National Institutes of Health
Office of Disease Prevention

Prevention in Focus Webinar Series

Emerging Evidence for Strategies to Prevent Alzheimer's Disease

Wade Self, Ph.D.
Presenter | Instructor, Washington University School of Medicine in St. Louis

Marcel Salive, Ph.D.
Speaker Introduction and Q&A Moderator | Medical Officer, National Institute on Aging (NIA)

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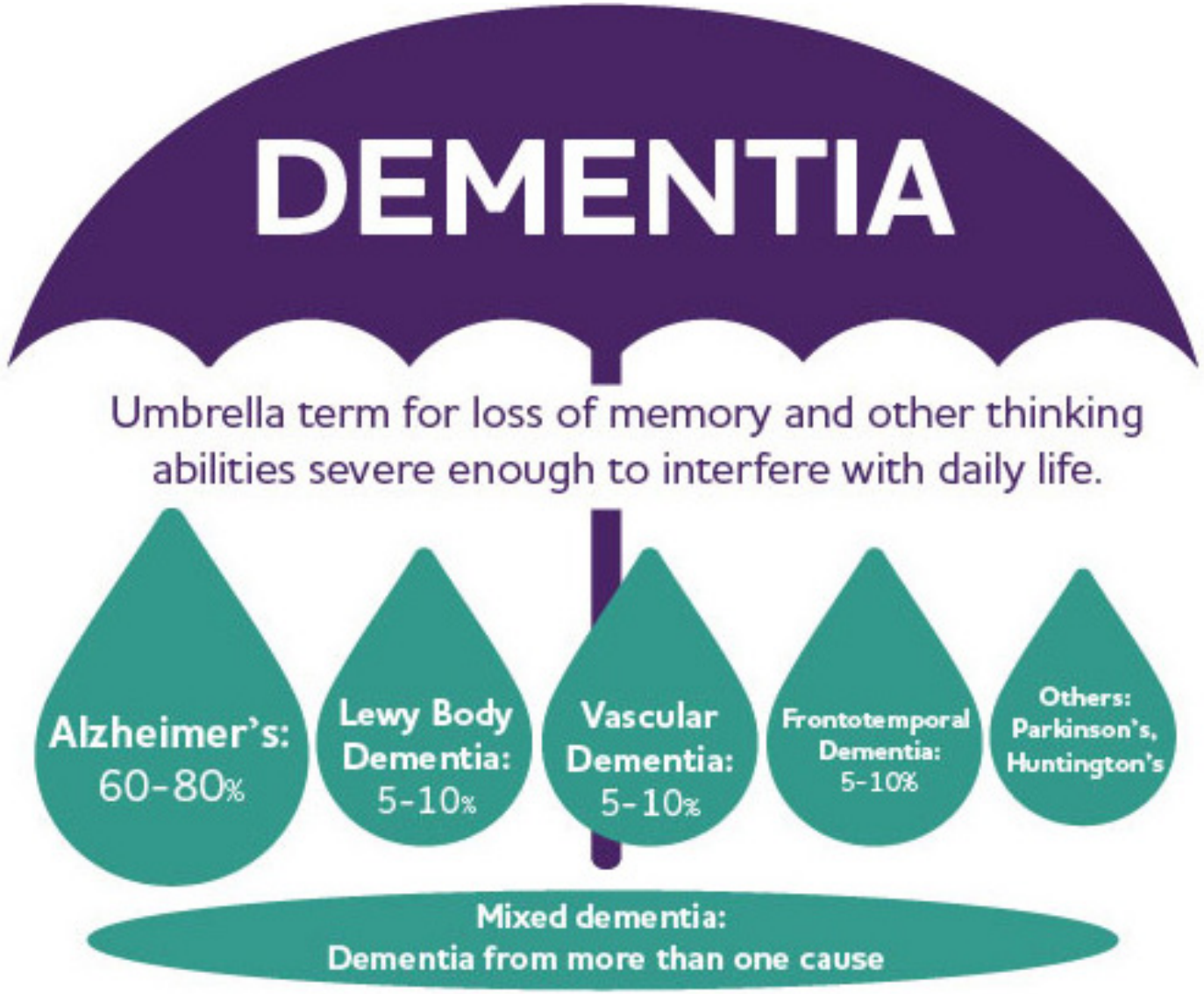
Emerging Evidence for Strategies to Prevent Alzheimer Disease

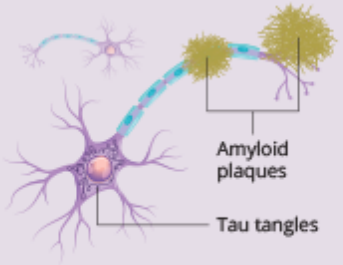
Wade Self, Ph.D.
Laboratory of David Holtzman, M.D.
Department of Neurology

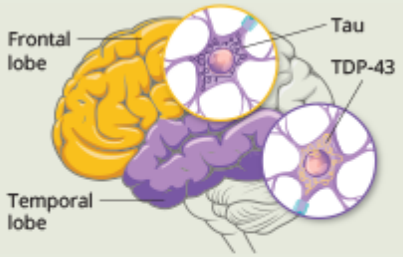


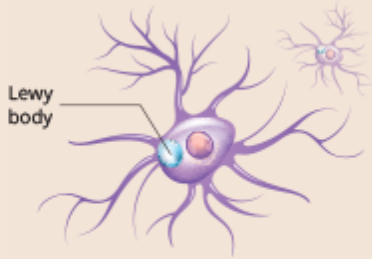
Source: Alzheimer's Association

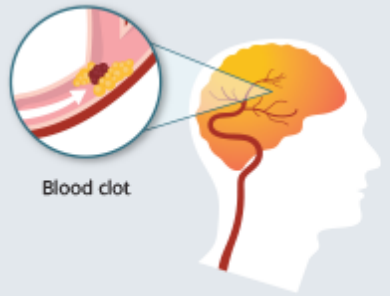
TYPES OF DEMENTIA

Alzheimer's Disease	Frontotemporal Dementia	Lewy Body Dementia	Vascular Dementia
What Is Happening in the Brain?*			
Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain.	Abnormal amounts or forms of tau and TDP-43 proteins accumulate inside neurons in the frontal and temporal lobes.	Abnormal deposits of the alpha-synuclein protein, called "Lewy bodies," affect the brain's chemical messengers.	Conditions, such as blood clots, disrupt blood flow in the brain.

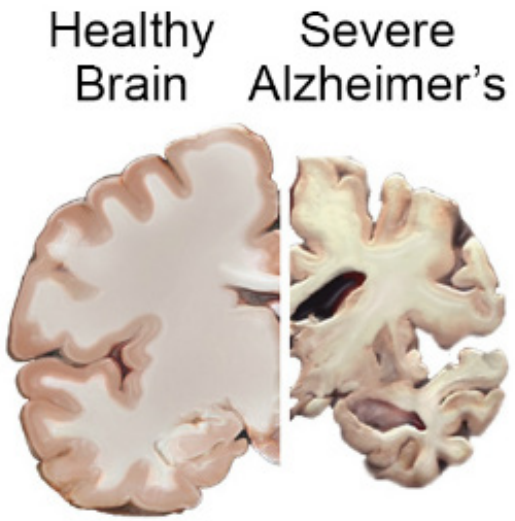


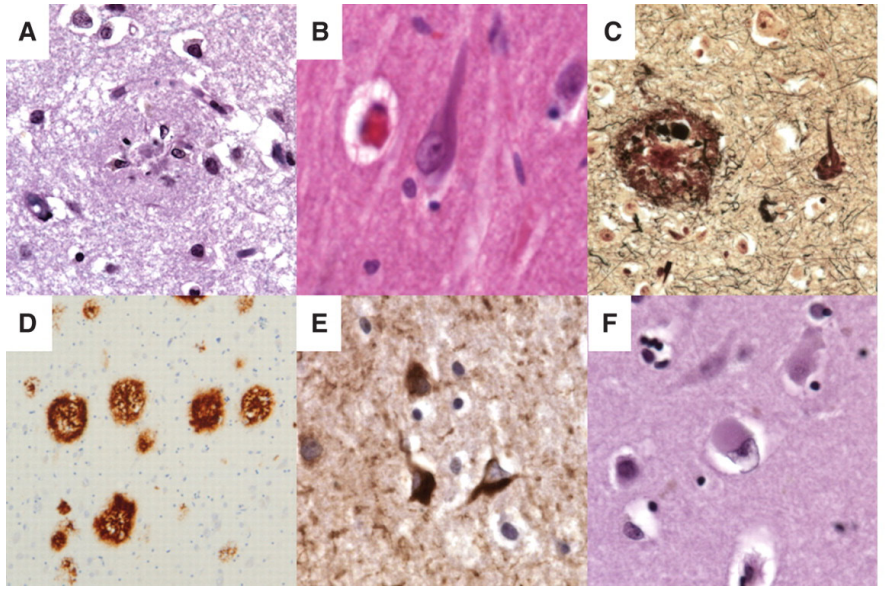






*These changes are just one piece of a complex puzzle that scientists are studying to understand the underlying causes of these forms of dementia and others.



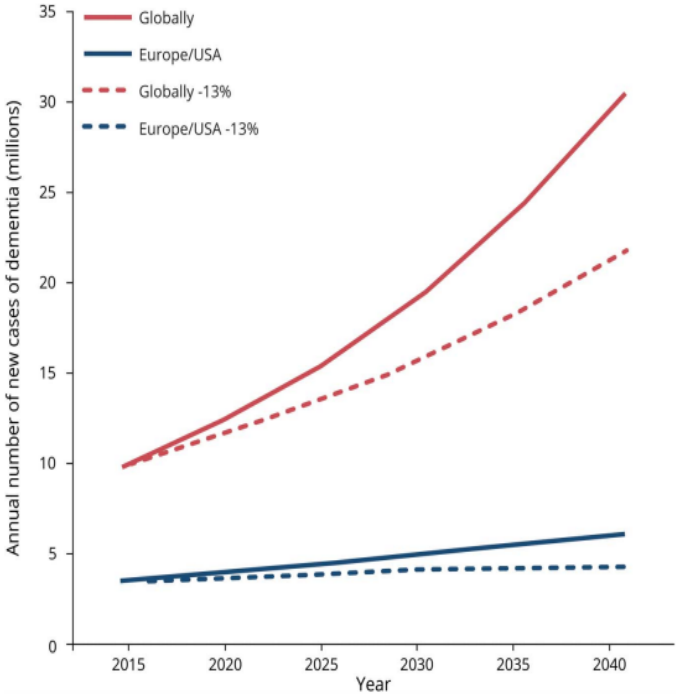


Source: National Institute on Aging
Serrano-Pozo et al., PMID: 22229116

Alzheimer Disease (AD) in the United States

- 2022: 6.5 Million, ~180,000 Deaths, $325B in healthcare costs.
  - does not include **$271.6 B** in unpaid caregiving by family and friends
- 2050: 13.8 Million, $1T in healthcare costs
- Some data from the United States and Europe suggests that age-specific dementia incidence rates have decreased over the past 2 decades
  - High-income countries, predominantly Caucasian cohorts.

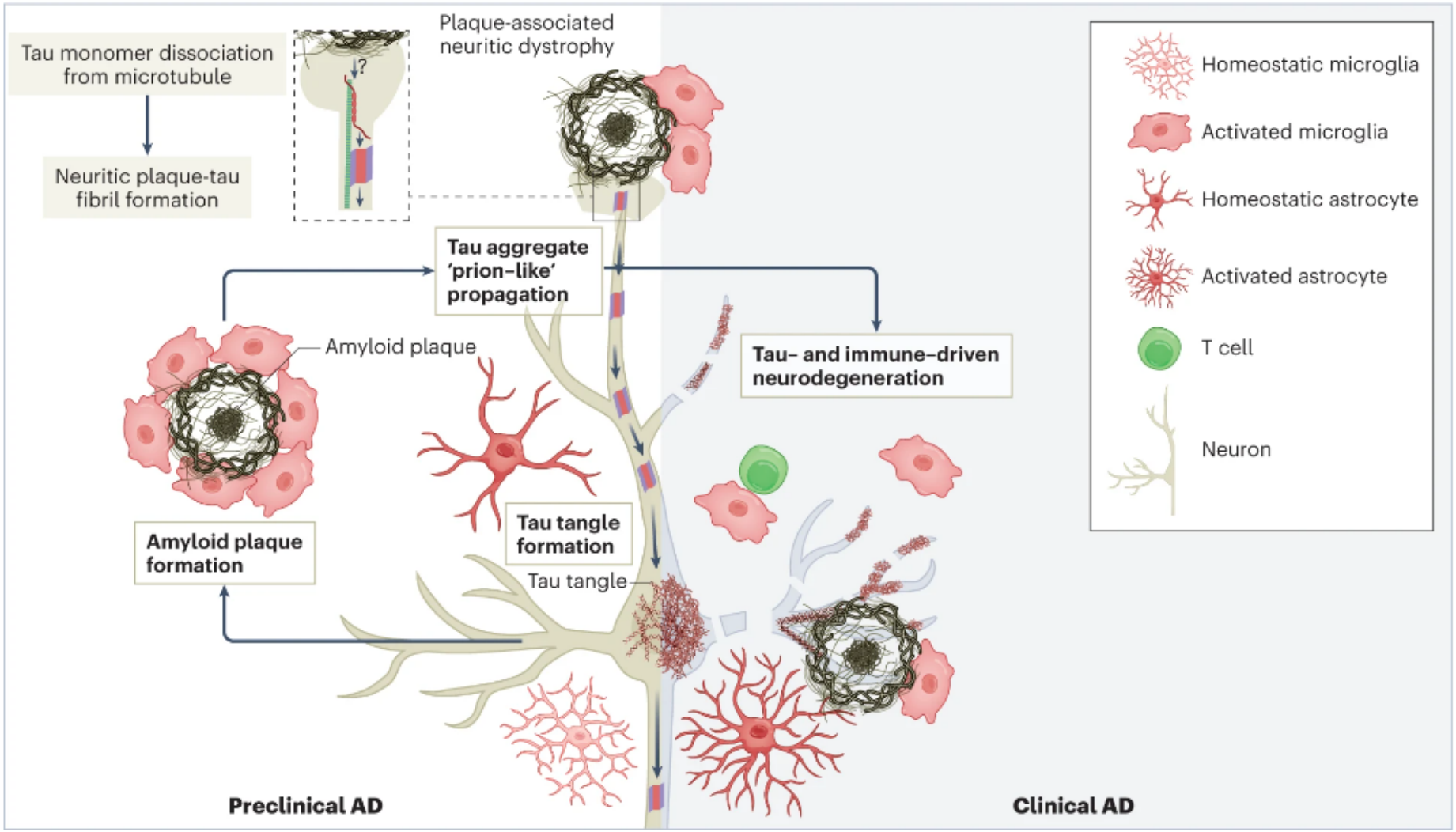
Figure 4 Projected incidence of dementia in millions



Projected yearly incidence of dementia on the basis of current rates (solid lines) and projected incidence of dementia assuming continuation of a decreasing trend (dashed lines). Current rates are based on estimates from the 2012 World Alzheimer Report, which at the time estimated that 682 million new cases would occur over the 2010 to 2050 period.

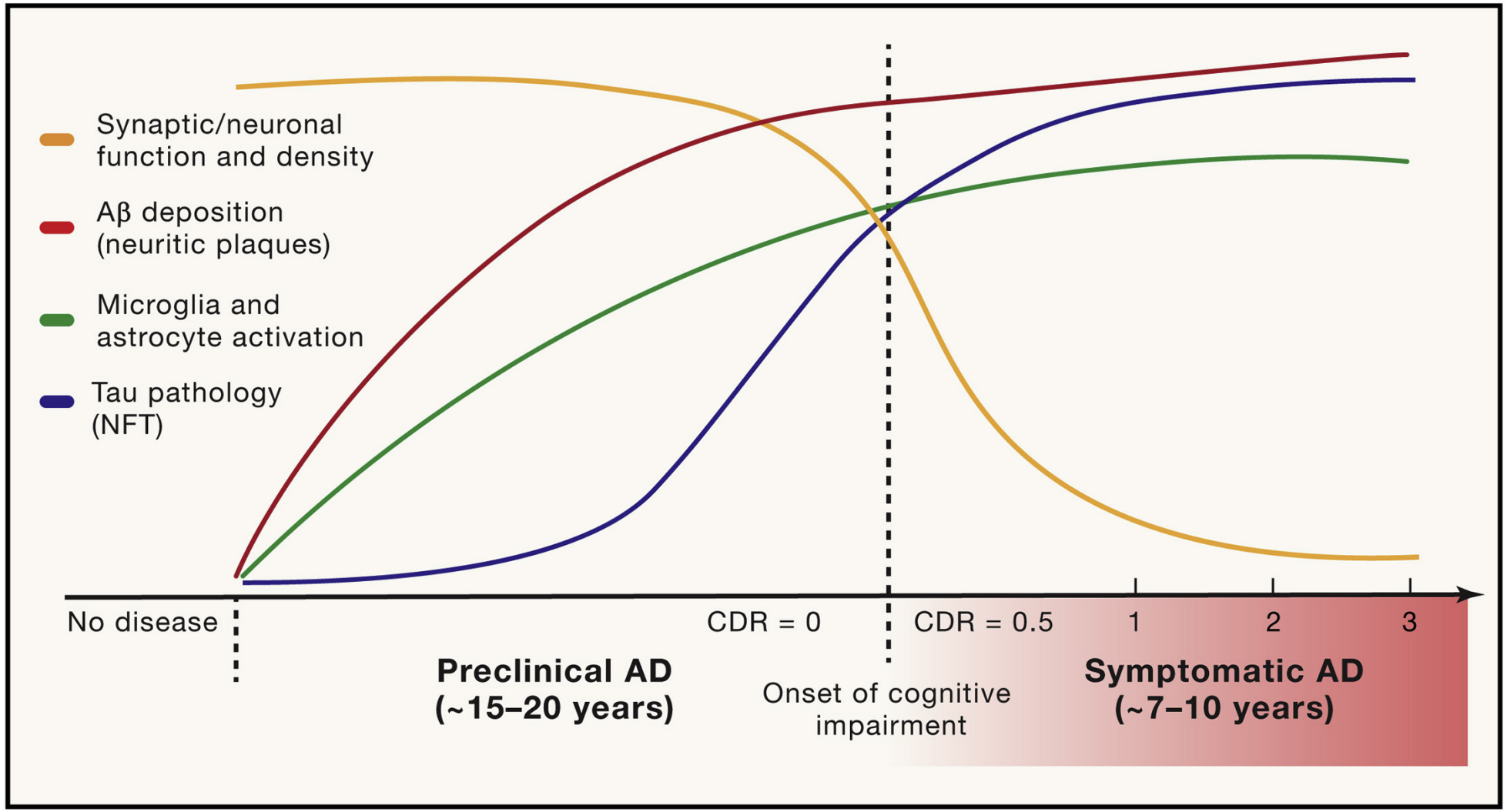
Source: Alzheimer's Association
Wolters et al., PMID: 32611641

The proposed molecular and cellular progression of AD



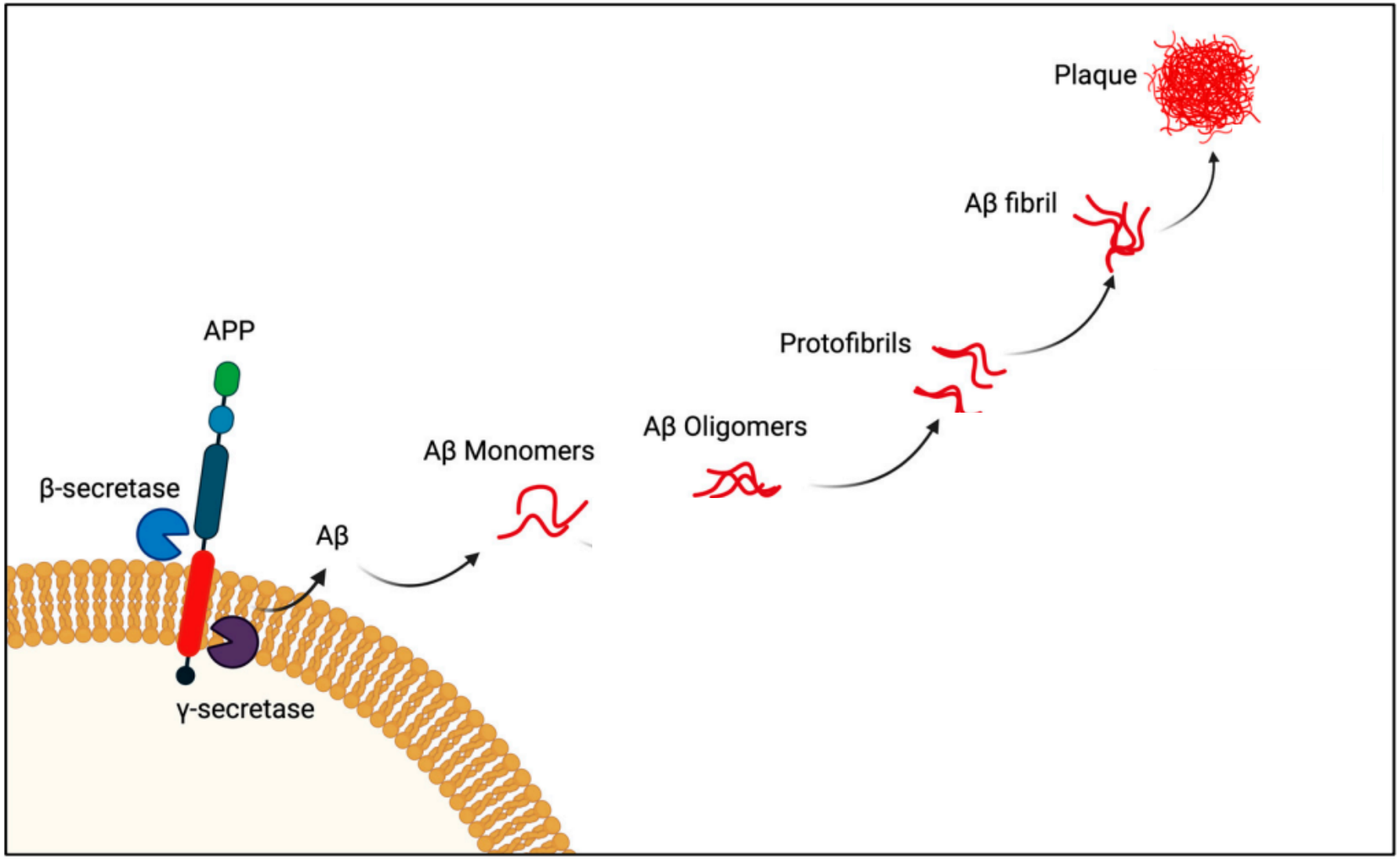
Source: Self and Holtzman, PMID: 37667136

Clinical AD is the manifestation of a long, progressive process



Source: Long and Holtzman, PMID: 31564456

Lessons learned from anti-amyloid clinical trials



Source: Vogt et al., PMID:36835301

Lessons learned from anti-amyloid clinical trials (continued)

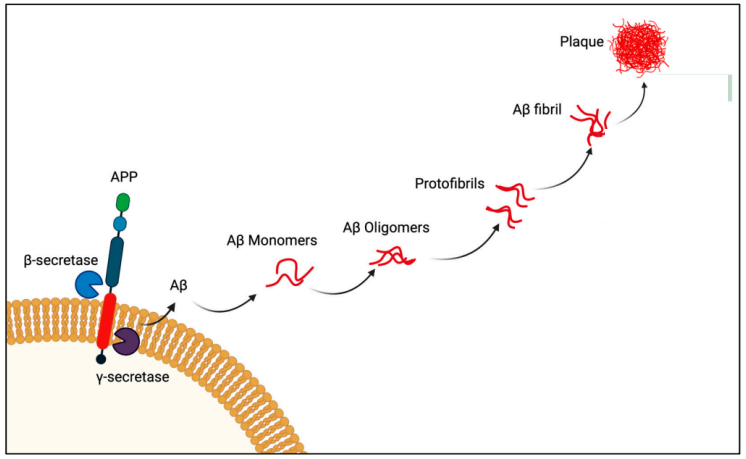
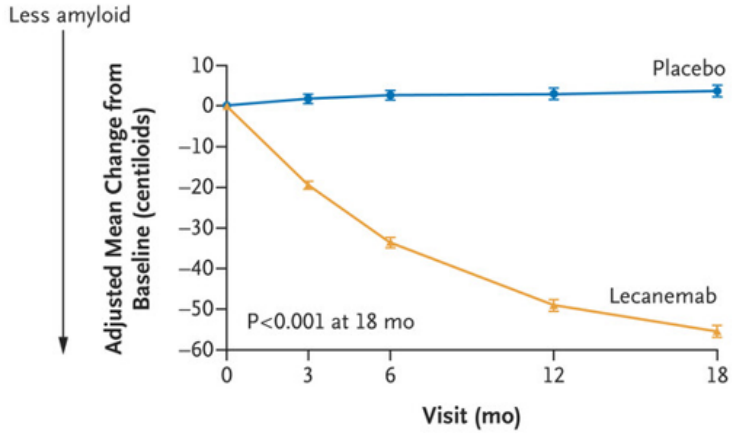


Table 1 | Summary of large-scale clinical trials of anti-amyloid passive immunization

Monoclonal antibody (RCT)	Trial endpoint (weeks)	Number of trial participants	Amyloid negative in treatment group at end (%)[a]	Dose	Cognitive benefit compared to placebo	Aβ target
Solanezumab (Expedition 1,2)[69]	80	2,052	-	400 mg	No	Soluble monomer
Crenezumab (CREAD 1,2)[70]	102	1,619	-	60 mg/kg	No	Soluble oligomers
Gantenerumab (Graduate 1,2)[134]	116	1,965	27	1,020 mg	No	Insoluble fibrils
Aducanamab (EMERGE)[64]	78	1,638	48	10 mg/kg[b]	Yes	Insoluble fibrils
Aducanamab (ENGAGE)[64]	78	1,647	31	10 mg/kg[b]	No	Insoluble fibrils
Donanemab (TRAILBLAZER-ALZ 2)[4]	76	1,736	76	700 mg first 3 doses, 1,400 mg	Yes	Plaque-associated Aβ
Lecanemab (Clarity AD)[3]	78	1,734	81	10 mg/kg	Yes	Protofibrils

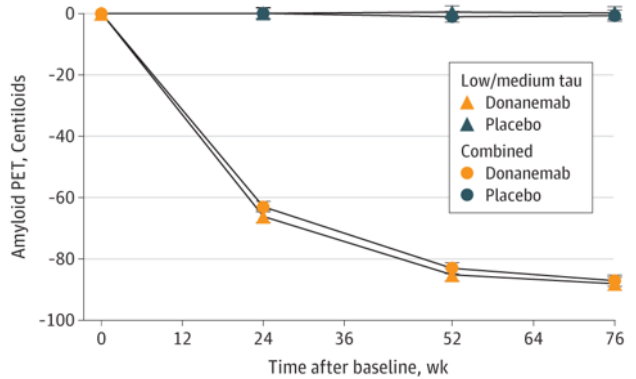
Source: Self and Holtzman, PMID: 37667136

Lessons learned from anti-amyloid clinical trials (continued)

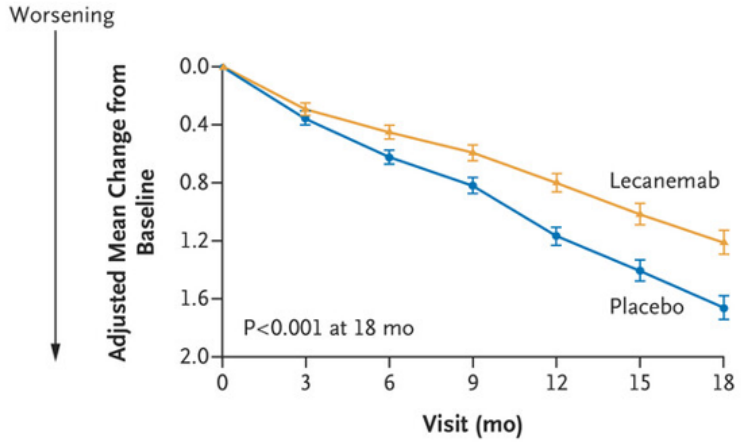


No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

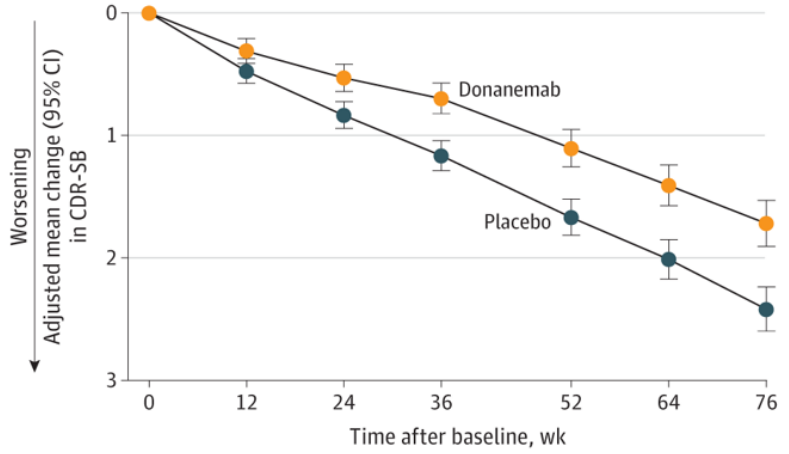


No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757



No. of participants							
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

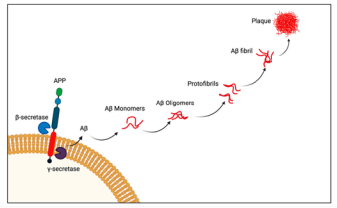
Source: Van Dyck et al., PMID: 36449413
Sims et al., PMID: 37459141

Lessons learned from anti-amyloid clinical trials (continued)

Table 1 | Summary of large-scale clinical trials of anti-amyloid passive immunization

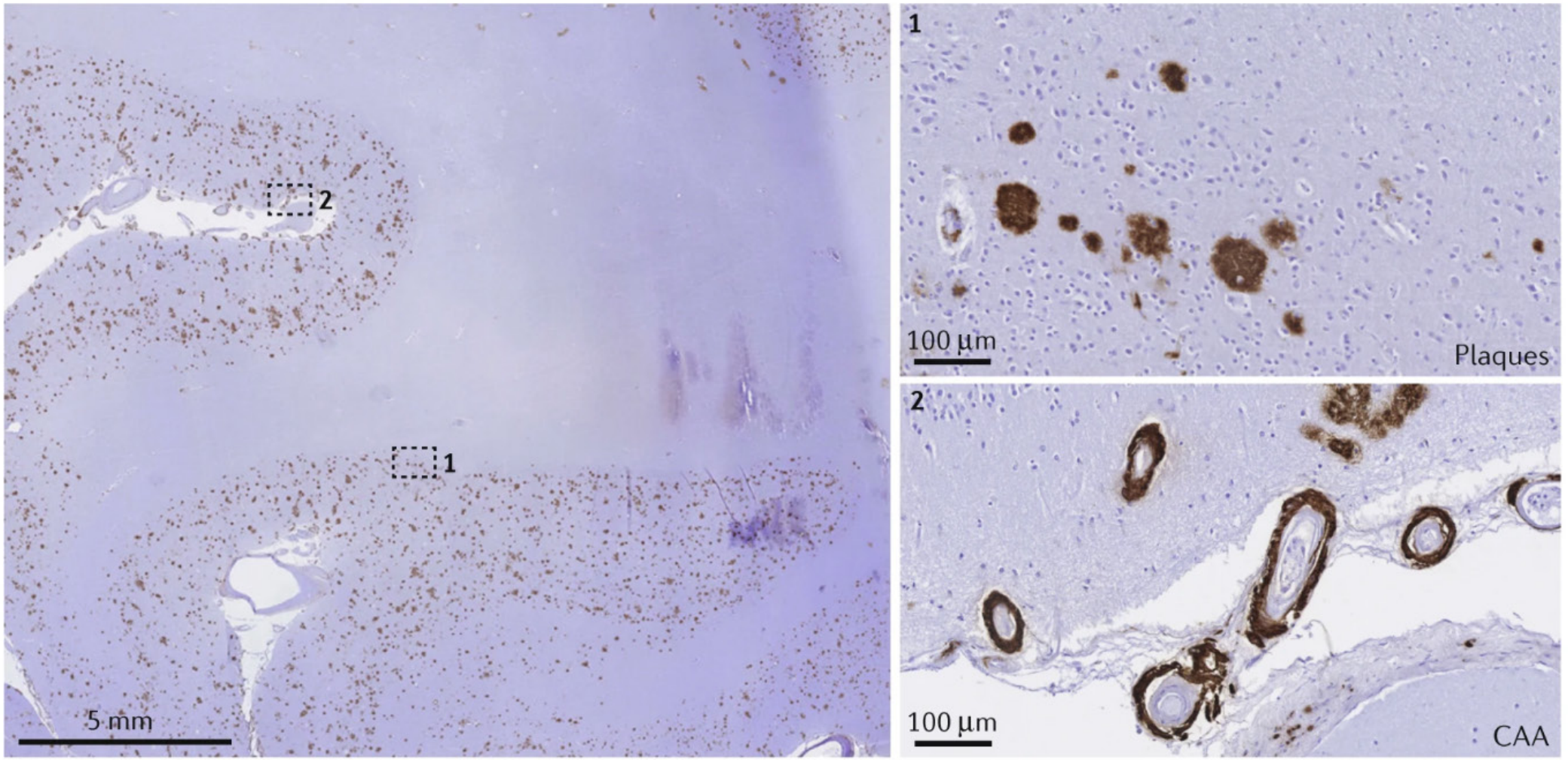
Monoclonal antibody (RCT)	Trial endpoint (weeks)	Number of trial participants	Amyloid negative in treatment group at end (%)[a]	Dose	Cognitive benefit compared to placebo	ARIA-E (% treatment greater than placebo)	ARIA-H (% treatment greater than placebo)	Aβ target
Solanezumab (Expedition 1,2)[69]	80	2,052	-	400 mg	No	0.5	−0.7	Soluble monomer
Crenezumab (CREAD 1,2)[70]	102	1,619	-	60 mg/kg	No	0.1	0.5	Soluble oligomers
Gantenerumab (Graduate 1,2)[134]	116	1,965	27	1,020 mg	No	-	-	Insoluble fibrils
Aducanamab (EMERGE)[64]	78	1,638	48	10 mg/kg[b]	Yes	33.0	13.0	Insoluble fibrils
Aducanamab (ENGAGE)[64]	78	1,647	31	10 mg/kg[b]	No	33.0	13.0	Insoluble fibrils
Donanemab (TRAILBLAZER-ALZ 2)[4]	76	1,736	76	700 mg first 3 doses, 1,400 mg	Yes	21.9	17.8	Plaque-associated Aβ
Lecanemab (Clarity AD)[3]	78	1,734	81	10 mg/kg	Yes	10.9	6.3	Protofibrils

Mostly asymptomatic



Source: Self and Holtzman, PMID: 37667136

Aβ also accumulates in blood vessels: Cerebral Amyloid Angiopathy



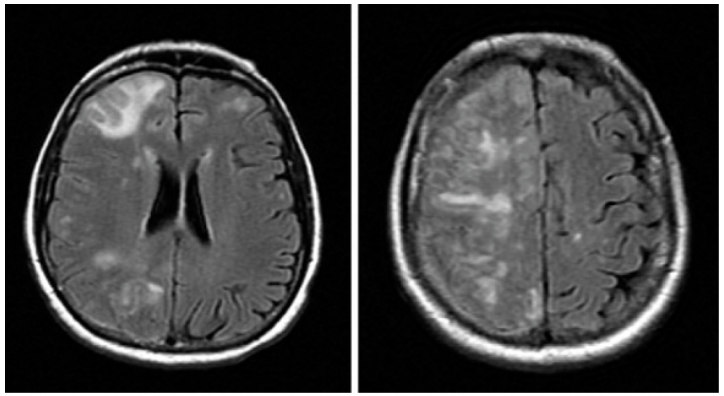
Source: Greenberg et al., PMID: 31827267

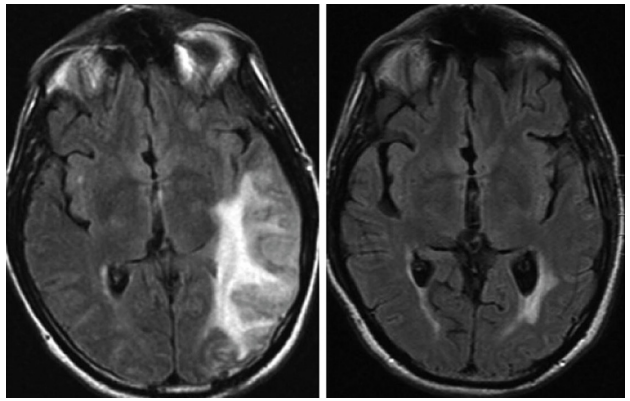
Safety concerns with anti-amyloid antibodies look like Cerebral Amyloid Angiopathy-related inflammation (CAA-ri)

Post anti-amyloid treatment

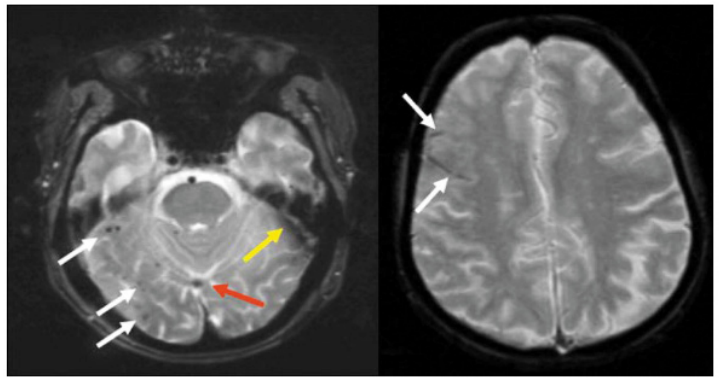
Spontaneous CAA-ri

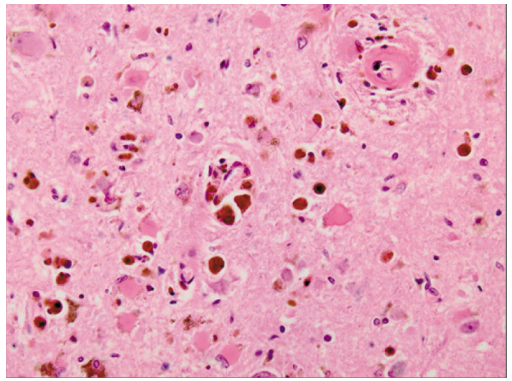
Vasogenic Edema/ Sulcal Effusion (ARIA-E)





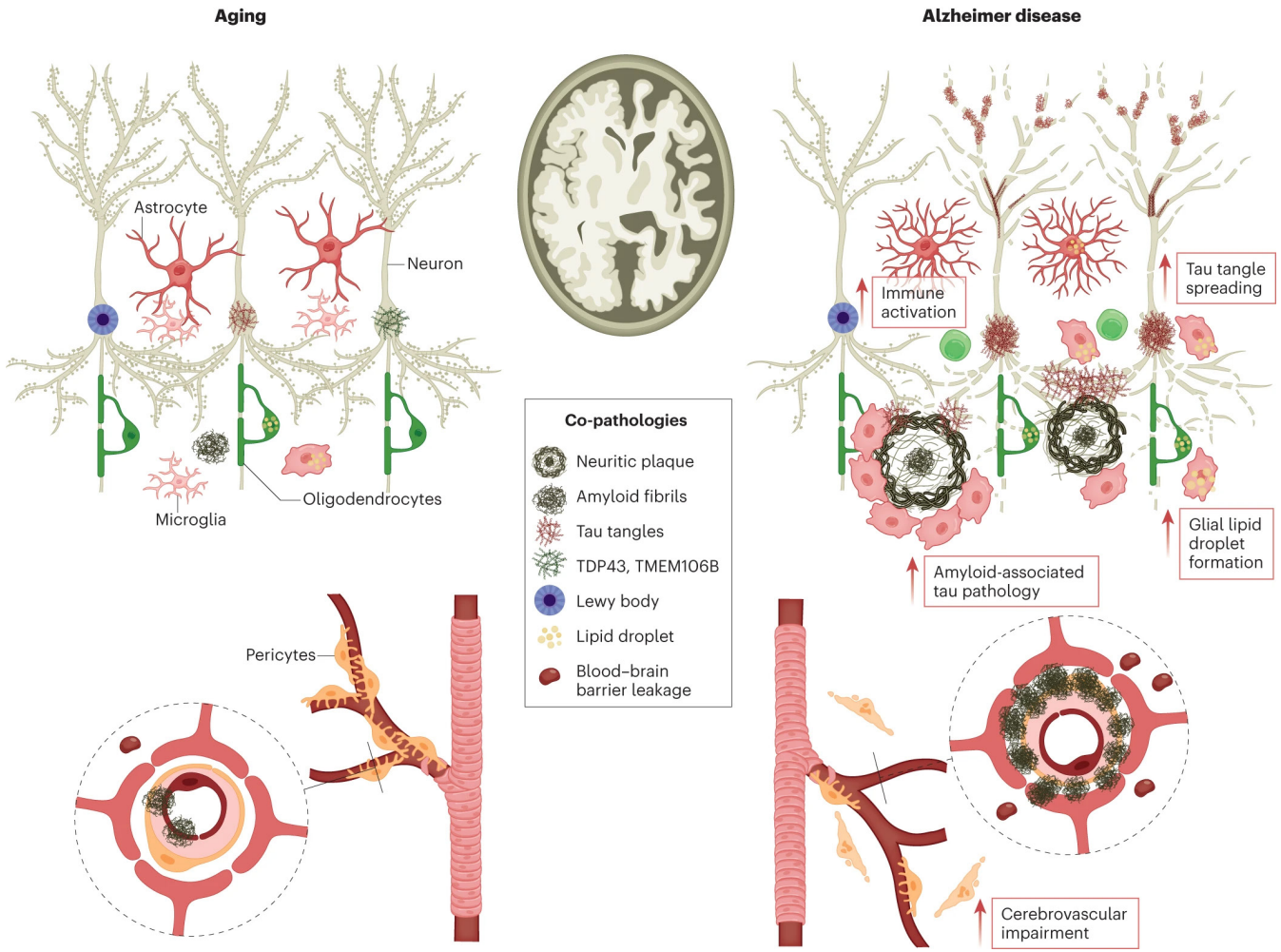
Microhemmorhage/Superficial Siderosis (ARIA-H)





Source: Sperling et al., PMID: 21784348

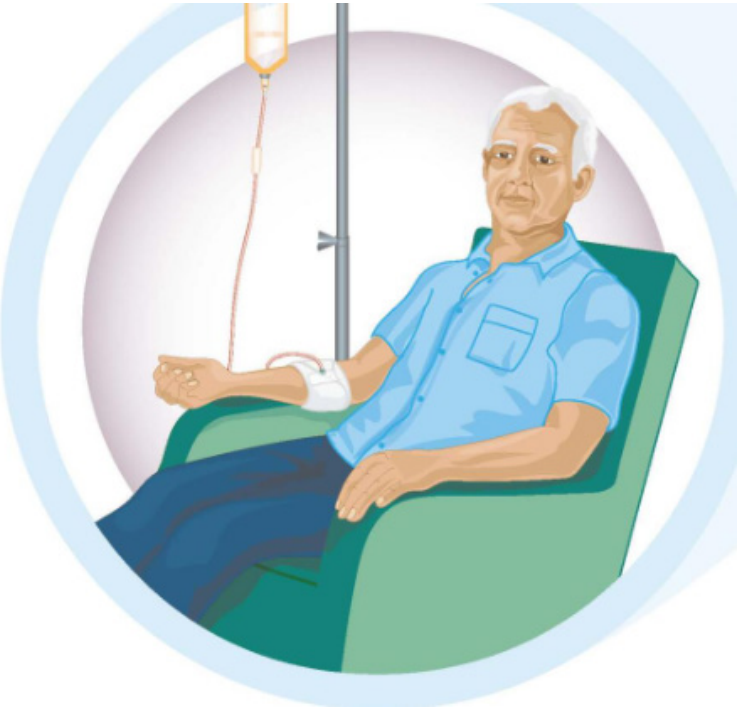
The older a person is when cognitive decline begins, the more likely that other, non-AD pathologies are also contributing



Source: Self and Holtzman, PMID: 37667136

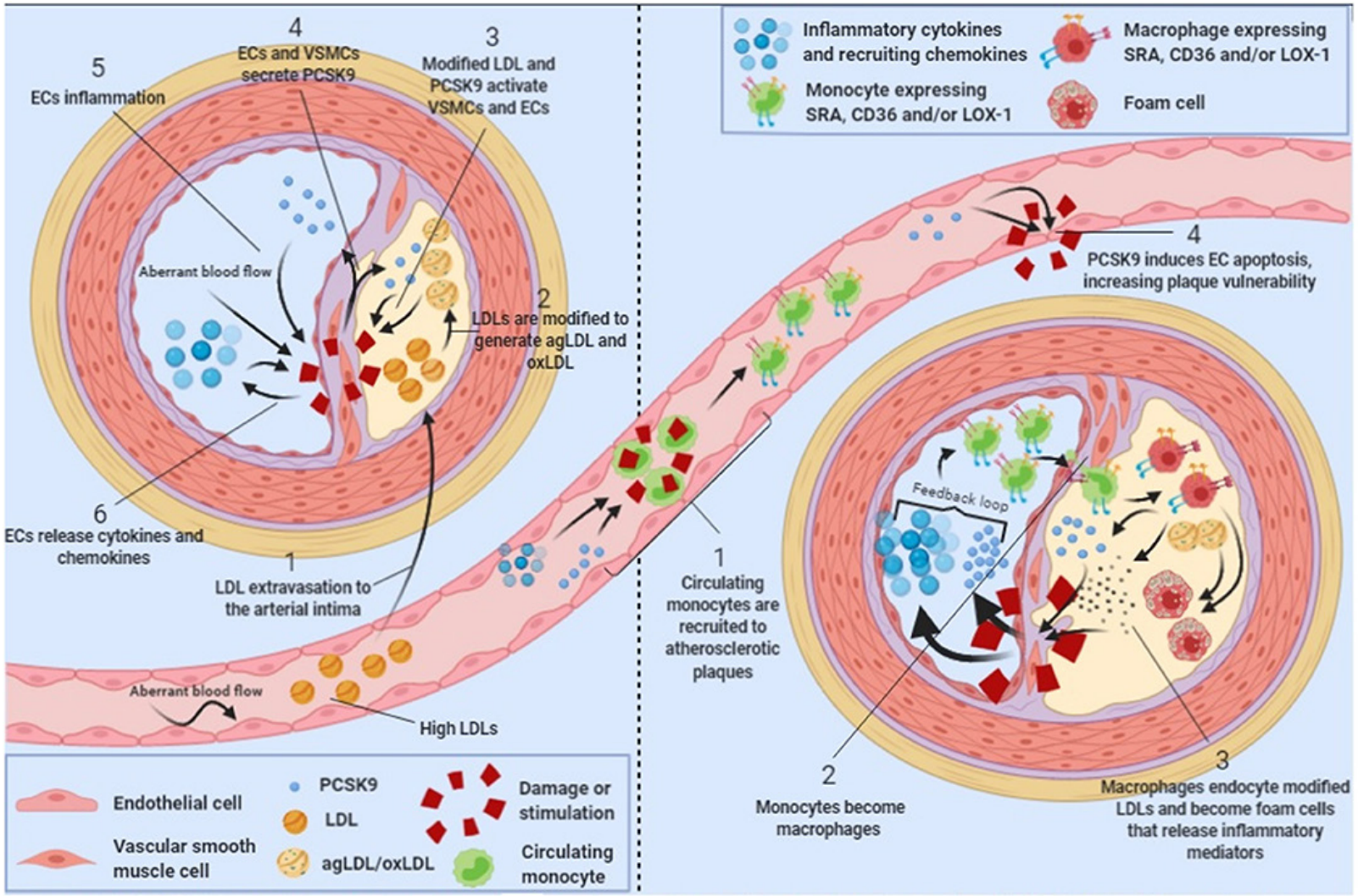
Challenges for anti-amyloid therapy implementation

- Appropriate patient selection: clinical trials of lecanemab enrolled patients with mild cognitive symptoms (CDR 0.5–1) and confirmation of amyloid pathology by PET imaging, CSF testing, or other tests such as appropriate blood tests. Cognitive screening and the presence of amyloid pathology are required for treatment based on the indication.
- Safety screening: APOE ε4 genotype is a risk factor for ARIA, and the FDA prescribing information of lecanemab states that testing for APOE ε4 status is recommended before initiation of treatment.
- Dosing and monitoring: intravenous infusions administered every 2 or 4 weeks combined with monitoring of ARIA by magnetic resonance imaging are a demanding regimen for patients and their families.



Source: Self and Holtzman, PMID: 37667136
Adapted from Alzheimer's Research UK

What can we learn from other fields for prevention?



Source: Luquero et al., PMID: 33834043

What can we learn from other fields for prevention? (continued)

Earlier intervention

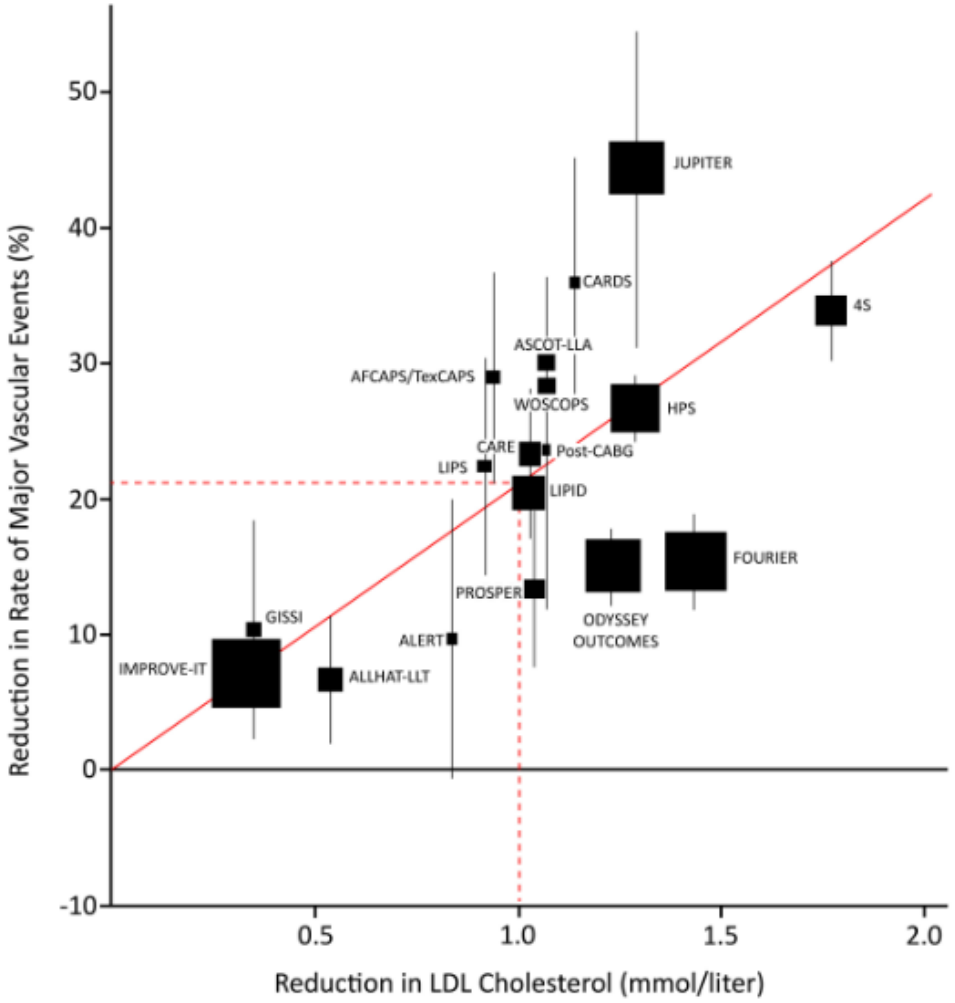
Increased efficacy

Trials with late initiation of LDL-C lowering therapy in patients without CAD or with stable CAD

Study	Population	Treatment	Time from index event to treatment	Primary endpoint	Results	Median FU
AFCAPS/TexCAPS	No CAD n= 6605	Lovastatin 20-40mg vs. placebo	N/A	MACE (fatal/nonfatal MI, UAP, SCD)	RR 0.63 (95% CI: 0.50 to 0.79; p<0.001)	5.2 years
JUPITER	No CAD, high CRP n = 17802	Rosuvastatin 20mg vs. placebo	N/A	MACE (MI, stroke, arterial revascularization, hospitalization for UAP, cardiovascular death)	HR 0.56 (95% CI: 0.46 to 0.69; p<0.00001)	1.9 years
Cholesterol and Recurrent Events (CARE)	Stable CAD n= 4159	Pravastatin 40mg vs. placebo	10 ± 5 months Mean ± SD	MACE (fatal coronary event, nonfatal MI)	RRR 24% (95% CI: 9% to 36%; p=0.003)	5.0 years
Scandinavian simvastatin survival study (4S)	Stable CAD n = 4444	Simvastatin 10- 40mg vs. placebo	> 6 months	Total mortality	RR 0.70 (95% CI: 0.58 to 0.85; p=0.003)	5.4 years
MRC/BHF Heart Protection Study	Stable CAD n = 20536	Simvastatin 40mg vs. placebo	Not reported	MACE (mortality, fatal/nonfatal vascular events)	RR 0.87 for any death (95% CI 0.81 to 0.94; p=0.0003) RR 0.83 for any vascular (95% CI: 0.75 to 0.91; p=<0.0001)	5.0 years
FOURIER	Stable CAD n = 27564	Evolocumab 140mg vs. placebo	3.4 (1.0 – 7.4) Median (IQR)	MACE (cardiovascular death, MI, UAP requiring hospitalization, coronary revascularization, stroke)	HR 0.85 (95% CI: 0.79 to 0.92; p<0.001)	2.2 years
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Stable CAD, prior MI n = 9014	Pravastatin 40mg vs. placebo	3 months – 3 years	Mortality from CHD	RRR 24% (95% CI: 12% to 35%; p<0.001)	6.1 years
ODYSSEY OUTCOMES	Stable CAD, prior MI n = 18924	Alirocumab 75mg vs. placebo	2.6 months (1.7 – 4.4) Median (IQR)	MACE (death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, UAP requiring hospitalization)	HR 0.85 (95% CI: 0.78 to 0.93; p<0.001)	2.8 years

Source: Mensink et al., PMID: 36568547

What can we learn from other fields for prevention? (continued)



- Relationship that therapeutic reduction of LDL reduces major vascular events from multiple randomized controlled trials.
- Most physician recommendations to lower LDL are non-pharmacologic (diet, exercise).

Source: Mensink et al., PMID: 36568547

What can we learn from other fields for prevention? (continued)

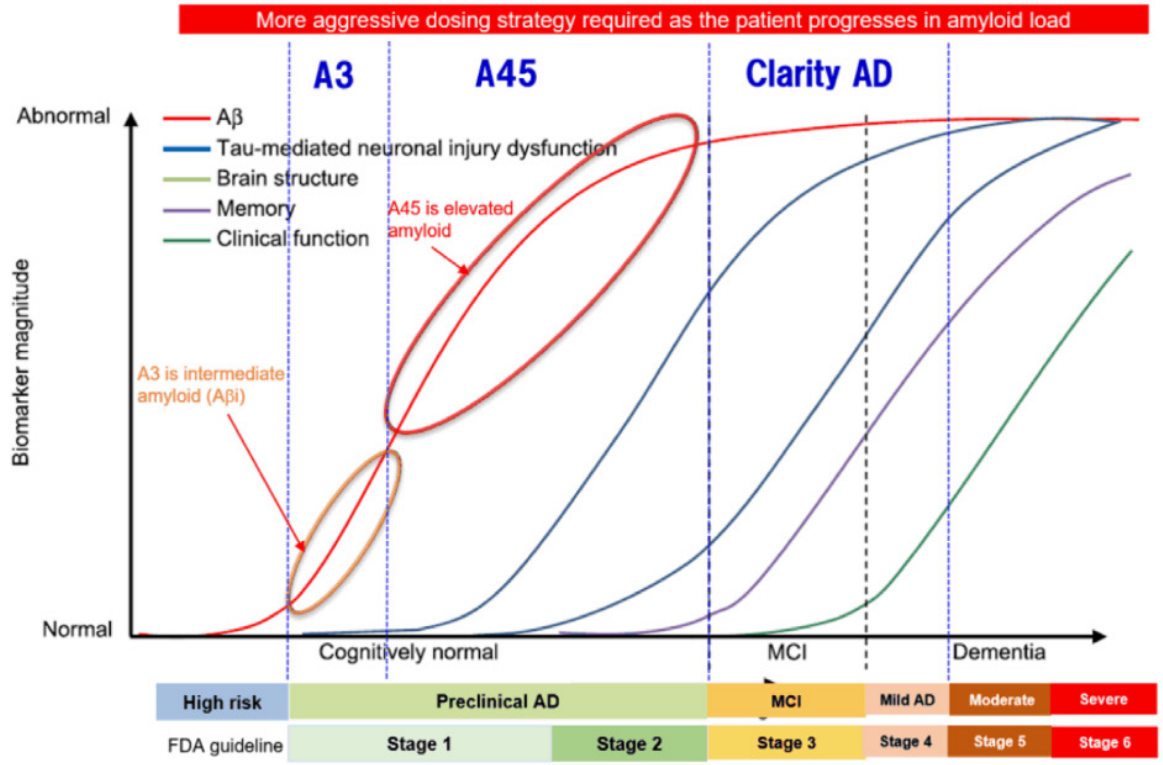
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Solanezumab in Preclinical Alzheimer's Disease

Reisa A. Sperling, M.D., Michael C. Donohue, Ph.D., Rema Raman, Ph.D., Michael S. Rafii, M.D., Ph.D., Keith Johnson, M.D., Colin L. Masters, M.D., Christopher H. van Dyck, M.D., Takeshi Iwatsubo, M.D., Gad A. Marshall, M.D., Roy Yaari, M.D., Michele Mancini, M.D., Karen C. Holdridge, M.P.H., Michael Case, M.S., John R. Sims, M.D., and Paul S. Aisen, M.D., for the A4 Study Team*

- Targets monomeric Aβ, amyloid levels increased in both placebo and solanezumab group.
- Did not slow cognitive decline compared to placebo

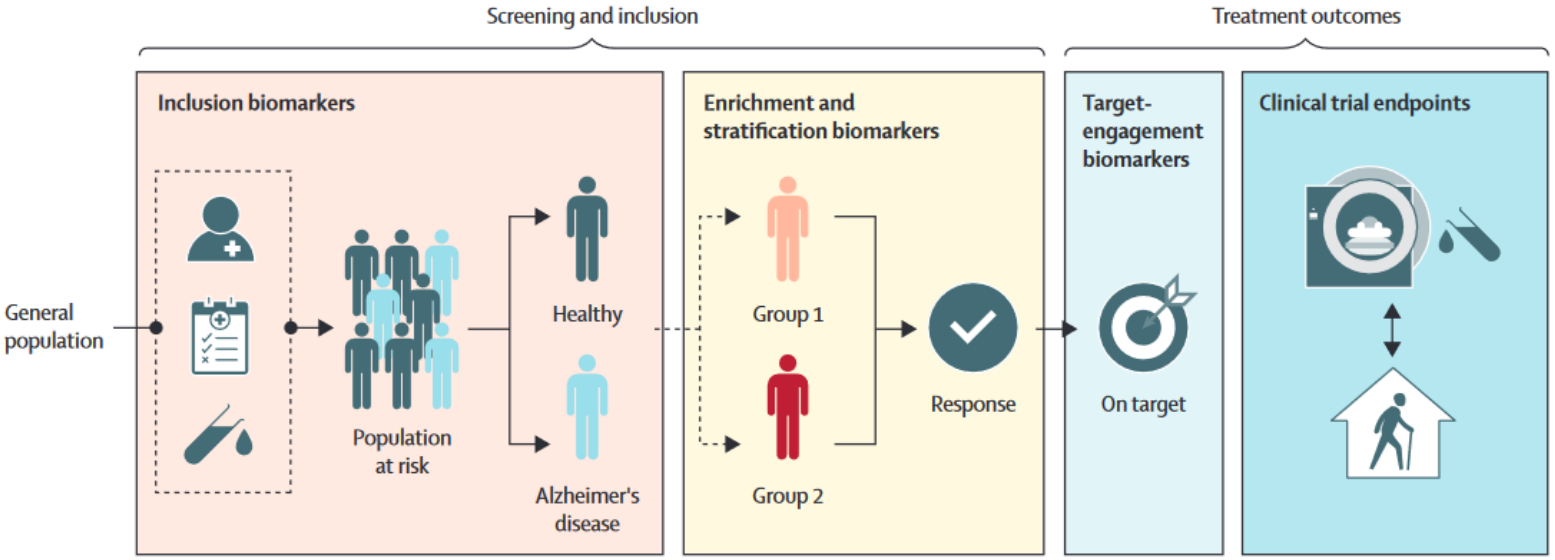


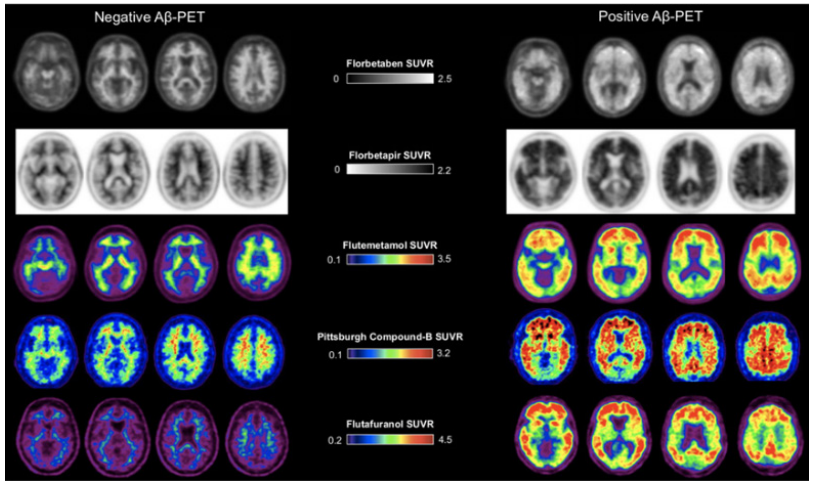
Trailblazer-ALZ 3

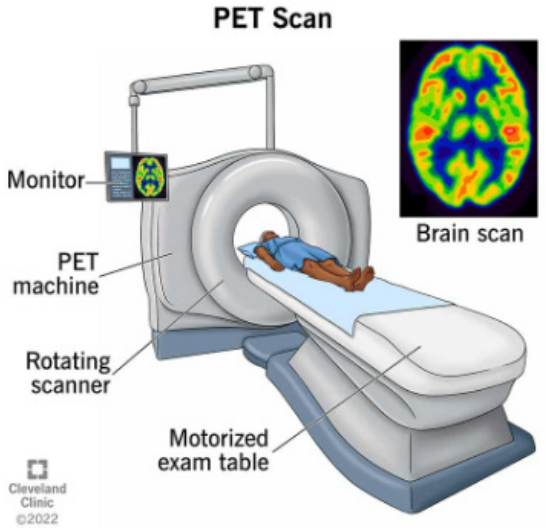
A Donanemab (LY3002813) Prevention Study in Participants With Alzheimer's Disease (TRAILBLAZER-ALZ 3)

Source: Sperling et al., PMID: 37458272
Rafii et al., PMID: 35971310

How do we identify eligible participants for prevention studies?

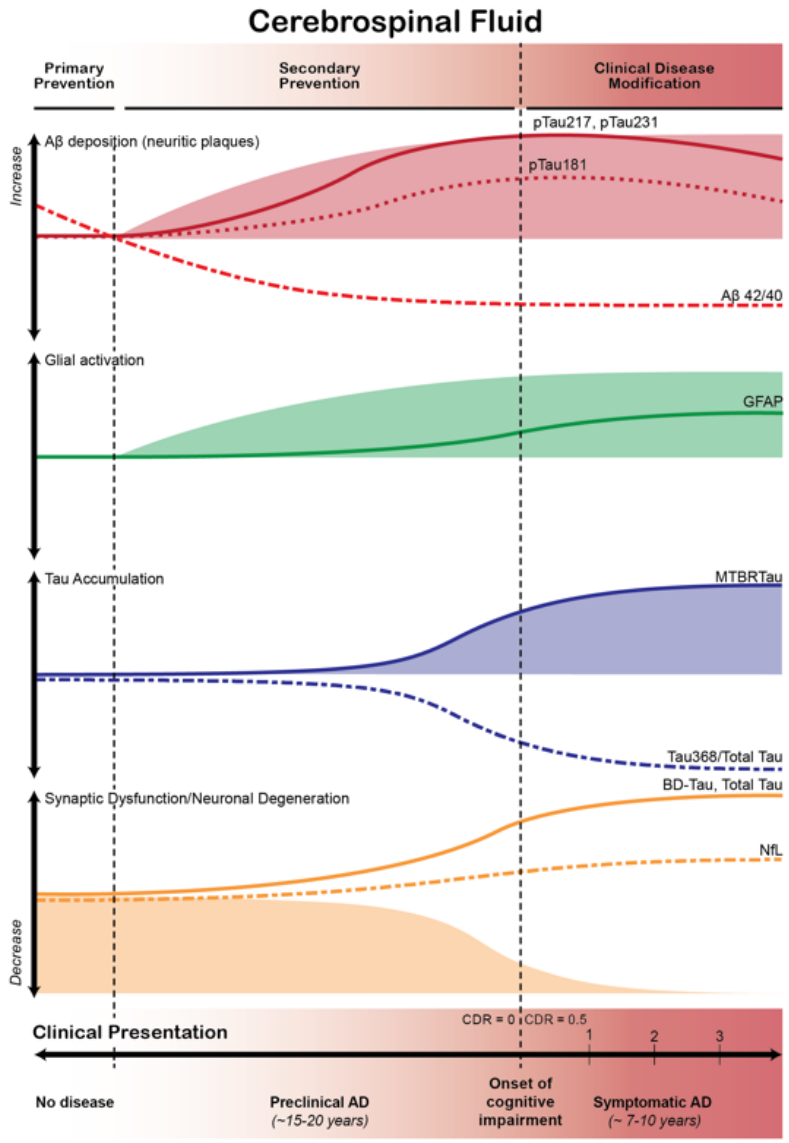


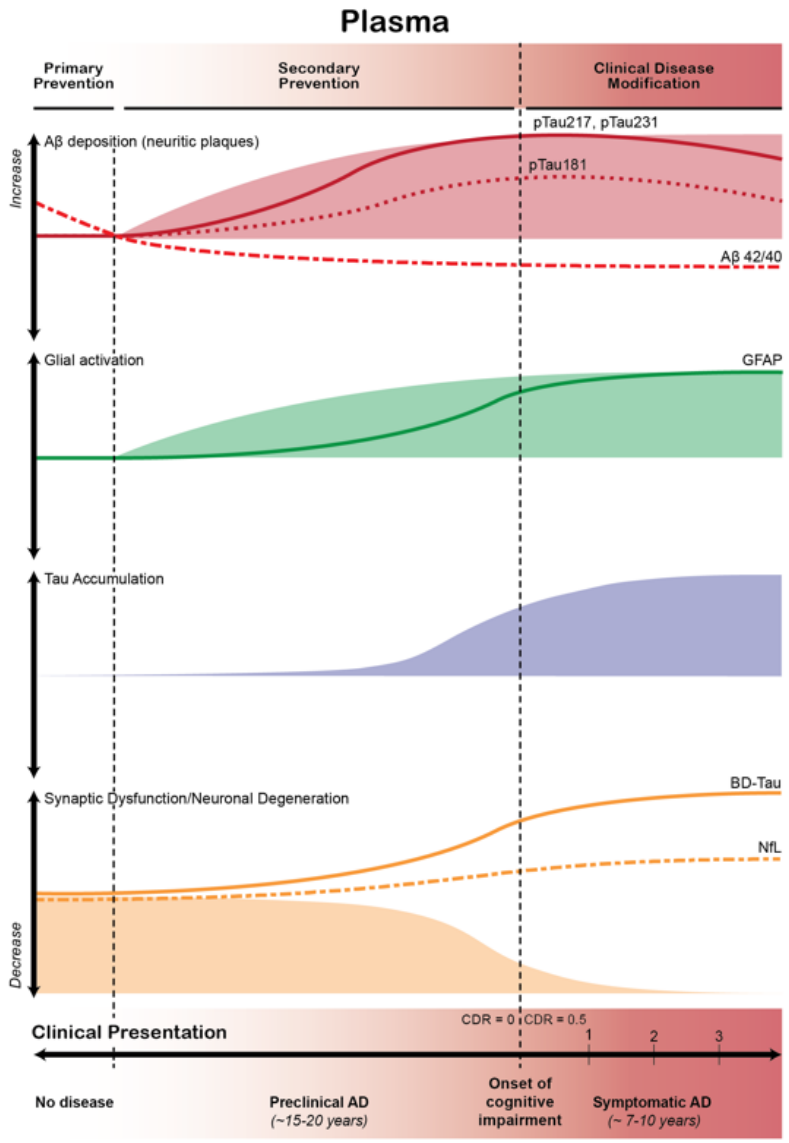




Source: Livingston et al., PMID: 39096926
Chapleau et al., PMID: 35649652

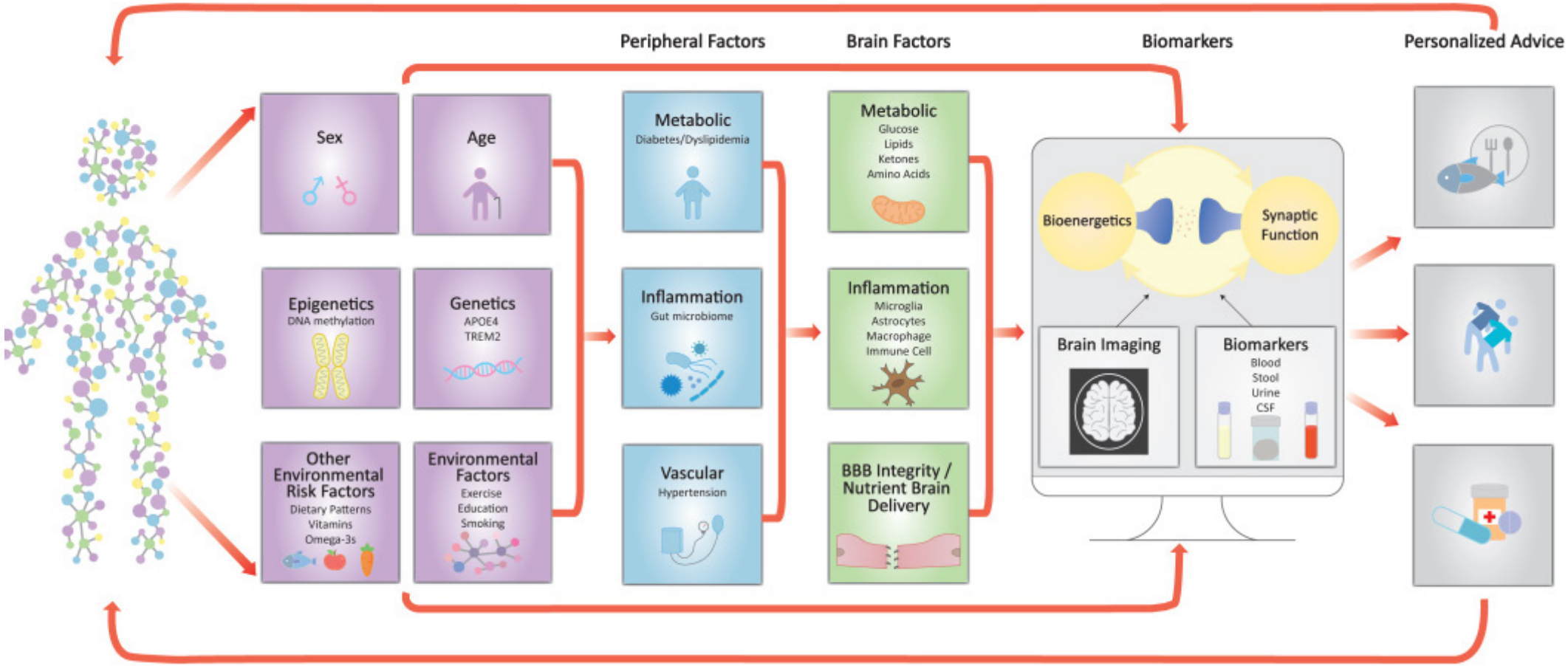
Fluid-based biomarkers for identifying eligible participants for prevention studies





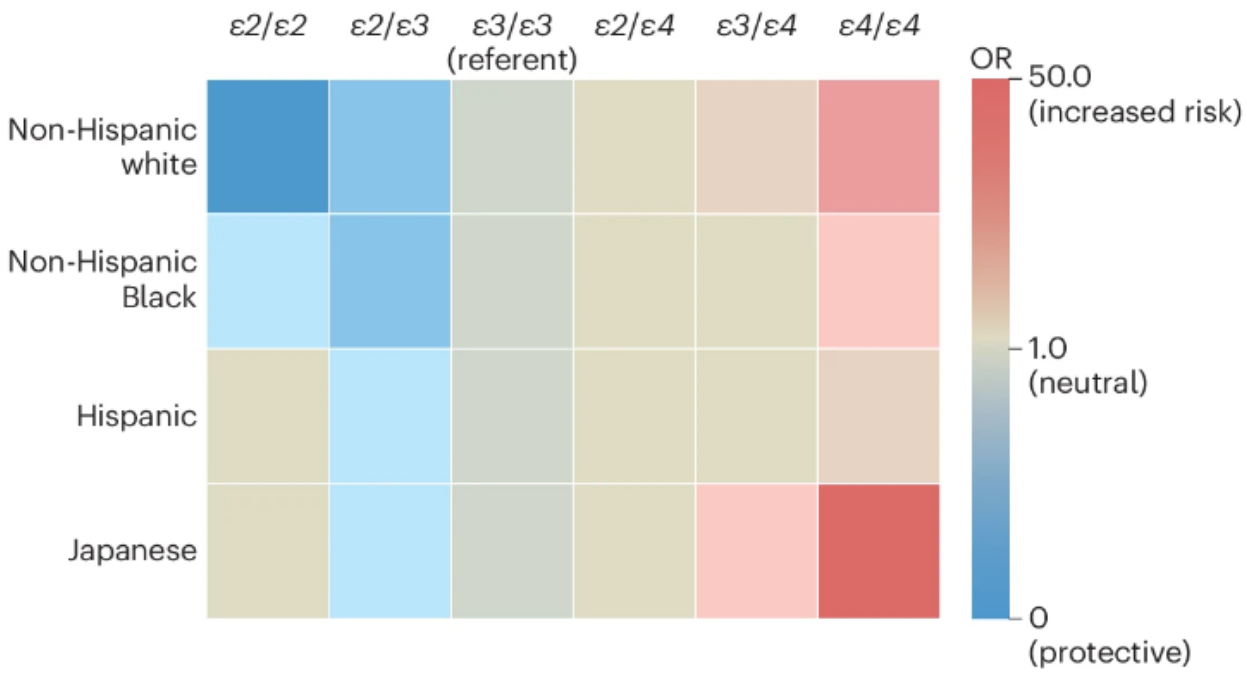
Source: Adapted from Self and Holtzman, PMID: 37667136

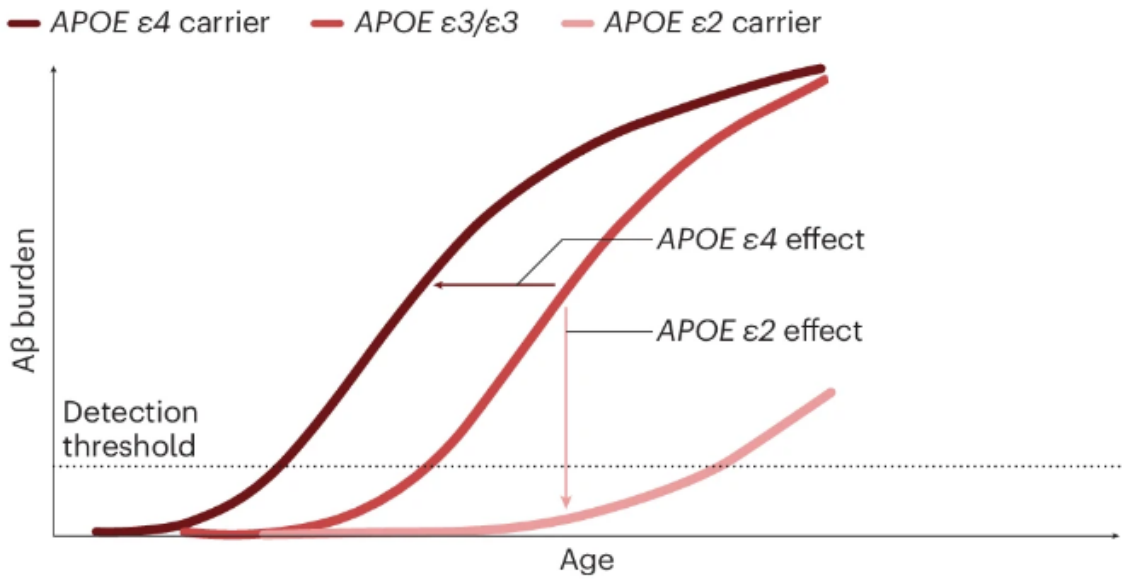
The Goal: Personalized Approaches to Modify and Prevent AD



Source: Yassine, Self, et al., PMID: 36479795

Example: APOE Genotype in populations affected by this gene





Source: Narasimhan, et al., PMID: 38898183

Evidence that there are modifiable risk factors for dementia without pharmacological intervention (1 of 3)

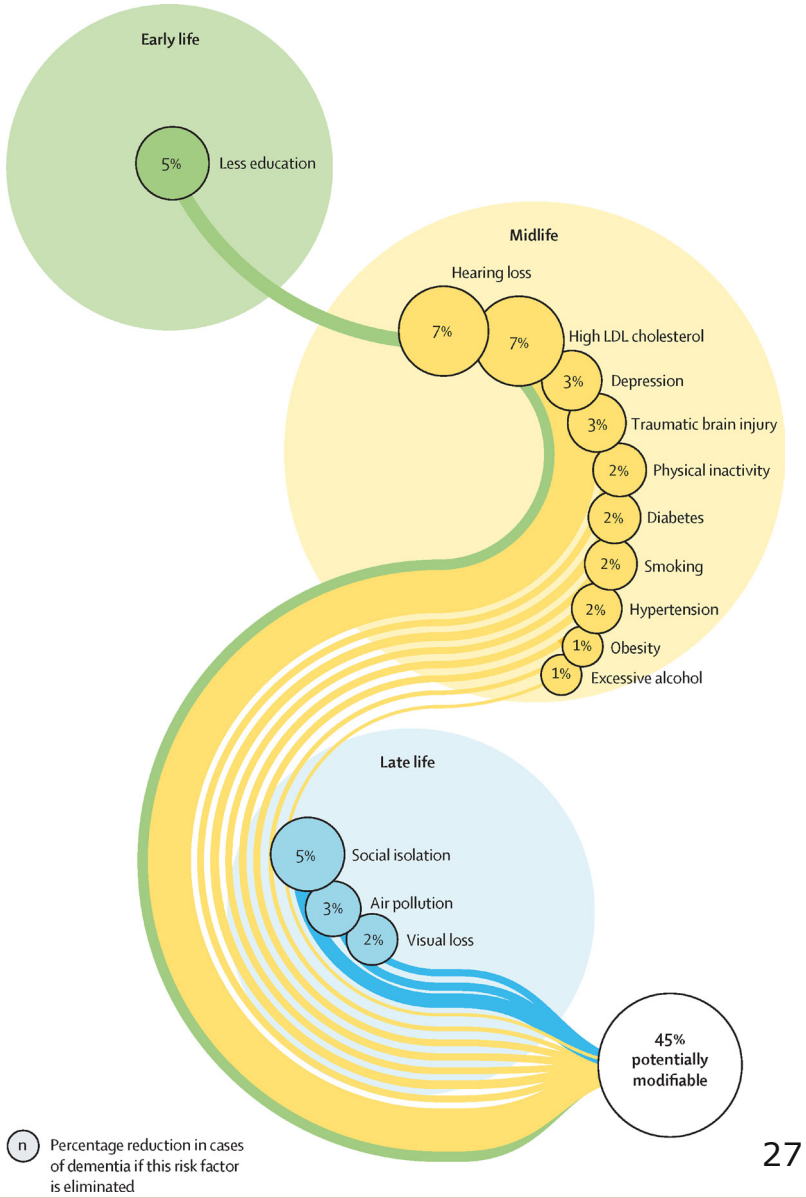
Source: Livingston et al., PMID: 39096926

Evidence that there are modifiable risk factors for dementia without pharmacological intervention (2 of 3)

	RR for dementia (95% CI)	Risk factor prevalence, %	Communality, %	Unweighted PAF, %	Weighted PAF, %	Weighted PAF rounded to nearest whole number, %
Early life						
Less education	1·6 (1·3–2·0)[302]	23·2%[303]	0·608	12·2%	4·5%	5%
Midlife						
Hearing loss	1·4 (1·0–1·9)*	59·0%[304]	0·609	19·1%	7·0%	7%
High LDL cholesterol	1·3 (1·3–1·4)[36]	76·5%†	0·469	18·7%	6·9%	7%
Depression	2·2 (1·7–3·0)*	7·2%[305]	0·452	8·3%	3·0%	3%
Traumatic brain injury	1·7 (1·4–1·9)[127]	12·1%[306]	0·423	7·8%	2·9%	3%
Physical inactivity	1·2 (1·2–1·3)[173]	27·5%[307]	0·567	6·4%	2·4%	2%
Smoking	1·3 (1·2–1·4)[148]	22·3%[308]	0·650	6·3%	2·3%	2%
Diabetes	1·7 (1·6–1·8)[309]	9·3%[310]	0·493	6·4%	2·3%	2%
Hypertension	1·2 (1·1–1·4)[311]	31·1%[312]	0·595	5·9%	2·2%	2%
Obesity	1·3 (1·0–1·7)[206]	13·0%[313]	0·622	3·8%	1·4%	1%
Excessive alcohol consumption	1·2 (1·0–1·5)[213]	13·3%[213]	0·772	2·6%	1·0%	1%
Late life						
Social isolation	1·6 (1·3–1·8)[221]	24·0%[314]	0·408	12·6%	4·6%	5%
Air pollution	1·1 (1·1–1·1)[315]	75·0%[315]	0·341	7·0%	2·6%	3%
Untreated vision loss	1·5 (1·4–1·6)[262]	12·7%[260]	0·553	6·0%	2·2%	2%
Overall PAF for all risk factors	..	..	..	..	45·3%	45%

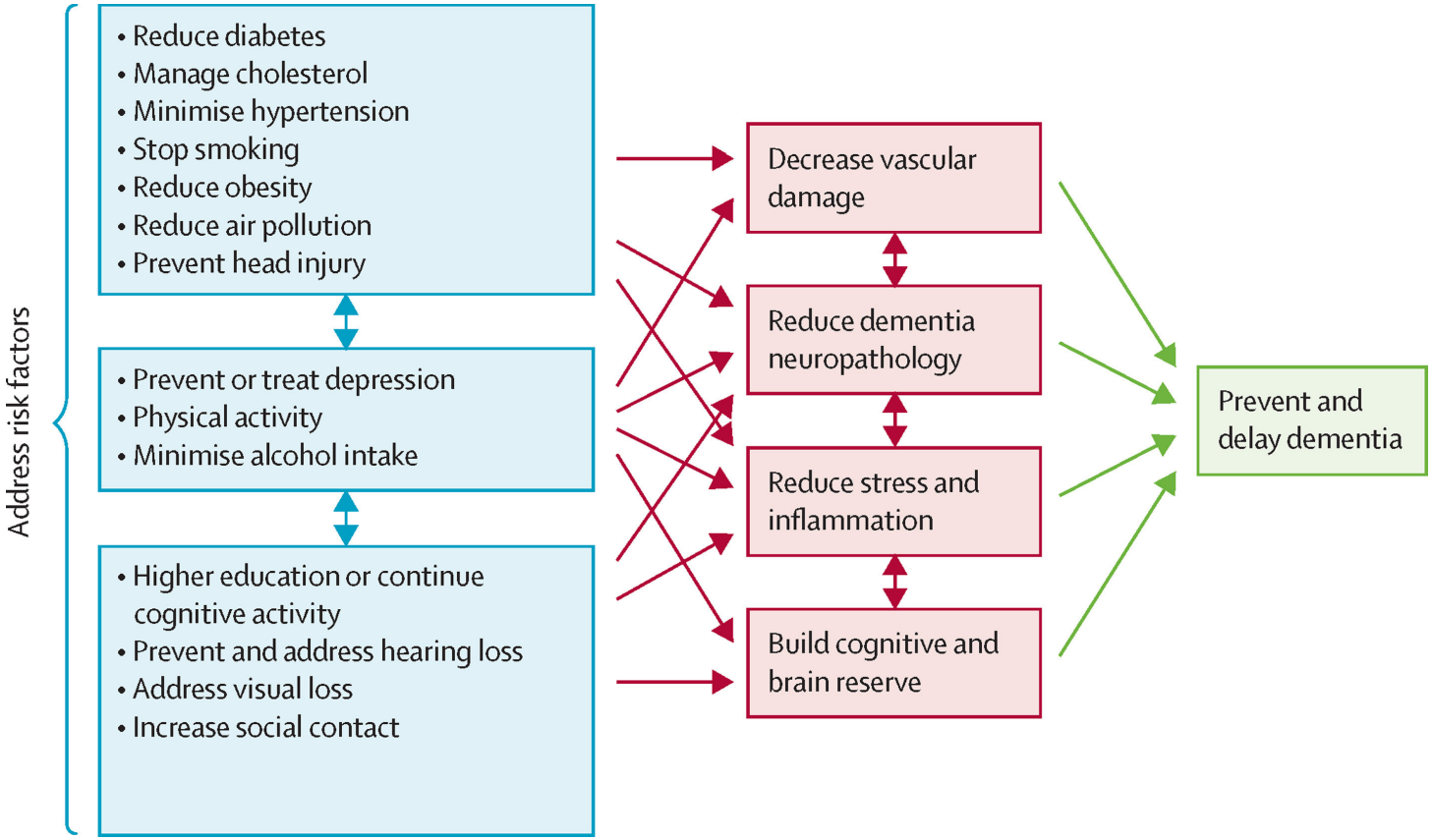
RR=relative risk. PAF=population attributable fraction. *Calculated by the authors in this Commission. †Prevalence derived from 37 000 participants aged ≥45 years from the Norwegian HUNT study.[316]

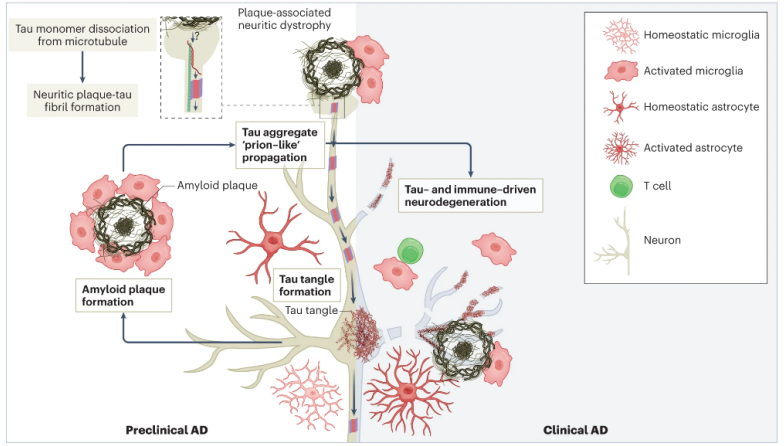
Table 1: **RR, prevalence, and PAF for all 14 potentially modifiable dementia risk factors**

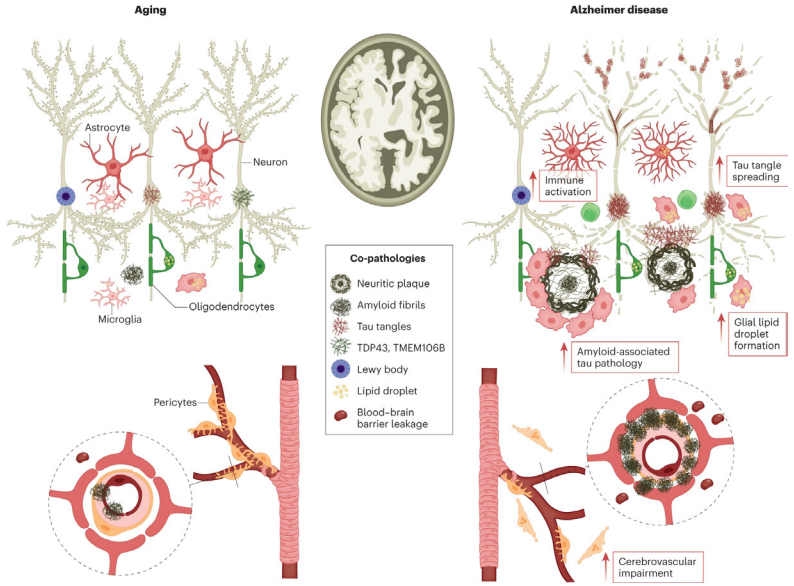


Source: Livingston et al., PMID: 39096926

Evidence that there are modifiable risk factors for dementia without pharmacological intervention (3 of 3)







Source: Livingston et al., PMID: 39096926

Recommendations of the Lancet Commission on Dementia

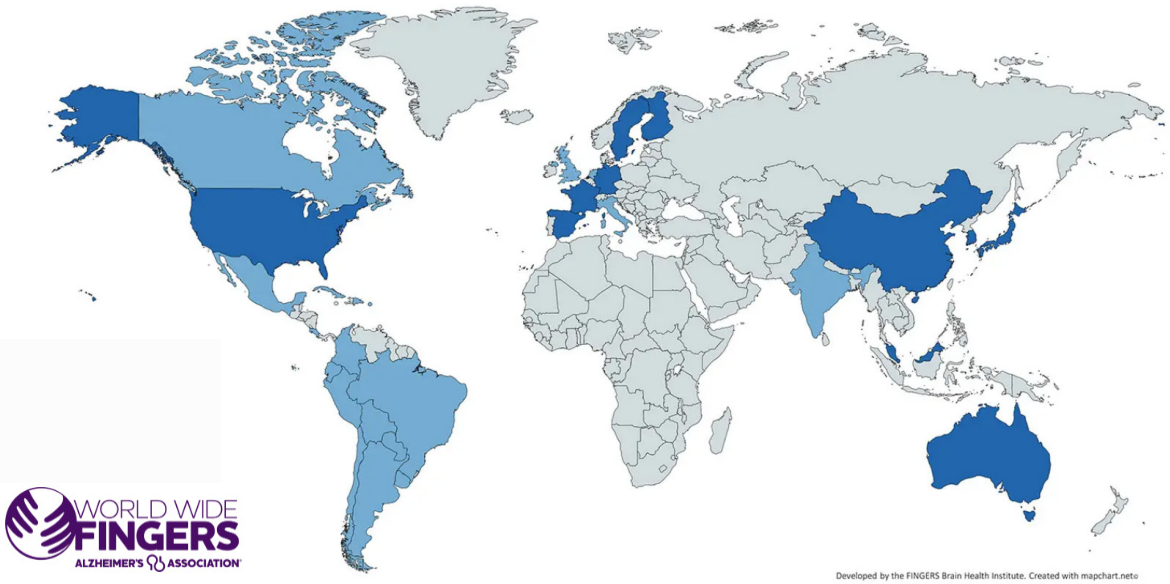
- Ensure good quality education is available for all and encourage cognitively stimulating activities in midlife to protect cognition
- Make hearing aids accessible for people with hearing loss and decrease harmful noise exposure to reduce hearing loss
- Treat depression effectively
- Encourage use of helmets and head protection in contact sports and on bicycles
- Encourage exercise because people who participate in sport and exercise are less likely to develop dementia
- Reduce cigarette smoking through education, price control, and preventing smoking in public places and make smoking cessation advice accessible
- Prevent or reduce hypertension and maintain systolic blood pressure of 130 mm Hg or less from age 40 years;
- Detect and treat high LDL cholesterol from midlife
- Maintain a healthy weight and treat obesity as early as possible, which also helps to prevent diabetes
- Reduce high alcohol consumption through price control and increased awareness of levels and risks of overconsumption
- Prioritize age-friendly and supportive community environments and housing and reduce social isolation by facilitating participation in activities and living with others
- Make screening and treatment for vision loss accessible for all
- Reduce exposure to air pollution

Source: Livingston et al., PMID: 39096926

Evidence that there are modifiable risk factors for dementia without pharmacological intervention in randomized, controlled trials

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



Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial

Dean Ornish[1,2*], Catherine Madison[1,3], Miia Kivipelto[4,5,6,7], Colleen Kemp[8], Charles E. McCulloch[9], Douglas Galasko[10], Jon Artz[11,12], Dorene Rentz[13,14,15], Jue Lin[16], Kim Norman[17], Anne Ornish[1], Sarah Tranter[8], Nancy DeLamarter[1], Noel Wingers[1], Carra Richling[1], Rima Kaddurah-Daouk[18], Rob Knight[19], Daniel McDonald[20], Lucas Patel[21], Eric Verdin[22,23], Rudolph E. Tanzi[13,24,25,26] and Steven E. Arnold[13,27]

Source: Ngandu et al., PMID: 29356827
Ornish et al., PMID: 38849944

Takeaways

1. Breakthroughs in fluid-based biomarkers of disease pathology and the demonstrated clinical efficacy of lecanemab and donanemab are long-awaited results for the AD field, representing efforts by thousands of scientists over the past 30 years, but future studies will bring us closer to transforming AD clinical care.
2. Results of future randomized controlled-trials of anti-amyloid agents in preclinical AD population will provide important insights into regulation of Aβ deposition as a preventative strategy.
3. What is good for the body is good for the brain: healthy aging will be an important component to lower/prevent dementia incidence.

Thank You!

See you for our next webinar on November 18, 2024!

Artist: Aurora Kroenke, “Community is Health” Submitted to ODP Art Challenge: How Prevention Can Create Better Health for Everyone, 1st Place Teen category Winner.

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PreventionInFocus@nih.gov

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