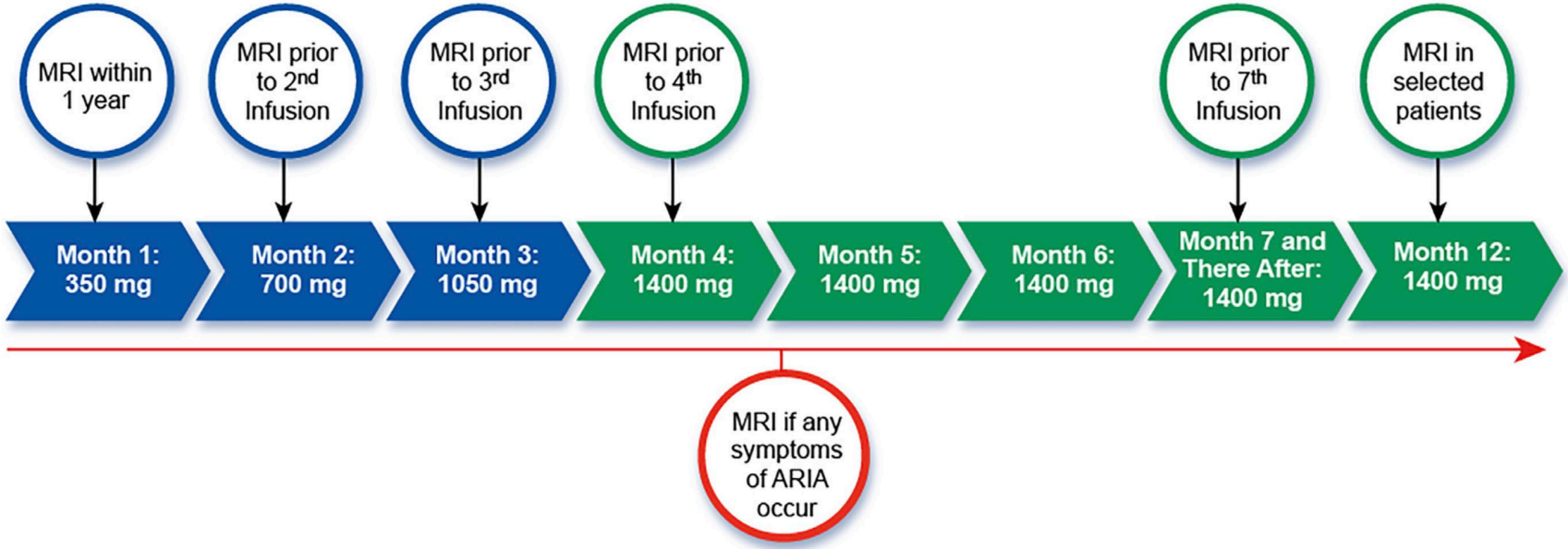
Prev Alzheimers Dis. 2025 Mar 27;12(5):100150. doi: 10.1016/j.tjpad.2025.100150

Donanemab: Appropriate use recommendations

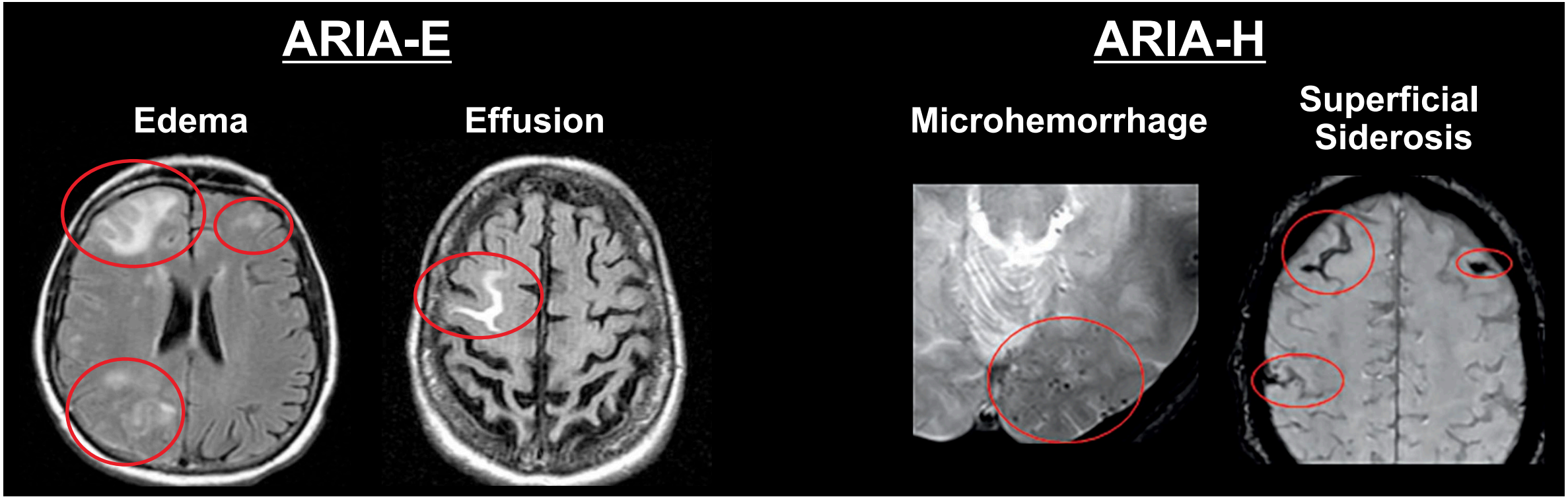
GD Rabinovici [a,*], DJ Selkoe [b], SE Schindler [c], P Aisen [d], LG Apostolova [e], A Atri [f,g], SM Greenberg [h], SB Hendrix [i], RC Petersen [j], M Weiner [k], S Salloway [l,1], J Cummings [m,1]

Key points:

- MRI monitoring during therapy



Amyloid-Related Imaging Abnormalities (ARIA)



	Lecanemab	Donanemab [standard dosing]	Donanemab [modified dosing]
Any ARIA (E or H)	21.5%	36.8%	23.6%
Symptomatic ARIA	2.8%	6.0%	2.8%

Sperling et al. (2011); Cogswell et al. (2025); van Dyck et al. (2023); Sims et al. (2023); Wang et al. (2025)

ARIA Risk Varies by APOE Genotype

Greater ARIA risk for Apolipoprotein E (APOE) ε4 carriers

- ε4 homozygote 2.5 to 6 times greater risk in main Phase 3 RCTs

ARIA-E (Edema/Effusion)

APOE Status	Lecanemab	Donanemab [standard dosing]	Donanemab [modified dosing]
Non-Carrier	5.4%	15.7%	12.0%
Heterozygote	10.9%	22.8%	13.9%
Homozygote	32.6%	40.6%	19.0%

ARIA-H (Hemorrhage)

APOE Status	Lecanemab	Donanemab [standard dosing]	Donanemab [modified dosing]
Non-Carrier	11.9%	18.8%	14.7%
Heterozygote	14.0%	32.3%	22.6%
Homozygote	39.0%	50.3%	28.6%

van Dyck et al. (2023); Sims et al. (2023); Wang et al. (2025)

ARIA Management: Appropriate Use Recommendations

	Radiographic Severity		
Clinical Severity	**Mild**	**Moderate**	**Severe**
Asymptomatic	Continue	Suspend	Discontinue
Mild	Suspend	Suspend	Discontinue
Moderate	Suspend	Suspend	Discontinue
Severe	Discontinue	Discontinue	Discontinue

- Monthly MRI until ARIA-E resolution and ARIA-H stabilization

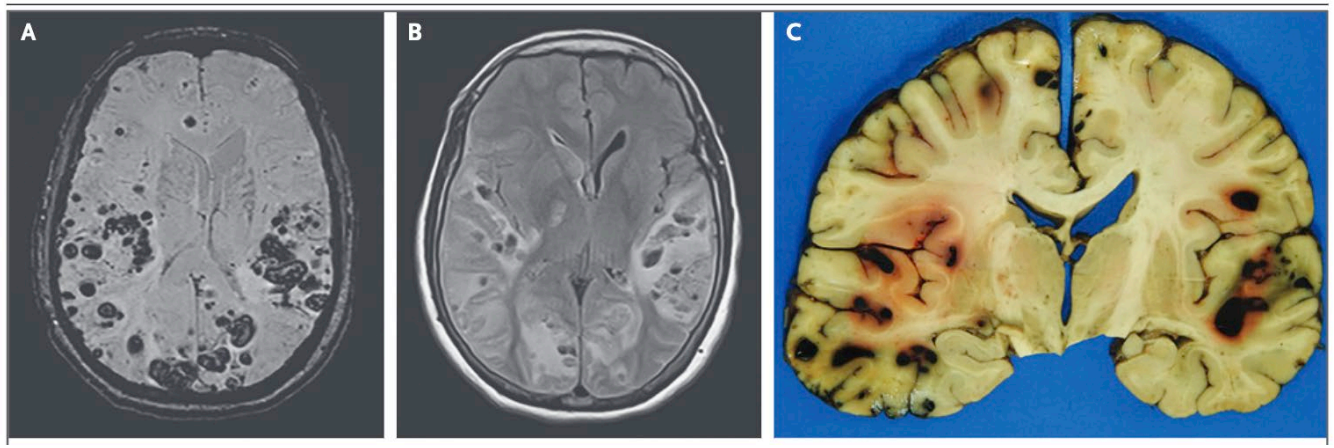
Cummings et al. (2023); Rabinovici et al. (2025)

ARIA Can be Serious or Life-threatening

Comment > N Engl J Med. 2023 Feb 2;388(5):478-479. doi: 10.1056/NEJMc2215148.
Epub 2023 Jan 4.

Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

Nicholas J Reish [1], Pouya Jamshidi [1], Brian Stamm [1], Margaret E Flanagan [1], Elizabeth Sugg [1], Mengxuan Tang [1], Kelly L Donohue [1], Matthew McCord [1], Chase Krumpelman [1], Marek-Marsel Mesulam [1], Rudolph Castellani [1], Sherry H-Y Chou [1]



Autopsy: Severe cerebral amyloid angiopathy with inflammatory/necrotizing vasculopathy

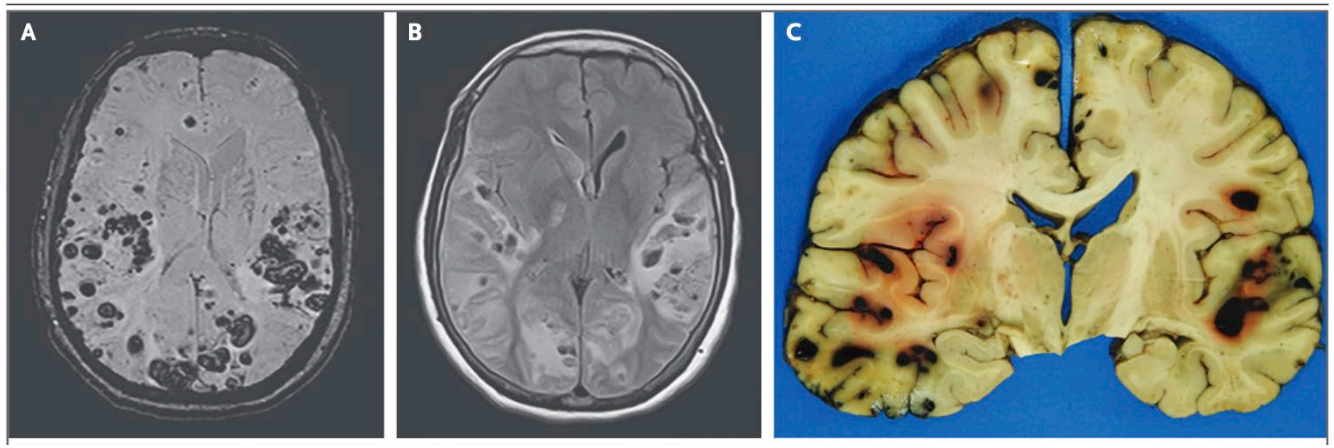
Reish et al. (2023); Honig et al. (2024); FDA (2024); Wang et al. (2025)

ARIA Can be Serious or Life-threatening

Comment > N Engl J Med. 2023 Feb 2;388(5):478-479. doi: 10.1056/NEJMc2215148.
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Autopsy: Severe cerebral amyloid angiopathy with inflammatory/necrotizing vasculopathy

Appropriate Use Recommendations advise against these high-risk scenarios

- IV thrombolysis
- Anticoagulation
- Baseline superficial siderosis

Reish et al. (2023); Honig et al. (2024); FDA (2024); Wang et al. (2025)

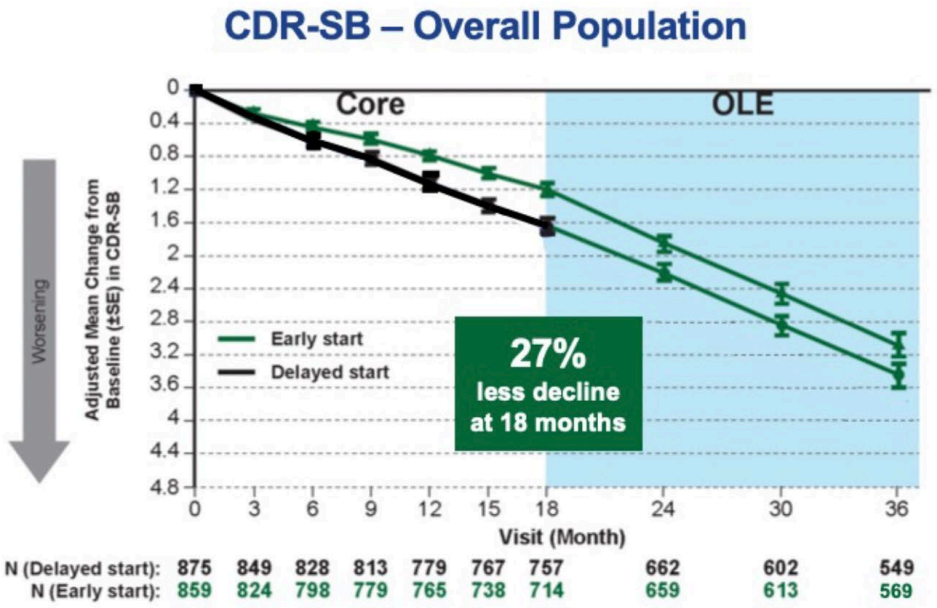
Anti-Amyloid Therapy, Where to Go Next?

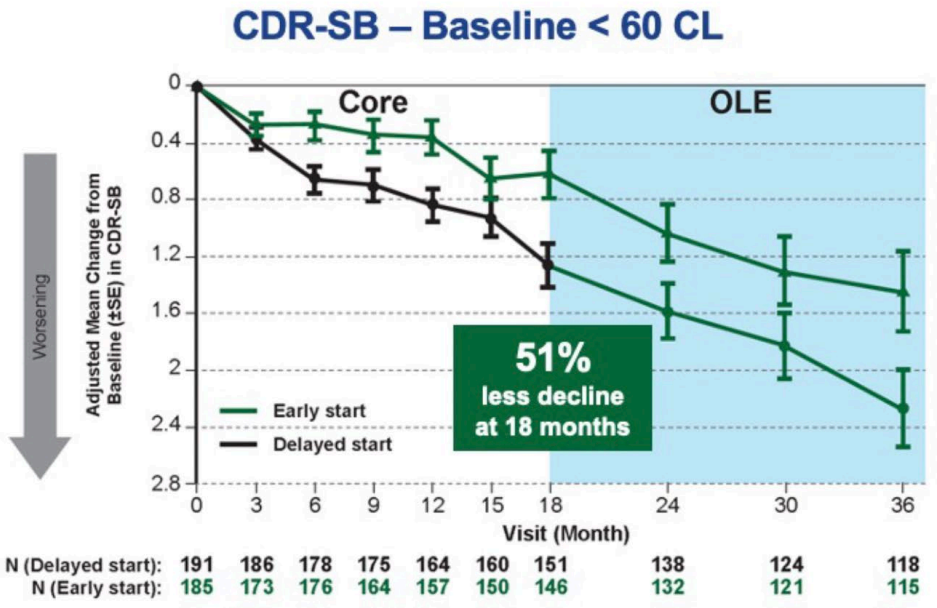
Anti-Amyloid Therapy, Where to Go Next?

Earlier treatment may be more effective

Phase 3 Lecanemab Clinical Outcomes Through 36 Month open label extension

- Lower baseline amyloid group shows greater continued benefit





Eisai. Presented at CTAD 2024

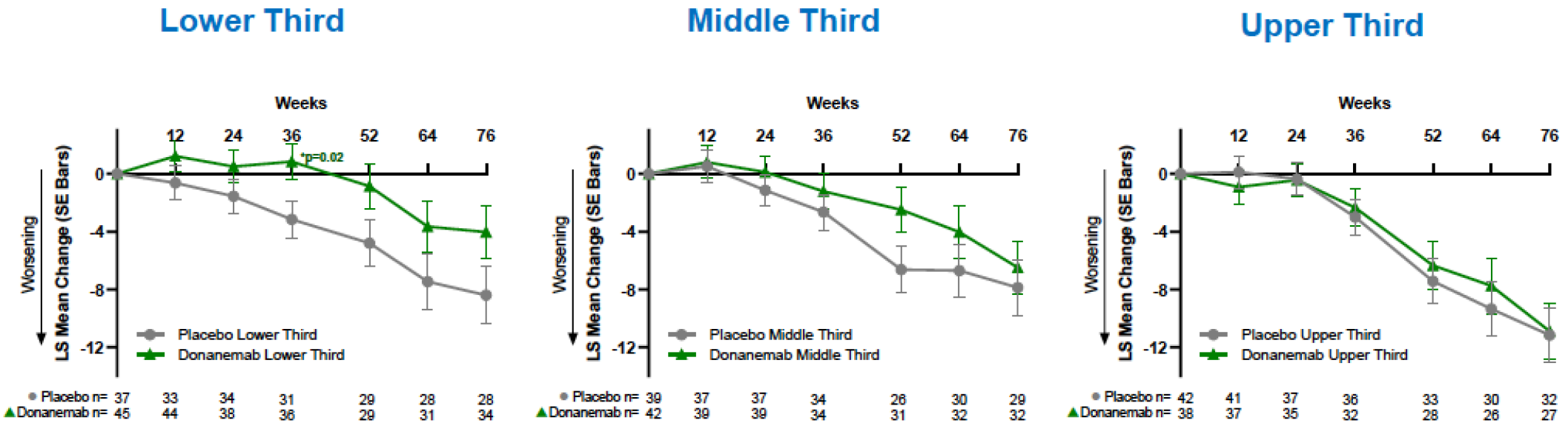
Anti-Amyloid Therapy, Where to Go Next?

Earlier treatment may be more effective

Phase 3 Donanemab Clinical Outcome by Tau Burden

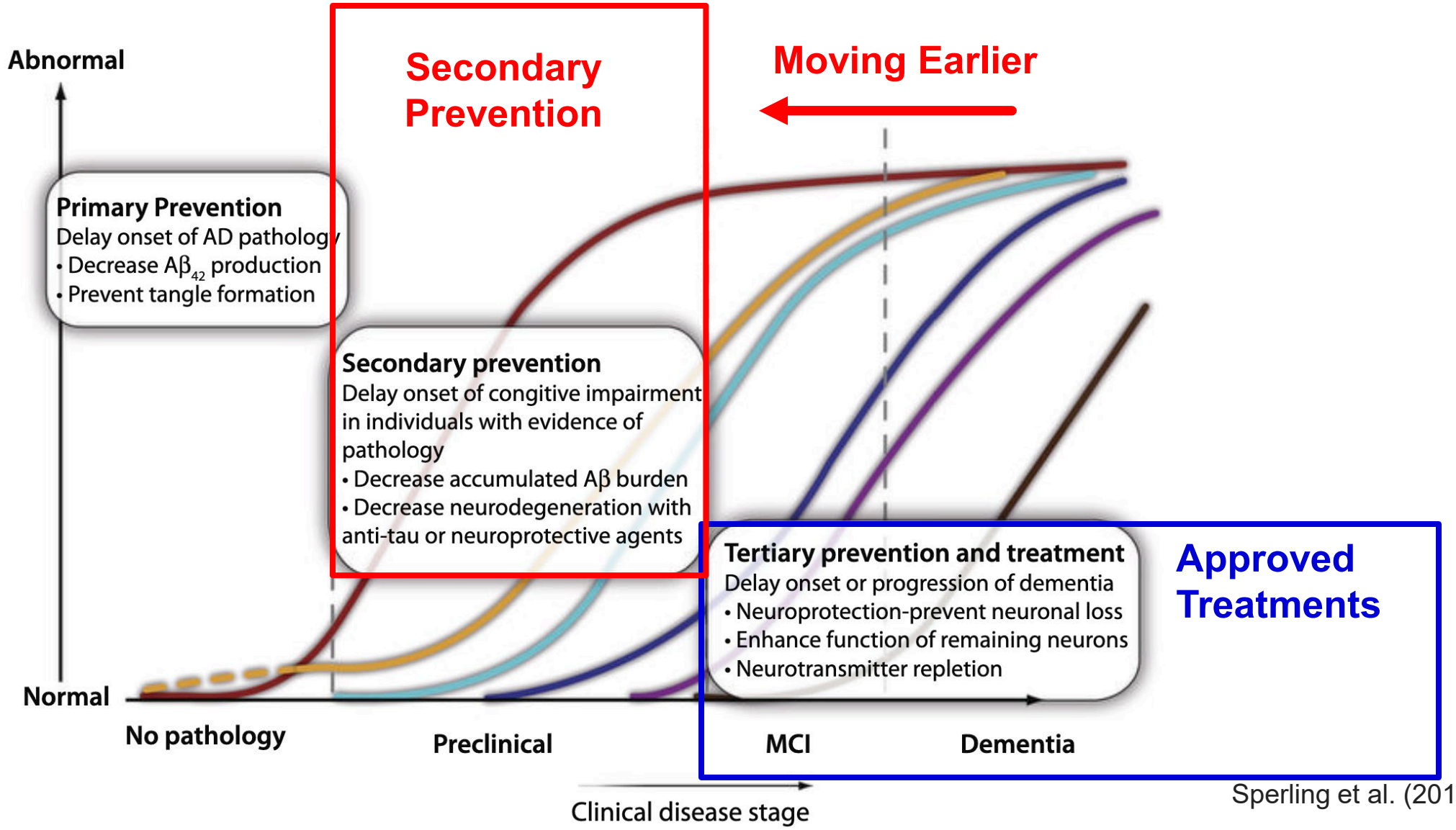
- Lower Baseline Tau Associated with Greater Clinical Benefit

iADRS Stratified by Baseline Tau PET



Mintun M, Eli Lilly

Anti-Amyloid Therapy, Where to Go Next?



Sperling et al. (2011)

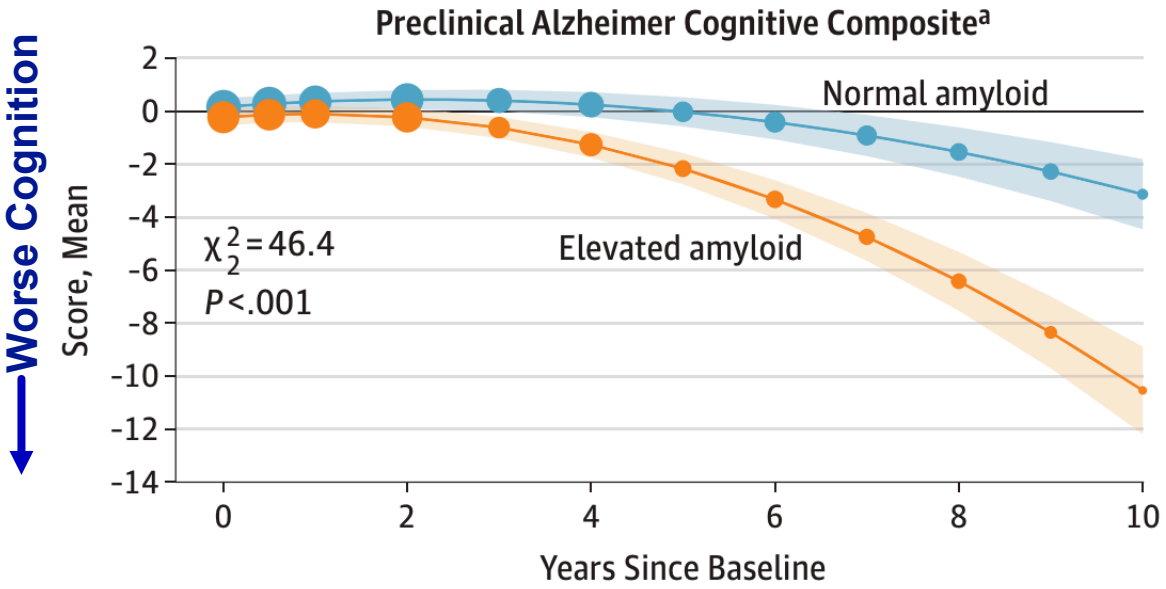
Anti-Amyloid Therapy, Where to Go Next?

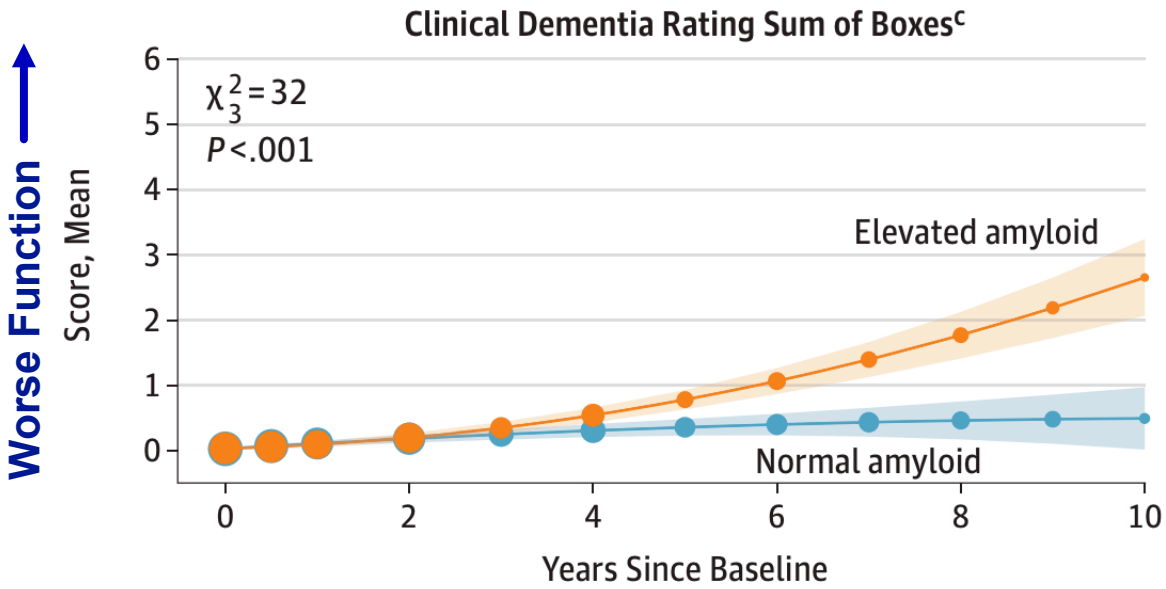
Secondary prevention

JAMA | Original Investigation

Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons

Michael C. Donohue, PhD; Reisa A. Sperling, MD, MMSc; Ronald Petersen, MD, PhD; Chung-Kai Sun, MS; Michael W. Weiner, MD; Paul S. Aisen, MD; for the Alzheimer's Disease Neuroimaging Initiative





Anti-Amyloid Therapy, Where to Go Next?

Secondary prevention

– Lowering amyloid before cognitive/functional impairment!

- Lecanemab: AHEAD Study

AHEAD STUDY

www.aheadstudy.org

- Donanemab: TRAILBLAZER-ALZ3

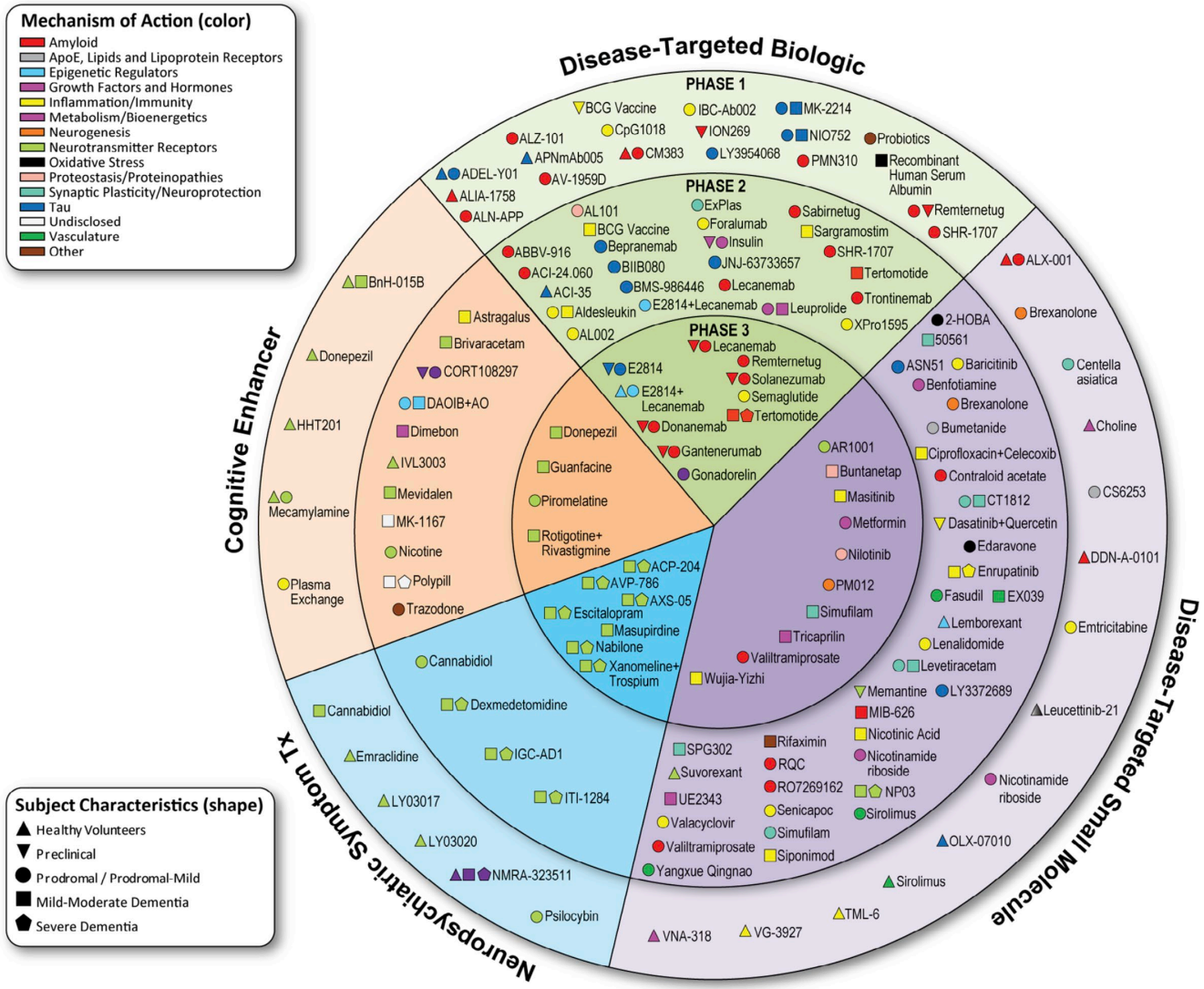
Active, not recruiting ⓘ

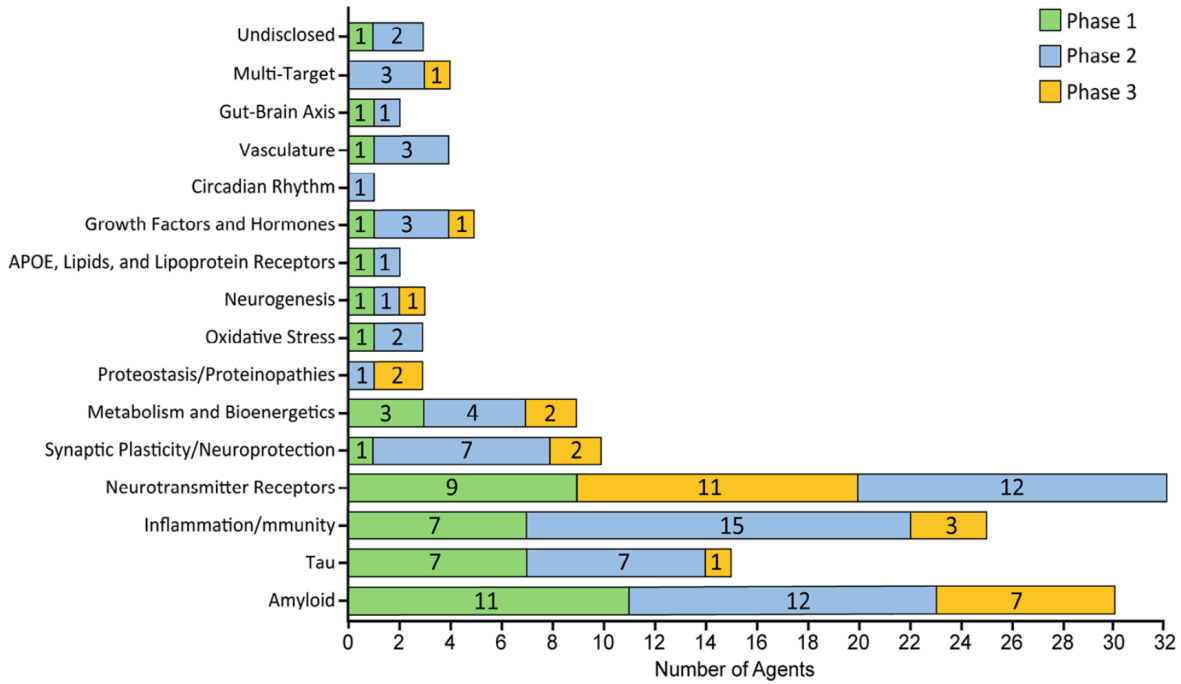
No longer looking for participants

Beyond Amyloid: Other Treatment Targets

clinicaltrials.gov

2025 Alzheimer's Drug Development Pipeline



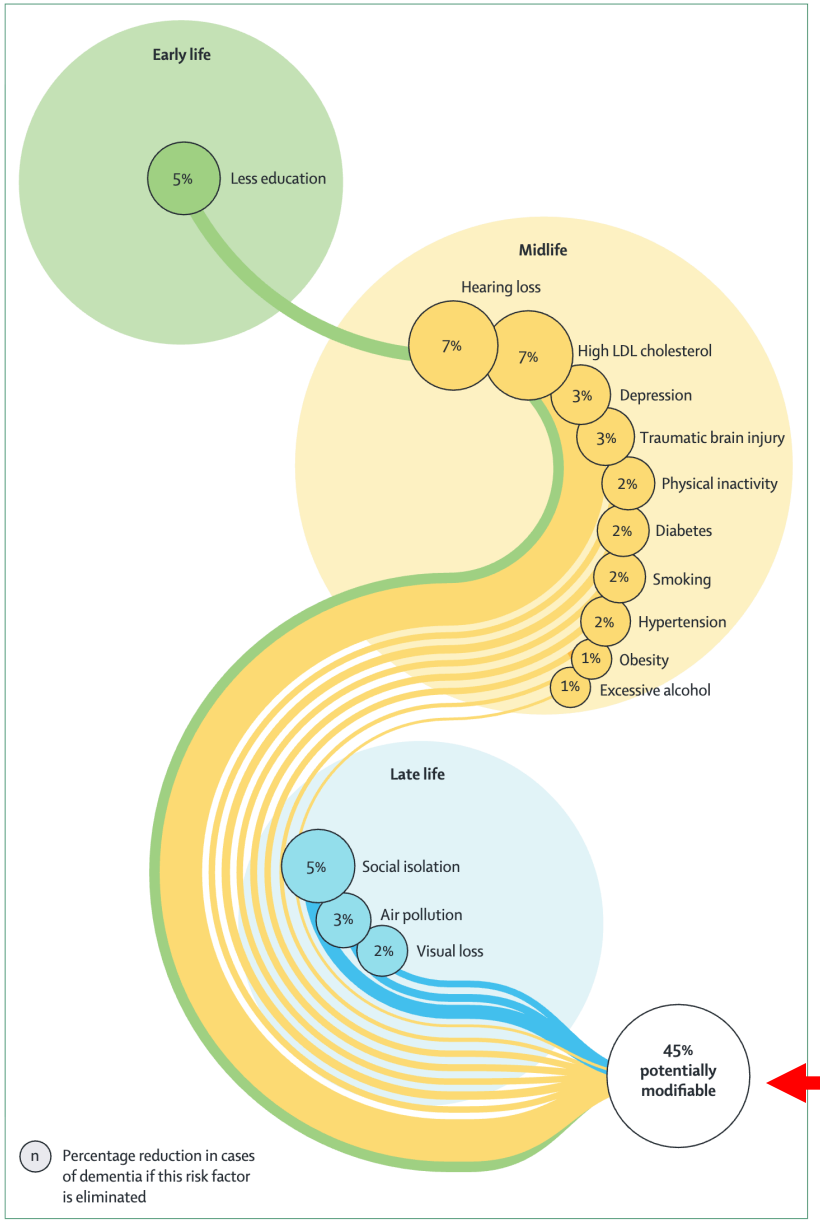


Cummings et al. (2025)

Beyond Amyloid: Lifestyle Interventions

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad, Naaheed Mukadam**



Multidomain Lifestyle Intervention

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

JAMA | Original Investigation

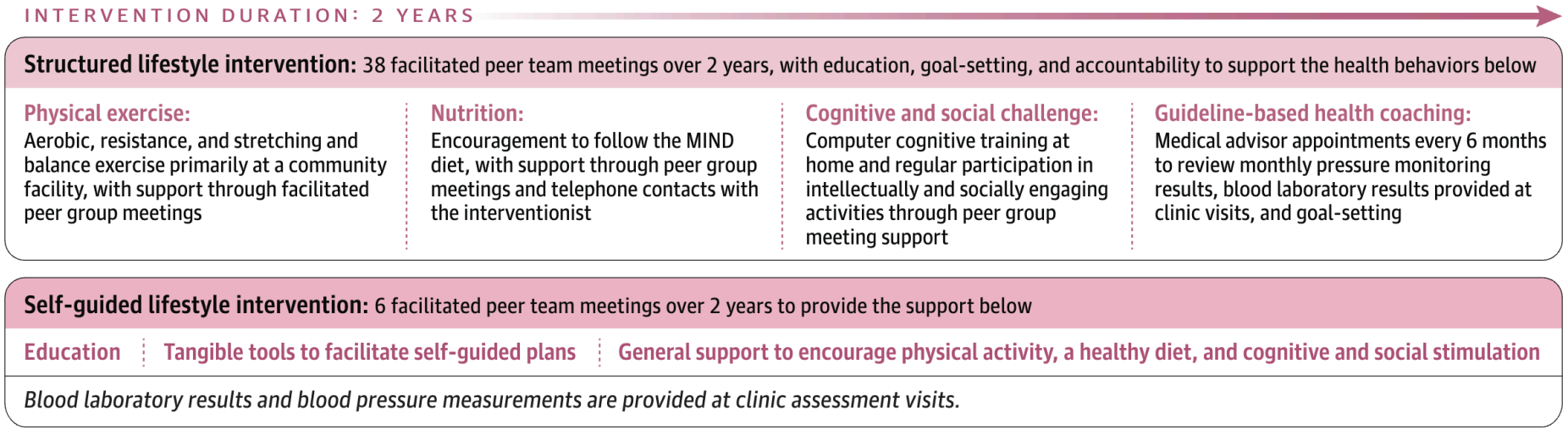
Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function
The US POINTER Randomized Clinical Trial

Laura D. Baker, PhD; Mark A. Espeland, PhD; Rachel A. Whitmer, PhD; Heather M. Snyder, PhD; Xiaoyan Leng, MD, PhD; Laura Lovato, MS; Kathryn V. Papp, PhD; Melissa Yu, MD; Miia Kivipelto, MD, PhD; Ashley S. Alexander, MHSA; Susan Antkowiak, BS; Maryjo Cleveland, MD; Claire Day, BSW; Richard Elbein, MS; Sarah Tomaszewski Farias, PhD; Deborah Felton, BS; Katelyn R. Garcia, MS; Darren R. Gitelman, MD; Sarah Graef, DC; Marjorie Howard, MSPH; Jeffrey Katula, PhD; Katherine Lambert, BA; Olivia Matongo, MPH; Anne Marie McDonald, MEd; Valory Pavlik, PhD; Rema Raman, PhD; Stephen Salloway, MD, MS; Christy Tangney, PhD; Jennifer Ventrelle, MS; Sharon Wilmoth, BA; Benjamin J. Willliams, MD, PhD; Rena Wing, PhD; Nancy Woolard; Maria C. Carrillo, PhD

Multidomain lifestyle intervention for the prevention of cognitive decline in at-risk older adults in Latin America (LatAm-FINGERS): a single-blind, multicentre, randomised controlled trial

*Lucia Crivelli, Claudia Kimie Suemoto, Ana Luisa Sosa, Francisco Lopera, David Aguillón, Ricardo Francisco Allegri, Ricardo Nitrini, Ismael Luis Calandri, Lina Velilla-Jiménez, Mônica Sanches Yassuda, Natalia Acosta-Baena, Rosa María Salinas, Ana Charamelo, Carolina Delgado Derio, Daisy Miguelina Acosta, Jorge Mario León-Salas, Lissette Duque-Peñailillo, María Isabel Cusicanqui, Nilton Custodio, Adriana Anchia-Alfaro, Alberto Núñez-Herrera, Alejandra De Rubens, Alice Leites, Ana Vigil-Martínez, Andrés Damian, Beatriz María Flores-Blanco, Belén Custodio, Carlos Laforcada, Carlos Márquez, Clarisse Vasconcelos Friedlaender, Clara Gabriela Espinoza-Cruz, Cristina Cañadas, Cristiane Peixoto, Darina Helen Muñoz, Diego Fernández Slezak, Elainy Felix, Esteban Aguirre-Salvador, Ezequiel Ignacio Surace, Francesca Mariani, Gabriela Rojas De La Torre, Graciet Verástegui, Greta Keller, Gustavo Henrique Peixoto, Handel Arturo Morilla, Ivonne Z Jiménez-Velázquez, Jamileth Yasmín More, Javiera Francisca Rodríguez, Jéssica Abdo Gonçalves Tosatti, João Victor de Faria Rocha, Jonathan Saldarriaga-Hernández, José Carlos Huilca, José Tomás García-Molina, Joyce Graciela Martínez-Galindo, Juan Carlos Duran, Juana Guillermina Rodriguez, Karina Braga Gomes, Karolina Gouveia César-Freitas, Katherine Agüero, Lara Mora-Villalobos, Laura Osorio Asprilla, Leonardo Cruz de Souza, Ligia Soto, Lucia Cortabarría, Lucy Baldeón, Luzia Lima Carreira, Lizeth Marin-Buitrago, Maira Camila Moreno, Maira Tonidandel Barbosa, Maren Torheim, Maria Aquimara Zambone Magalhães, Maria da Graça Morais Martin, Maria Eugenia Martin, Melissa Francisca Torres, Mercedes Menéndez, Micaela Anahi Hernandez, Mónica Sánchez Granizo, Myriam Gutiérrez, Nicolás Corvalán, Paula Jimena Mora, Pedro Peguero, Rocío Ramírez-Santos, Rodrigo Sebastian Fernández, Rosa Montesinos, Sebastian Ospina-Henao, Silvia Ysabel Montes, Sofía Santero, Sonia Maria Dozzi Brucki, Sylvia Josephy-Hernandez, Tomas Casildo Vazquez, Yanina Bérgamo, Yamile Bocanegra, Yleana Altagracia Muñoz, Yosselin Vicuña, Zoraida Del Carmen Lora, Miia Kivipelto, Rema Raman, Mark A Espeland, Laura D Baker, Heather M Snyder, Gustavo Emilio Sevlever, María C Carrillo, Paulo Caramelli, on behalf of the LatAm-FINGERS Study Group**

Multidomain Lifestyle Intervention: US POINTER



Baker et al. (2025)

Multidomain Lifestyle Intervention: US POINTER

INTERVENTION DURATION: 2 YEARS

Structured lifestyle intervention: 38 facilitated peer team meetings over 2 years, with education, goal-setting, and accountability to support the health behaviors below

Physical exercise:
Aerobic, resistance, and stretching and balance exercise primarily at a community facility, with support through facilitated peer group meetings

Nutrition:
Encouragement to follow the MIND diet, with support through peer group meetings and telephone contacts with the interventionist

Cognitive and social challenge:
Computer cognitive training at home and regular participation in intellectually and socially engaging activities through peer group meeting support

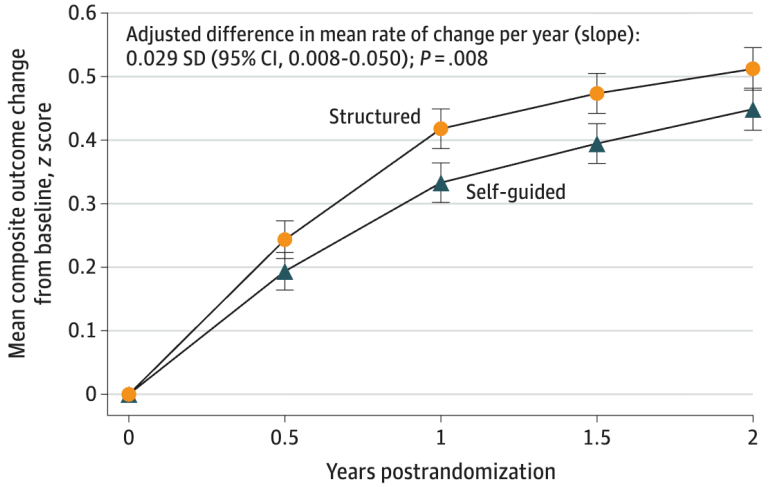
Guideline-based health coaching:
Medical advisor appointments every 6 months to review monthly pressure monitoring results, blood laboratory results provided at clinic visits, and goal-setting

Self-guided lifestyle intervention: 6 facilitated peer team meetings over 2 years to provide the support below

Education | Tangible tools to facilitate self-guided plans | General support to encourage physical activity, a healthy diet, and cognitive and social stimulation

Blood laboratory results and blood pressure measurements are provided at clinic assessment visits.

Figure 3. Change From Baseline in Global Cognitive Function Composite Score (Primary Outcome) by Structured vs Self-Guided Lifestyle Interventions

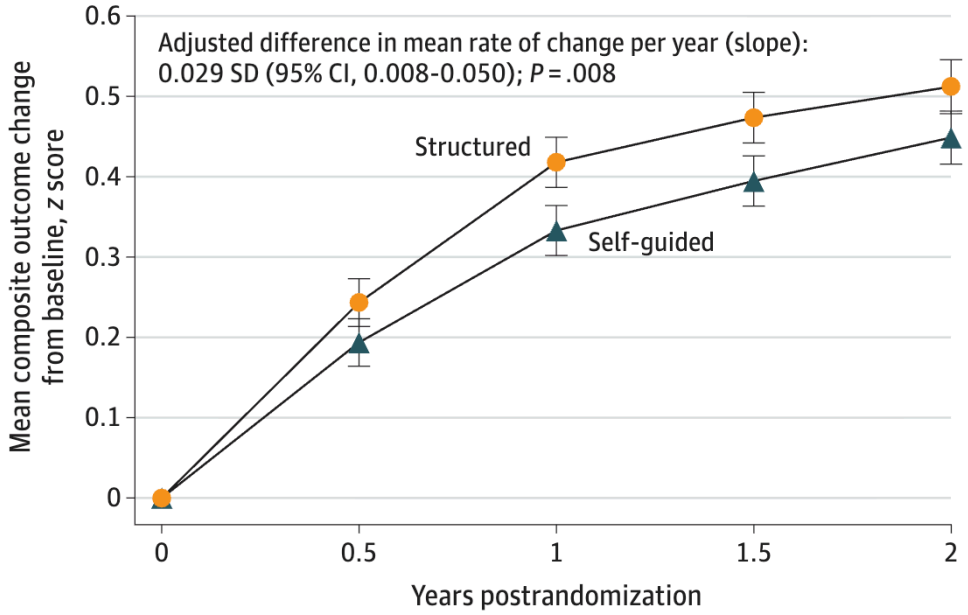


Total No.					
Structured	1056	965	949	918	923
Self-guided	1055	976	949	929	956

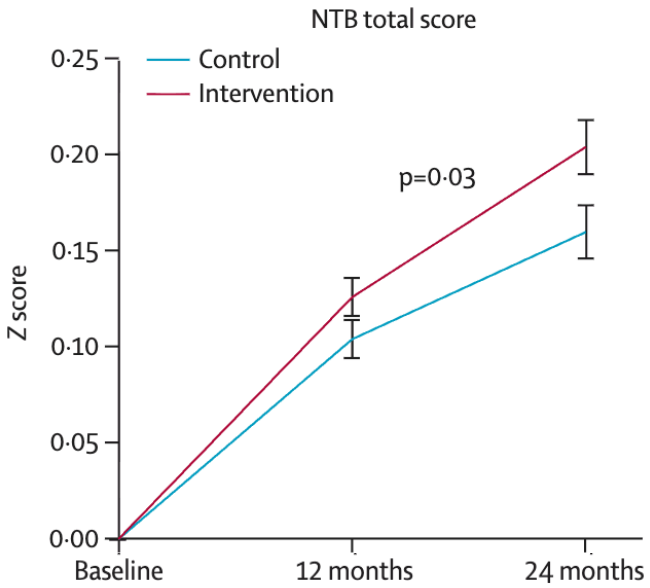
Baker et al. (2025)

Multidomain Lifestyle Intervention: Consistent Findings across Trials

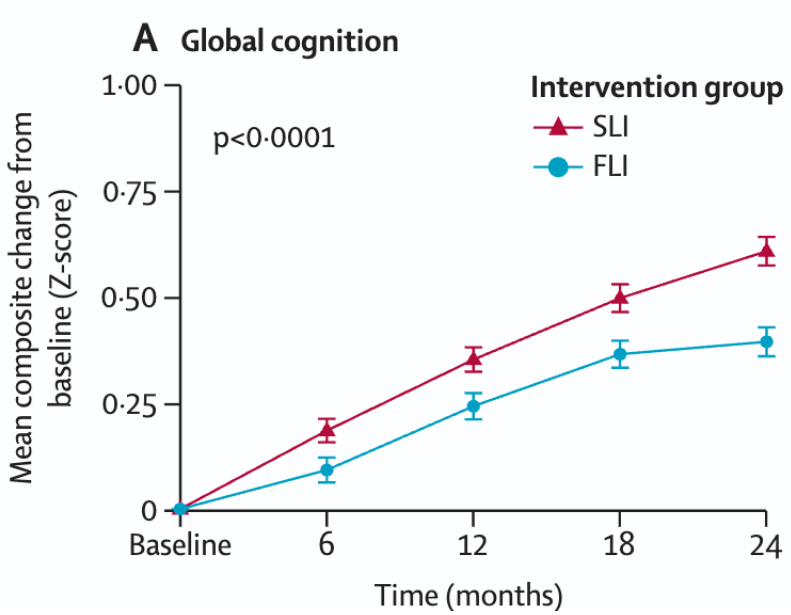
US POINTER



FINGER



LatAm-FINGERS



Ngandu et al. (2015), Baker et al. (2025); Crivelli et al. (2026)

Lifestyle Factors May Modify Trajectory of Preclinical Alzheimer's Disease

Physical activity as a modifiable risk factor in preclinical Alzheimer's disease

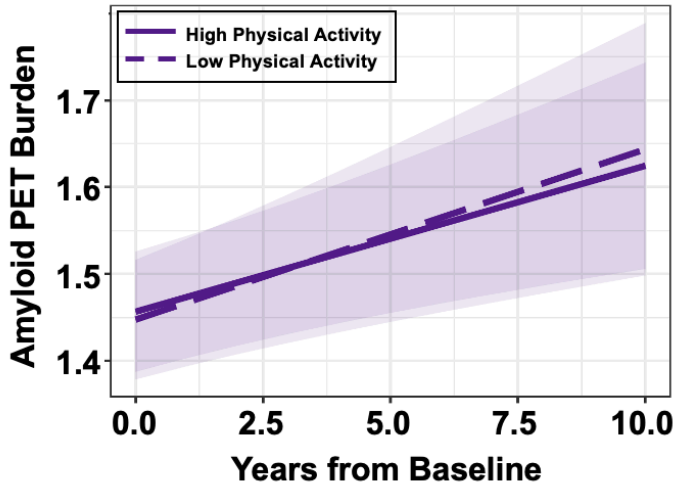
Wai-Ying Wendy Yau ✉, Dylan R. Kirn, Jennifer S. Rabin, Michael J. Properzi, Aaron P. Schultz, Zahra Shirzadi, Kailee Palmgren, Paola Matos, Courtney Maa, Jeremy J. Pruzin, Stephanie A. Schultz, Rachel F. Buckley, Dorene M. Rentz, Keith A. Johnson, Reisa A. Sperling & Jasmeer P. Chhatwal ✉

Nature Medicine **31**, 4075–4083 (2025) | Cite this article

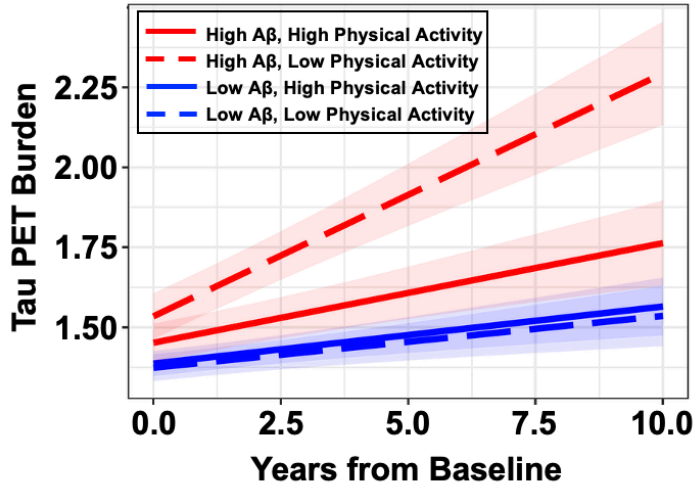
HARVARD AGING BRAIN

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

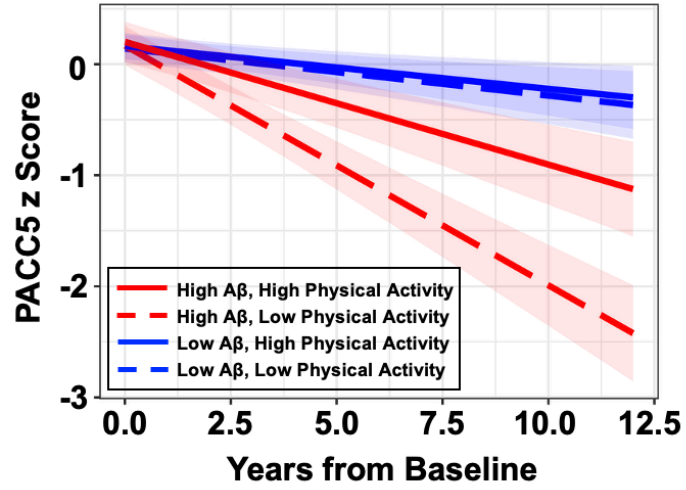
Global Amyloid (Aβ)



Inferior Temporal Tau



Cognitive Function



Acknowledgement



HABS team (all members current and past)

Jasmeer Chhatwal	Hyun-Sik Yang
Reisa Sperling	Stephanie Schultz
Keith Johnson	Zahra Shirzadi
Dorene Rentz	Gillian Coughlan
Rebecca Amariglio	Nicolas Vogt
Rachel Buckley	Kailee Palmgren
Michael Properzi	Paola Matos
Dylan Kirn	Jennifer Rabin
Alexa Coussoule	Jeremy Pruzin

Participants and study partners

HARVARD AGING BRAIN

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

Funding: NIA K23 AG084868

Mass General Brigham

HARVARD MEDICAL SCHOOL