Navigating the relationship between depression and dementia in older adults

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CONFLICTS

No conflicts of interest

Research support through NIH and private foundations

LEARNING OBJECTIVES

Describe how depression and dementia coexist in older adults and how one may lead to the other.

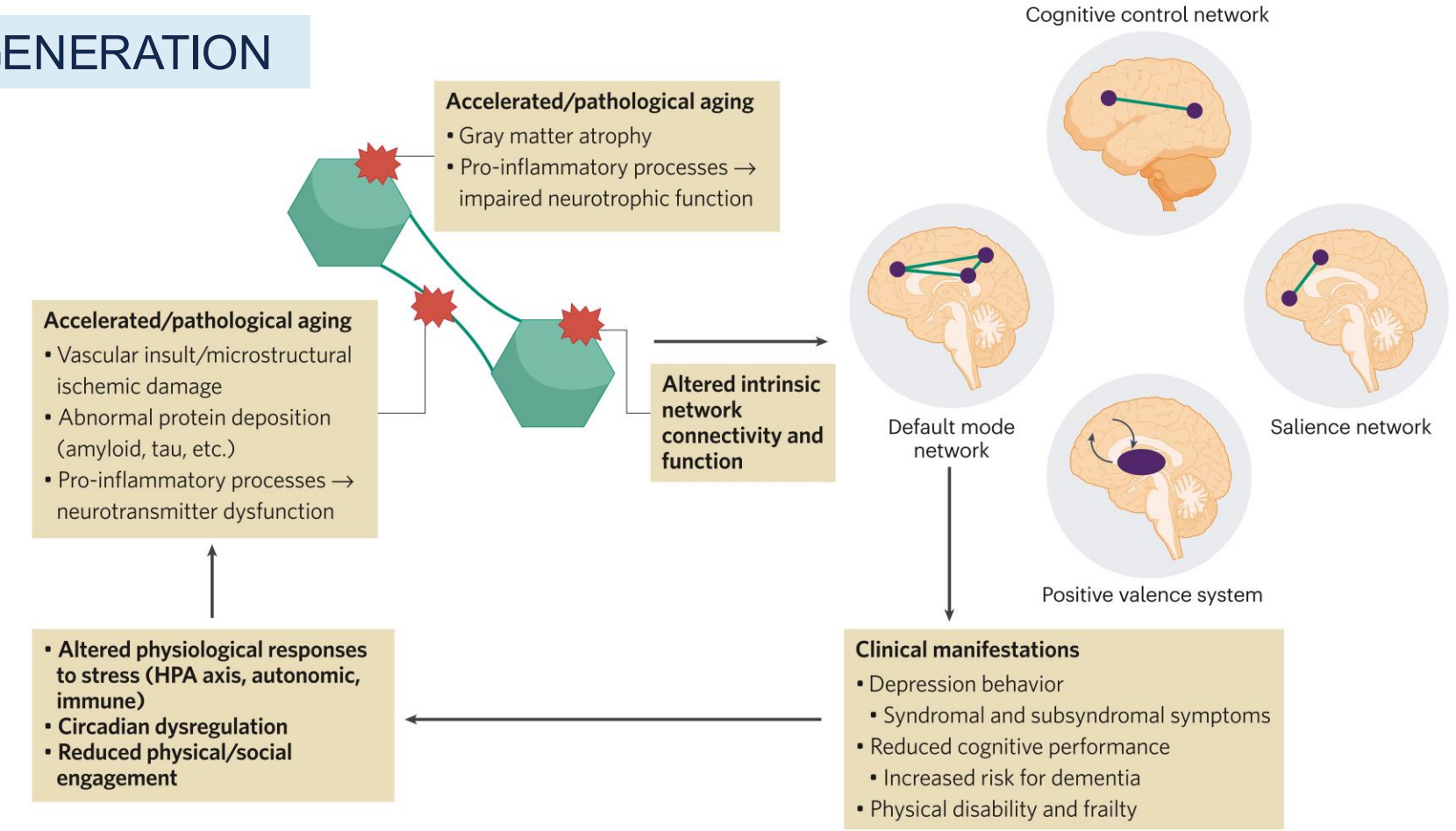
Differentiate clinical and cognitive presentations of depression and dementia in older adults.

Determine when to intervene with patients with depression and emergent cognitive symptoms for early identification and consideration of disease-modifying interventions

Describe current evidence-based approaches to managing older adults with depression and cognitive impairment to improve longer-term outcomes.

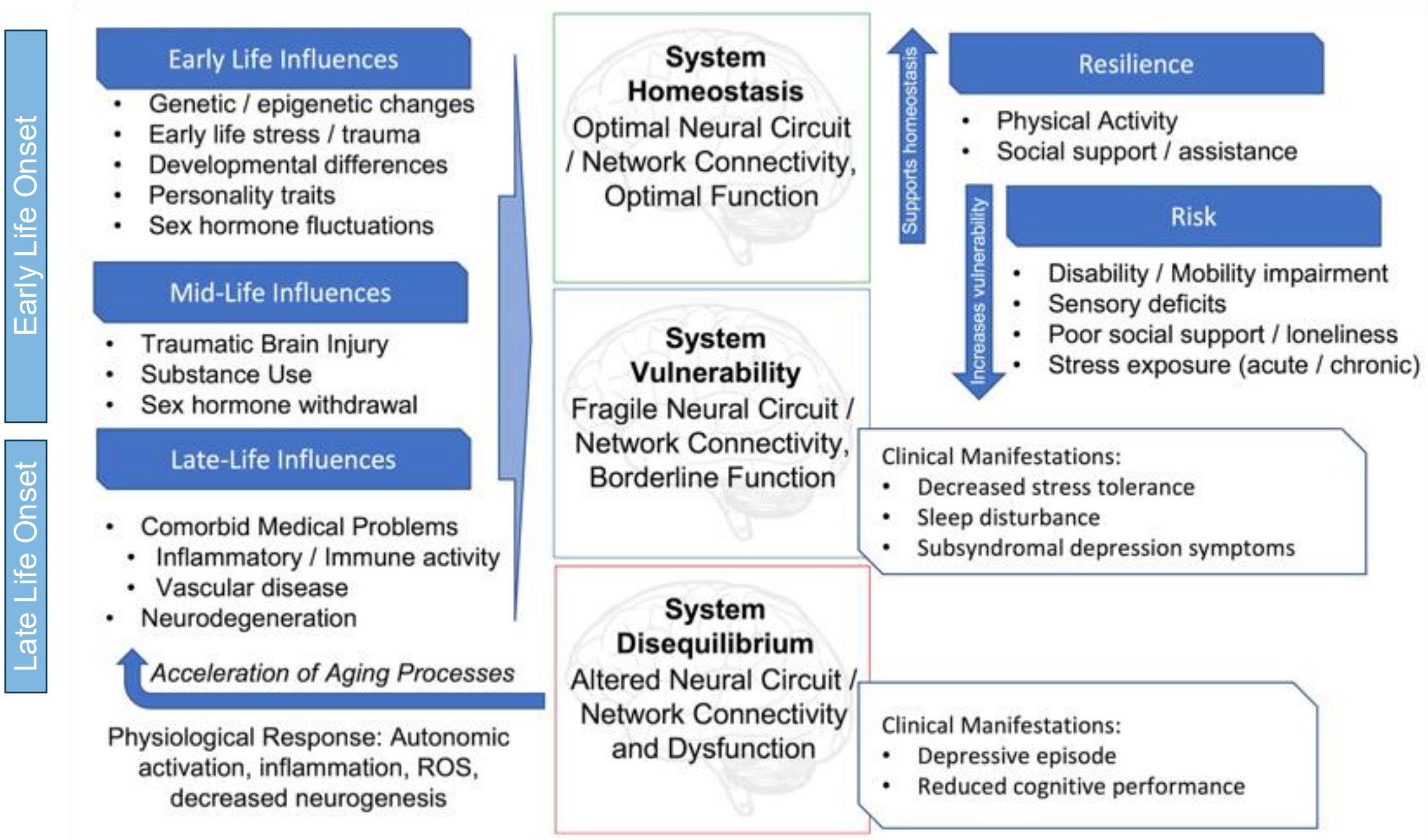
Bidirectional Relationship between Depression and Cognitive Decline

NEURODEGENERATION



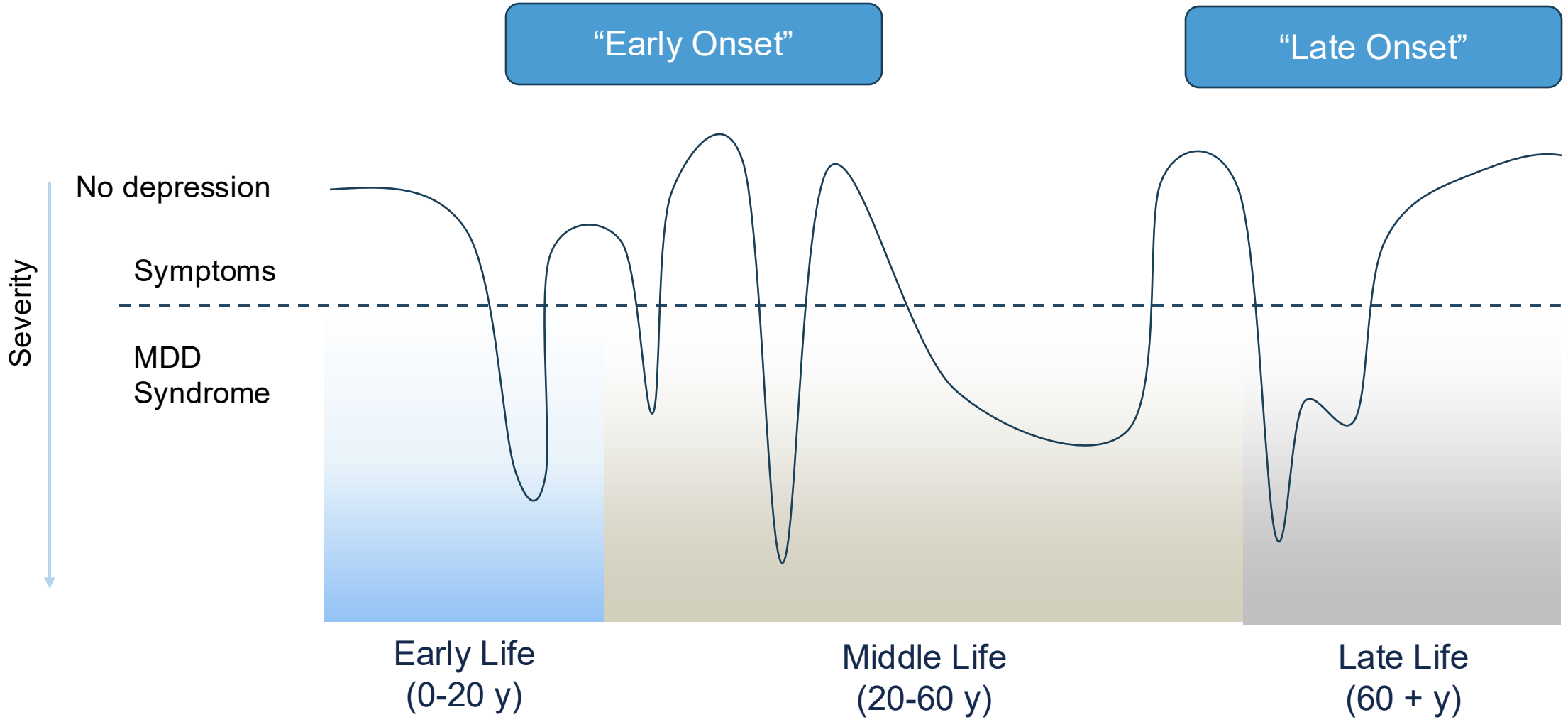
DEPRESSION

Taylor WD et al, NPP Reviews, 2026

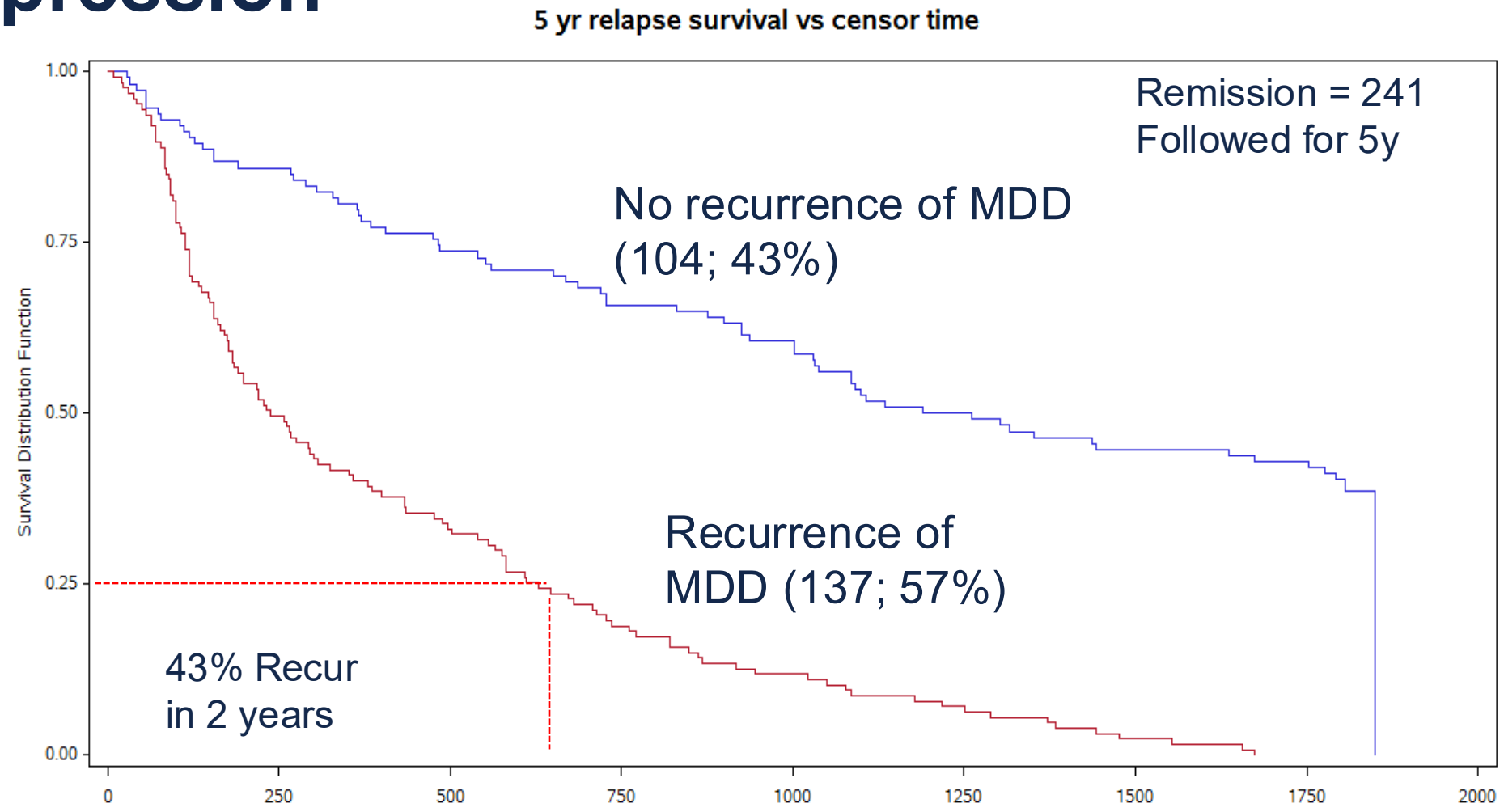


Szymkowicz, Gerlach, Homiack, Taylor WD. 2023

Older adults: Consider the Lifetime course of Major Depressive Disorder

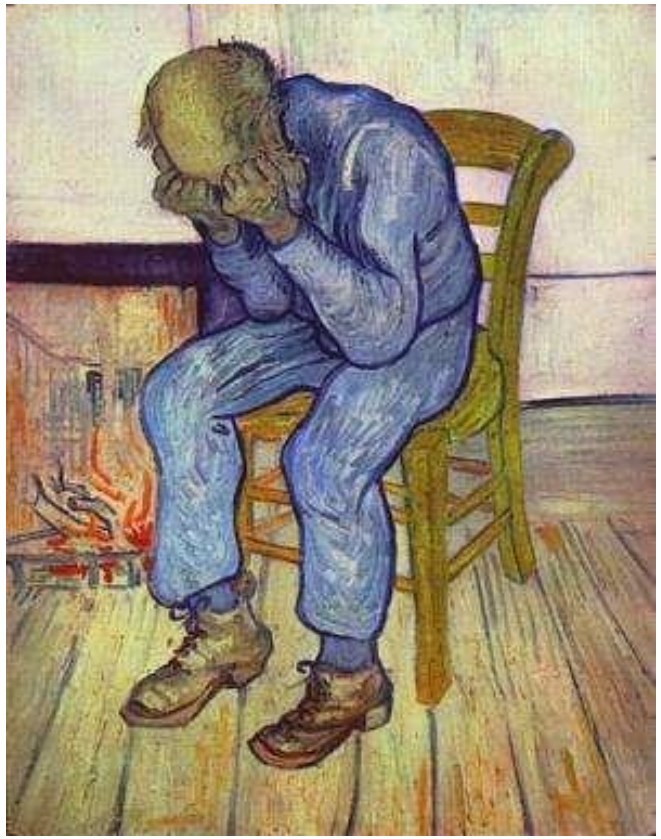


Clinical Outcomes of Remitted Late-Life Depression

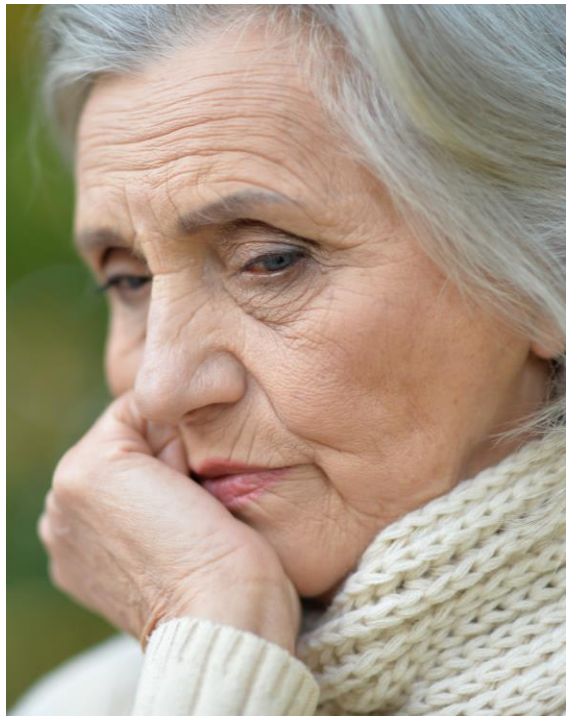


Deng Y…Taylor. *Depression & Anxiety*, 2018.

What's different clinically about depression occurring in older adults?



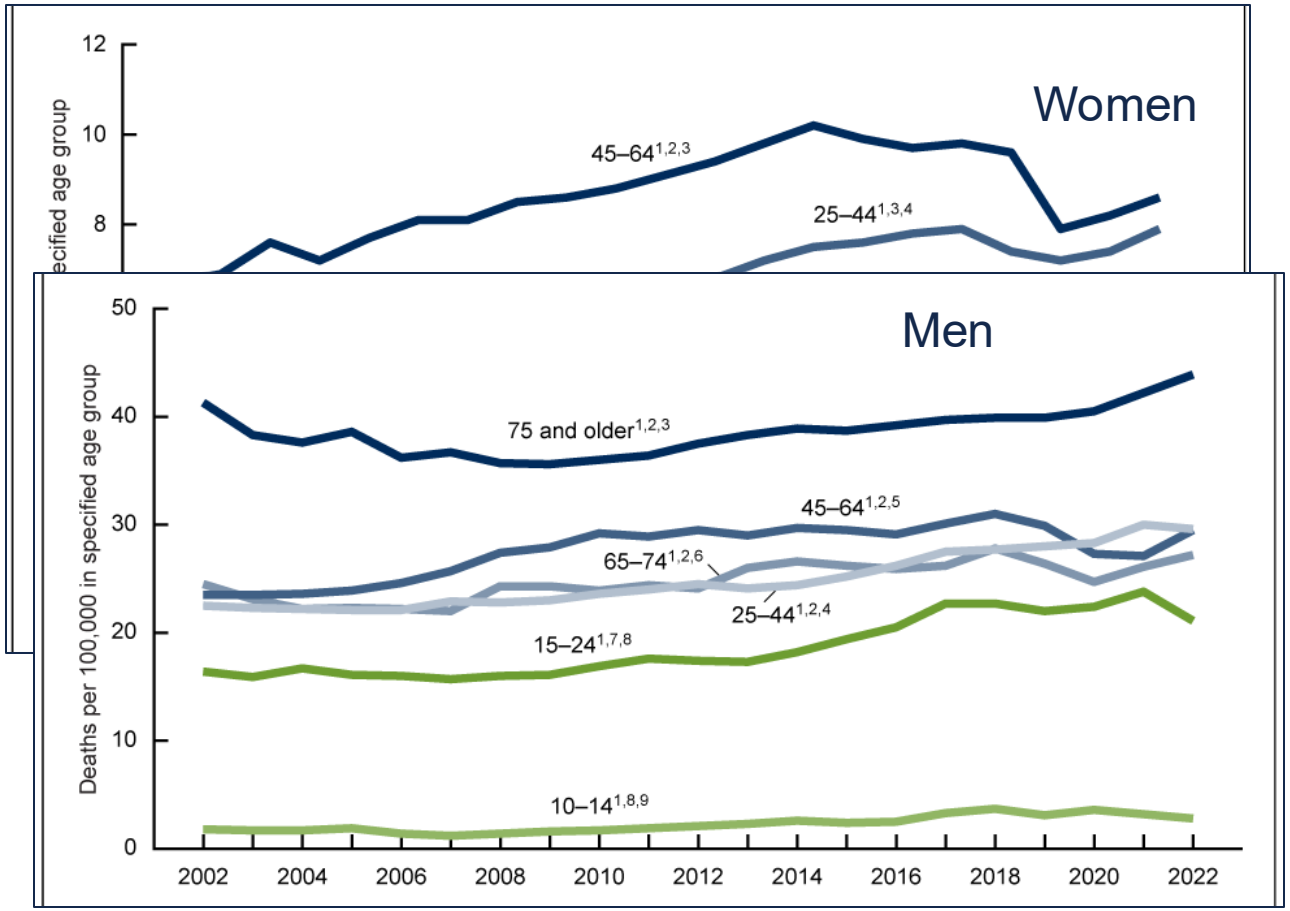
- Medical morbidity & polypharmacy
- Greater disability
- Poorer response to treatment
- Worse medical outcomes
- Elevated mortality



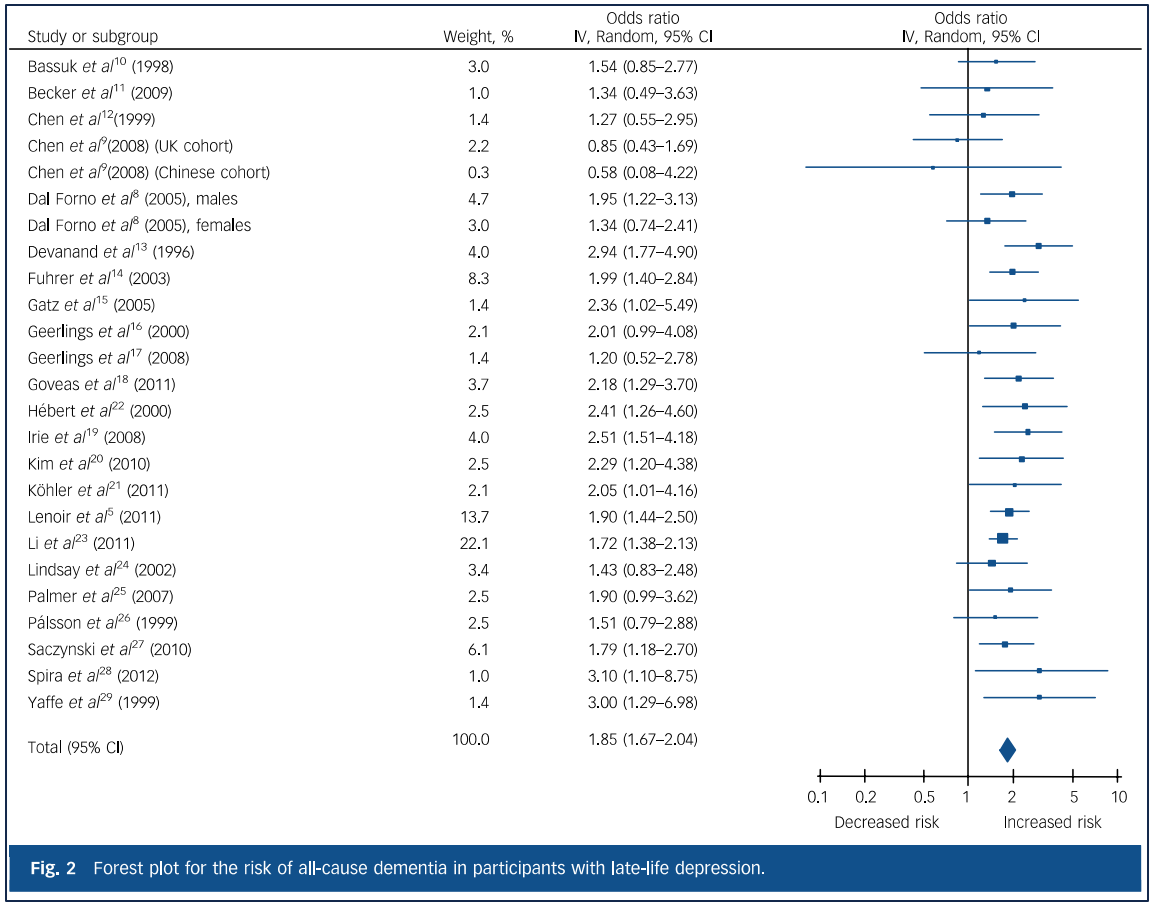
Taylor WD. NEJM 2014

Adverse LLD Outcomes

Suicide Risk



Dementia Risk

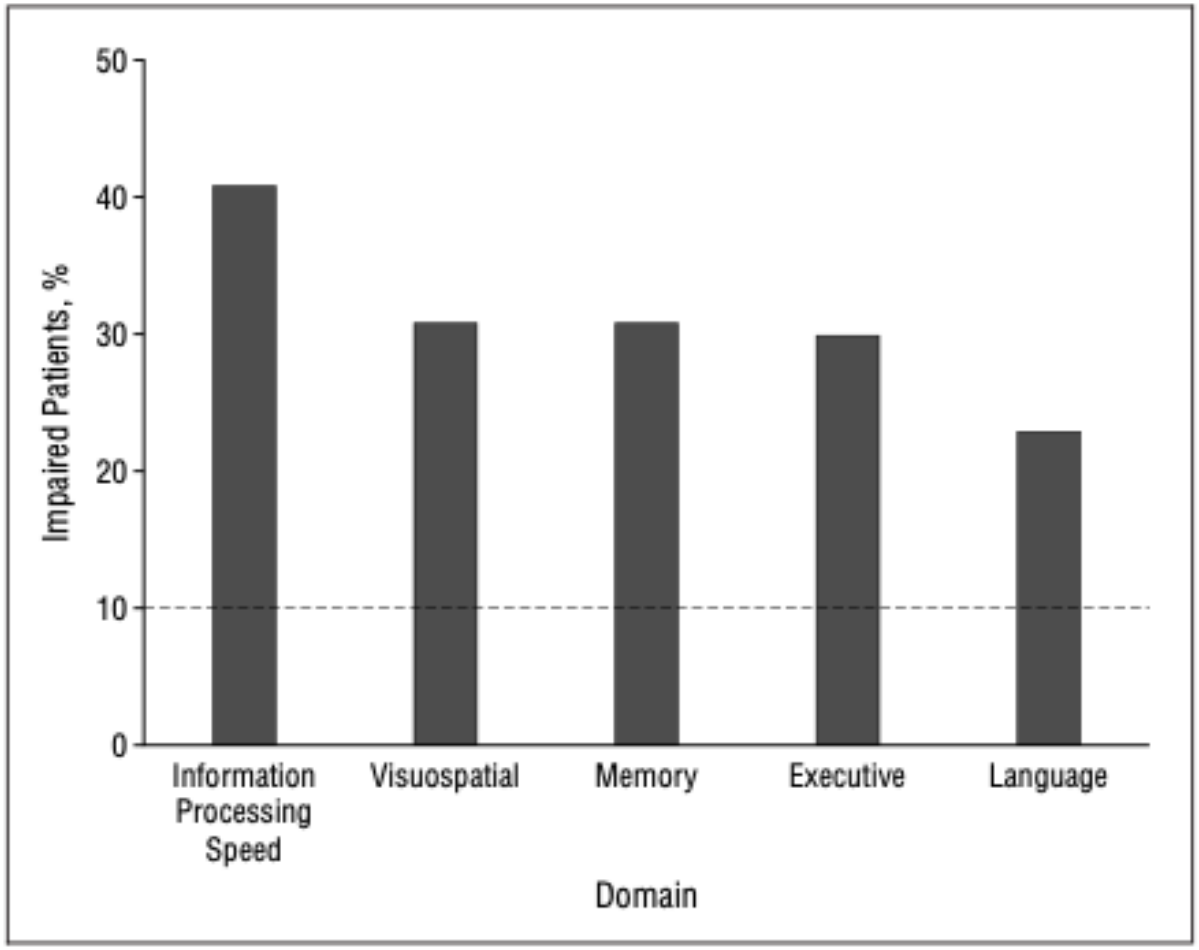


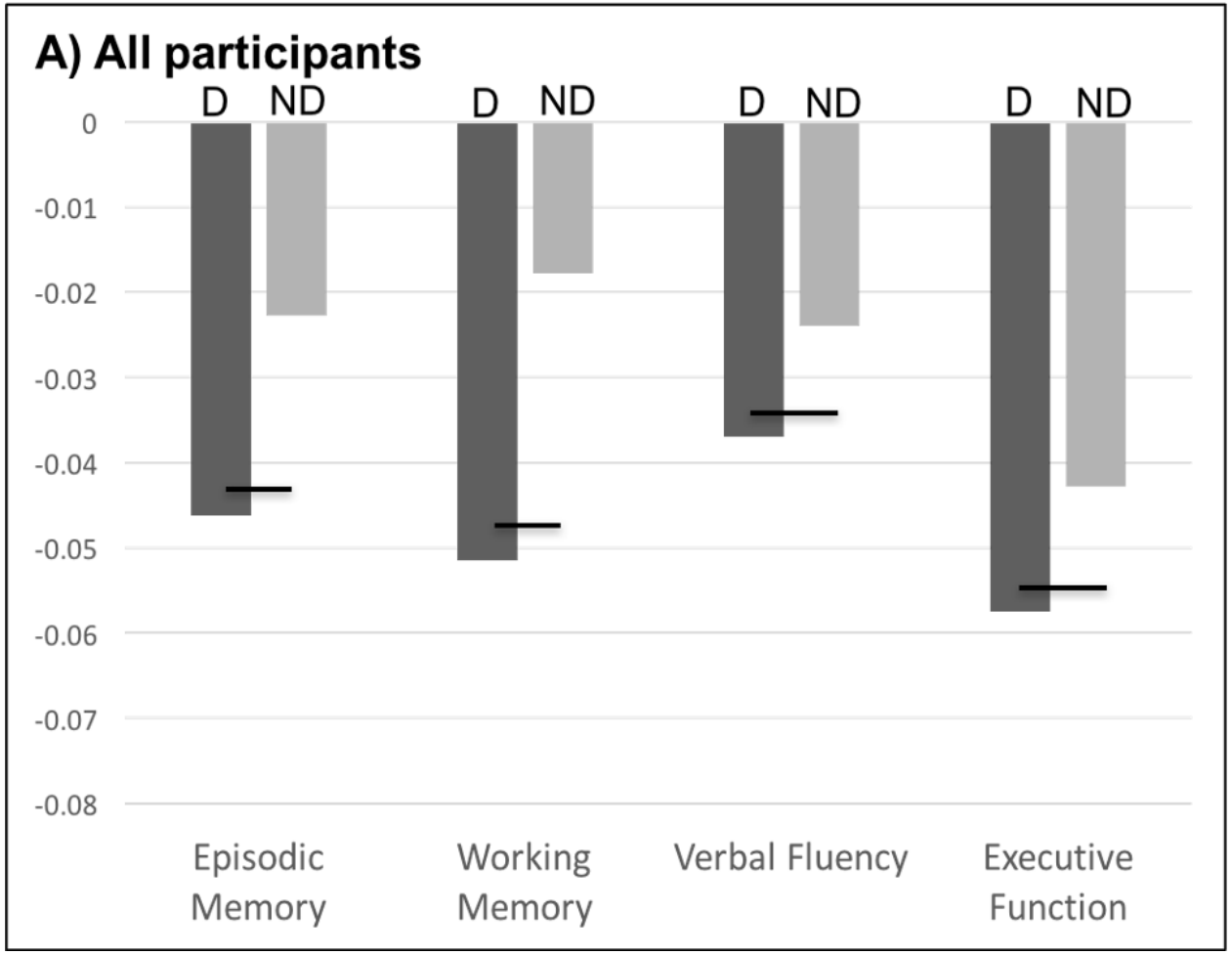
Study or subgroup	Weight, %	Odds ratio IV, Random, 95% CI
Bassuk *et al*[10] (1998)	3.0	1.54 (0.85–2.77)
Becker *et al*[11] (2009)	1.0	1.34 (0.49–3.63)
Chen *et al*[12](1999)	1.4	1.27 (0.55–2.95)
Chen *et al*[9](2008) (UK cohort)	2.2	0.85 (0.43–1.69)
Chen *et al*[9](2008) (Chinese cohort)	0.3	0.58 (0.08–4.22)
Dal Forno *et al*[8] (2005), males	4.7	1.95 (1.22–3.13)
Dal Forno *et al*[8] (2005), females	3.0	1.34 (0.74–2.41)
Devanand *et al*[13] (1996)	4.0	2.94 (1.77–4.90)
Fuhrer *et al*[14] (2003)	8.3	1.99 (1.40–2.84)
Gatz *et al*[15] (2005)	1.4	2.36 (1.02–5.49)
Geerlings *et al*[16] (2000)	2.1	2.01 (0.99–4.08)
Geerlings *et al*[17] (2008)	1.4	1.20 (0.52–2.78)
Goveas *et al*[18] (2011)	3.7	2.18 (1.29–3.70)
Hébert *et al*[22] (2000)	2.5	2.41 (1.26–4.60)
Irie *et al*[19] (2008)	4.0	2.51 (1.51–4.18)
Kim *et al*[20] (2010)	2.5	2.29 (1.20–4.38)
Köhler *et al*[21] (2011)	2.1	2.05 (1.01–4.16)
Lenoir *et al*[5] (2011)	13.7	1.90 (1.44–2.50)
Li *et al*[23] (2011)	22.1	1.72 (1.38–2.13)
Lindsay *et al*[24] (2002)	3.4	1.43 (0.83–2.48)
Palmer *et al*[25] (2007)	2.5	1.90 (0.99–3.62)
Pálsson *et al*[26] (1999)	2.5	1.51 (0.79–2.88)
Saczynski *et al*[27] (2010)	6.1	1.79 (1.18–2.70)
Spira *et al*[28] (2012)	1.0	3.10 (1.10–8.75)
Yaffe *et al*[29] (1999)	1.4	3.00 (1.29–6.98)
Total (95% CI)	100.0	1.85 (1.67–2.04)

Fig. 2 Forest plot for the risk of all-cause dementia in participants with late-life depression.

Diniz BS et al, Br J Psychiatry, 2013; NCHS Data Brief 509, CDC, Sept. 2024

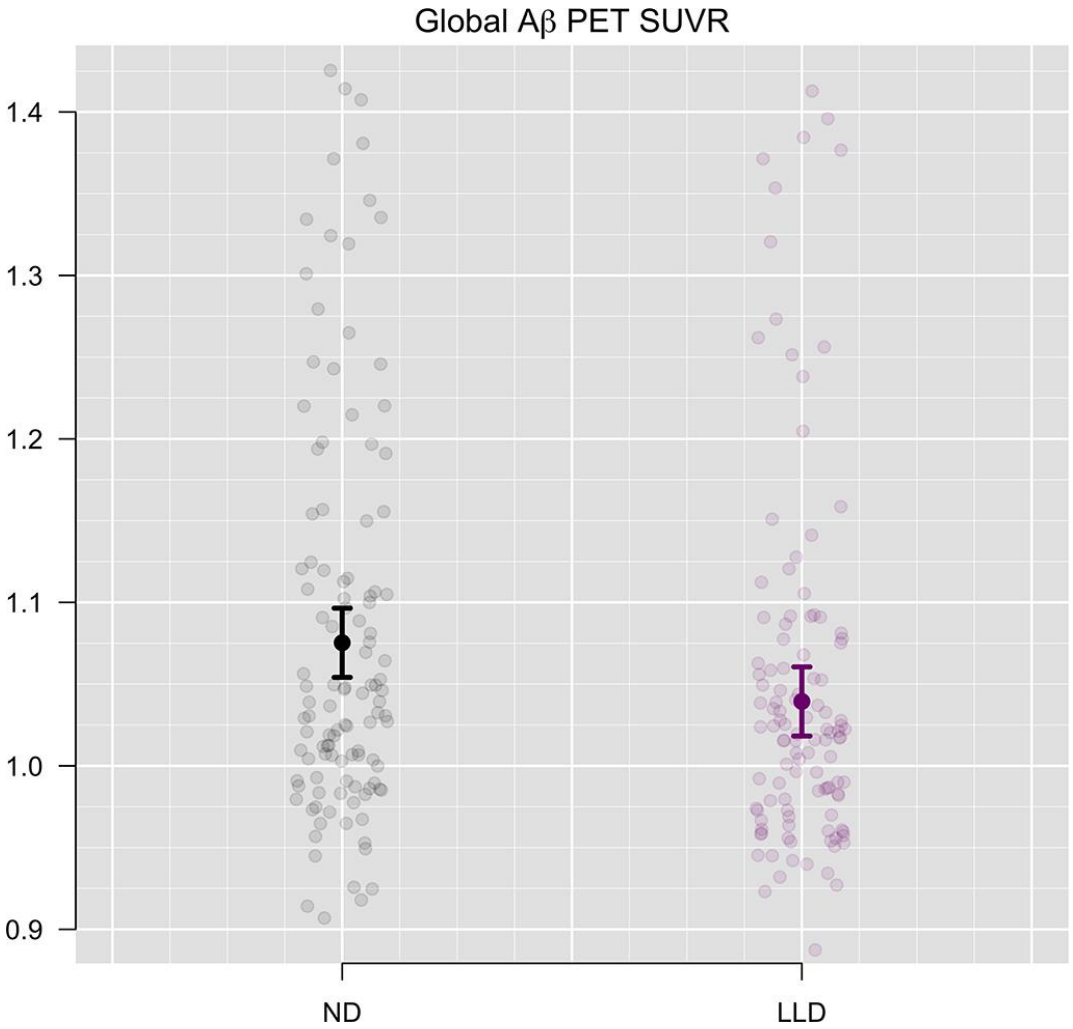
Cognitive Performance in Depression

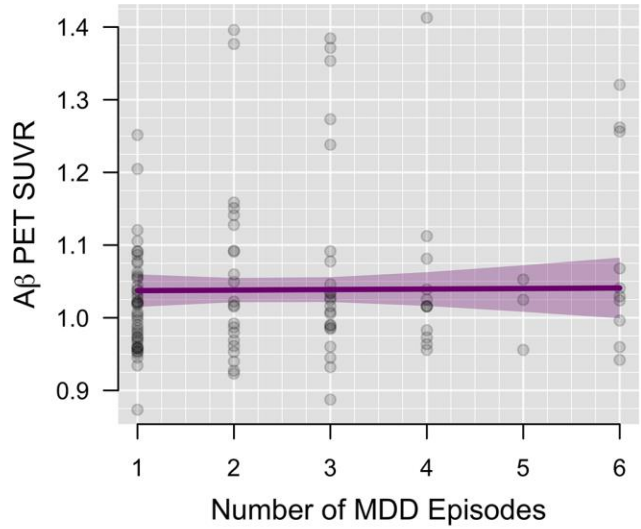


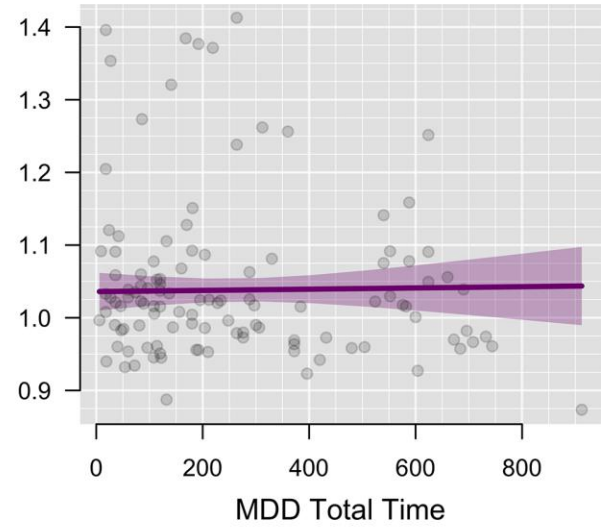


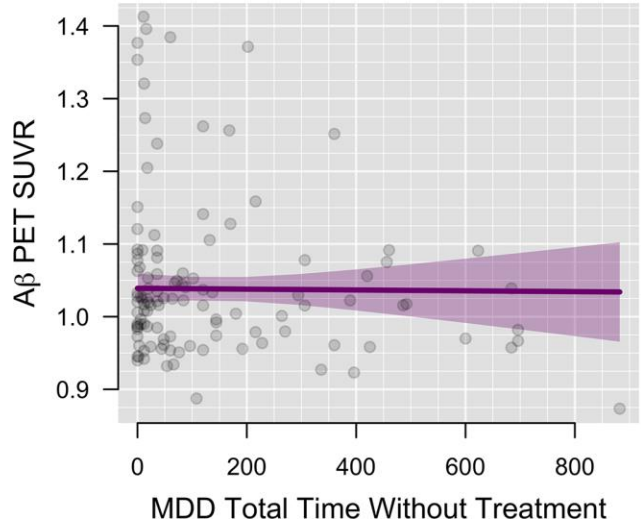
Butters MA et al, Arch Gen Psych 2004; Riddle …Taylor, *Am J Geriatr Psychiatry.* 2017.

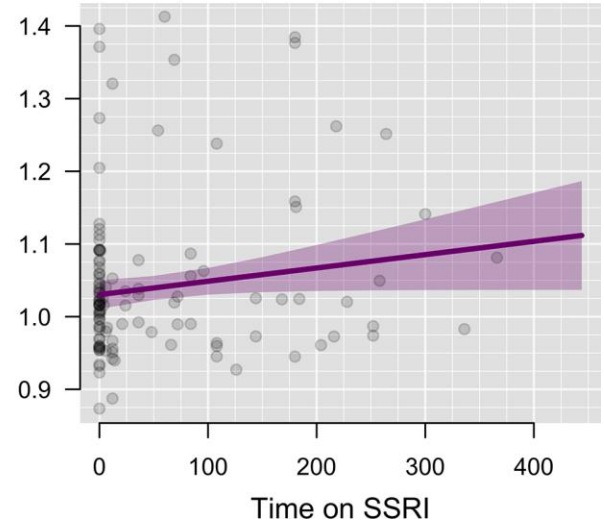
Amyloid is not the culprit





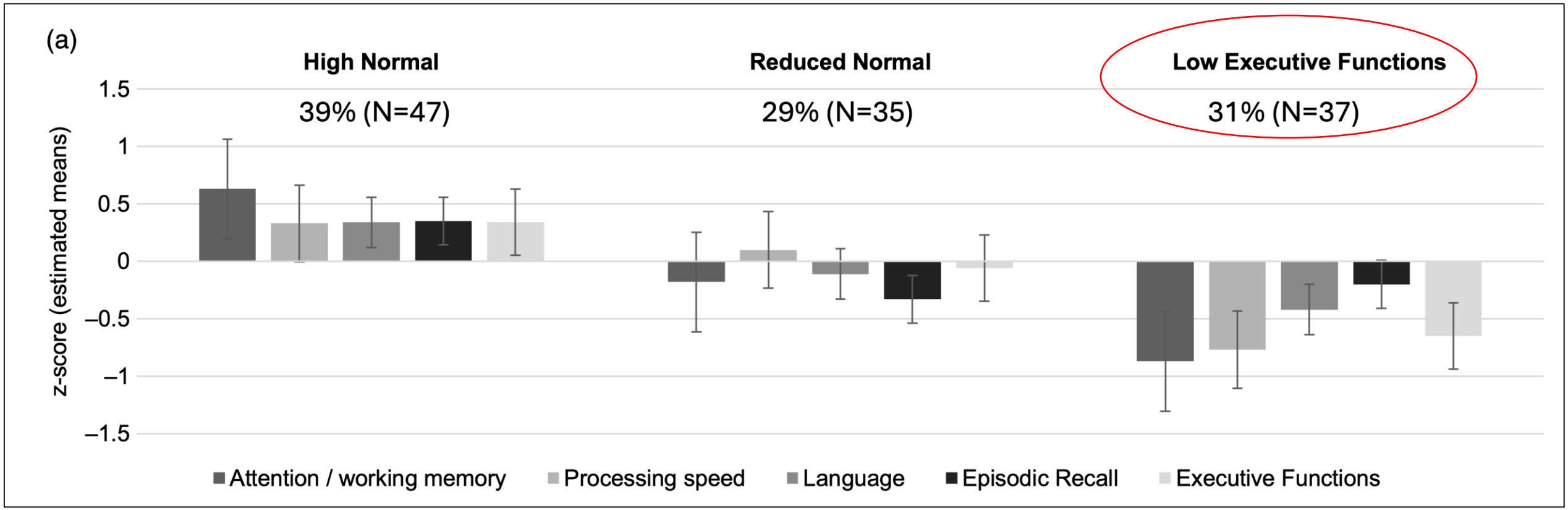






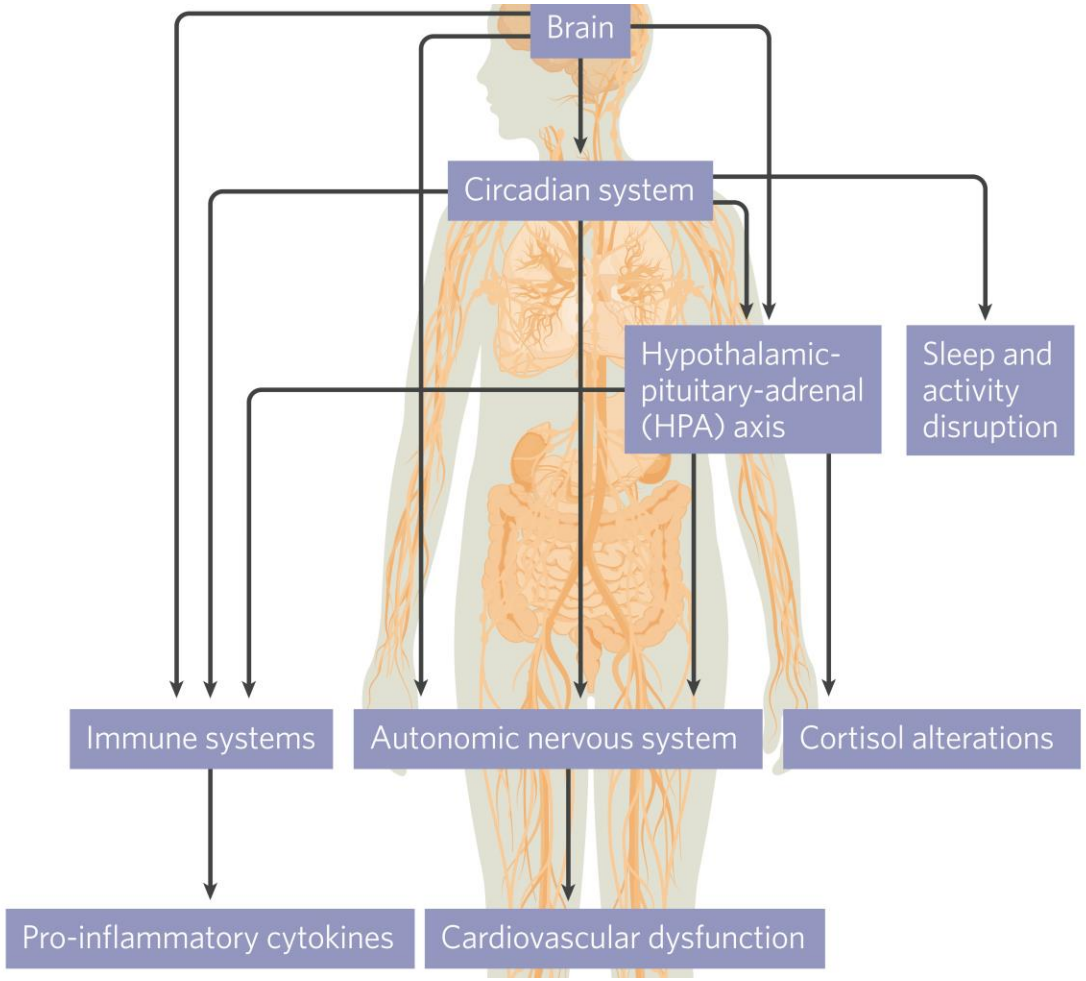
Mackin RS, et al. Biol Psychiatry, 2021

Heterogeneity in Cognitive Performance in LLD



Szymkowicz… Taylor. Int Psychogeriatrics, 2023

If not AD or amyloid, how does depression contribute to cognitive decline?



Accelerated Aging Hypothesis of LLD

- Exposure to MDEs is not benign
  - Increases allostatic load on brain & body – increased "wear and tear" over time
  - Impairs neurotrophic factor function
- High allostatic load…
  - Increases physical & cognitive disability
  - Accelerates brain aging
  - Limits neural and behavioral processes that compensate for aging
- Increases vulnerability to future depression and cognitive decline

Treatment Implications

- Work to achieve and maintain remission
- Less depression 'exposure' **<u>may</u>** lower risk

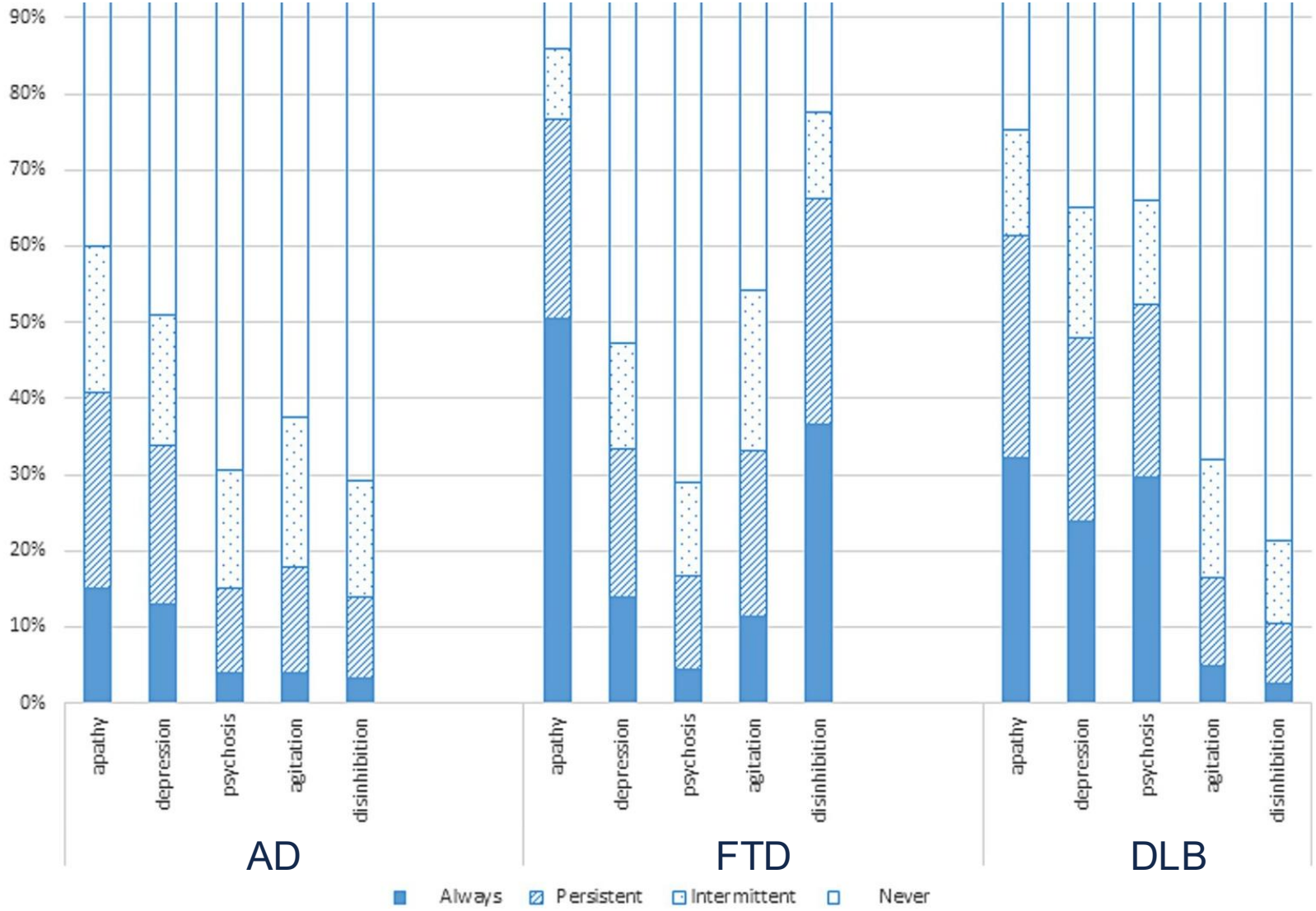
Taylor WD, et al. Neuropsychopharmacology Rev, 2026

Differences in Depression and Dementia

Clinical Features	Depression	Alzheimer's Disease	Frontotemporal Dementia	Lewy Body Dementia
Speed of onset	Rapid	Insidious in late life	Insidious in mid-adulthood	Insidious in late life
Mood	Sad, irritable	Variable	Apathetic, little empathy	Sadness, anxiety, apathy common
Attention	Often compromised	Intact simple, impaired complex	Intact simple, impaired complex	Fluctuating, impaired
Processing Speed	Slowed	Slows with progression	Intact	Slows with progression
Executive Fxn	Impaired flexibility and initiation	Impaired flexibility and problem-solving	Severely impaired	Mild impairment
Visuospatial	Intact	Declines with progression	Intact	Significantly impaired
Memory	Variable, intact	Impaired	Variable, reduced	Reduced, intact early

McClintock S & Gregg A, Reversible Causes of Cognitive Impairment and Dementia, 2025

Frequency of behavioral symptoms in dementia



Zhu CW, Schneider LS, et al. Frontiers Neurology, 2026

MBI: Mild Behavioral Impairment

- Decreased motivation (apathy, indifference)
- Affective dysregulation (anxiety, dysphoria, irritability)
- Impulse dyscontrol (agitation, disinhibition, obsessiveness)
- Social inappropriateness (loss of empathy, social graces or tact)
- Abnormal perception or thought content (hallucinations, delusions)

2016 by AA Working Group

MBI-Checklist

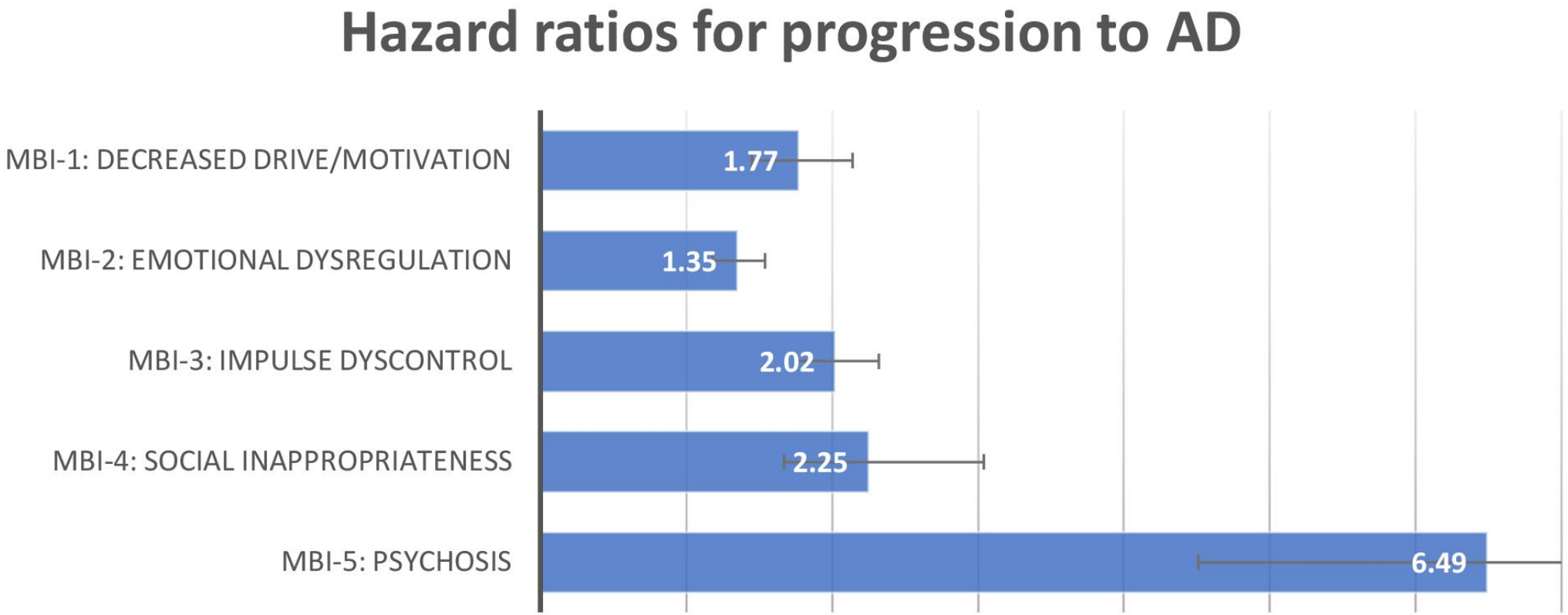
Core 5 symptoms

Changes at age > 50y

Produce impairment

Creese B, Ismail Z, Alzheimer's Research and Therapy, 2022.

MBI Symptoms have clinical implications

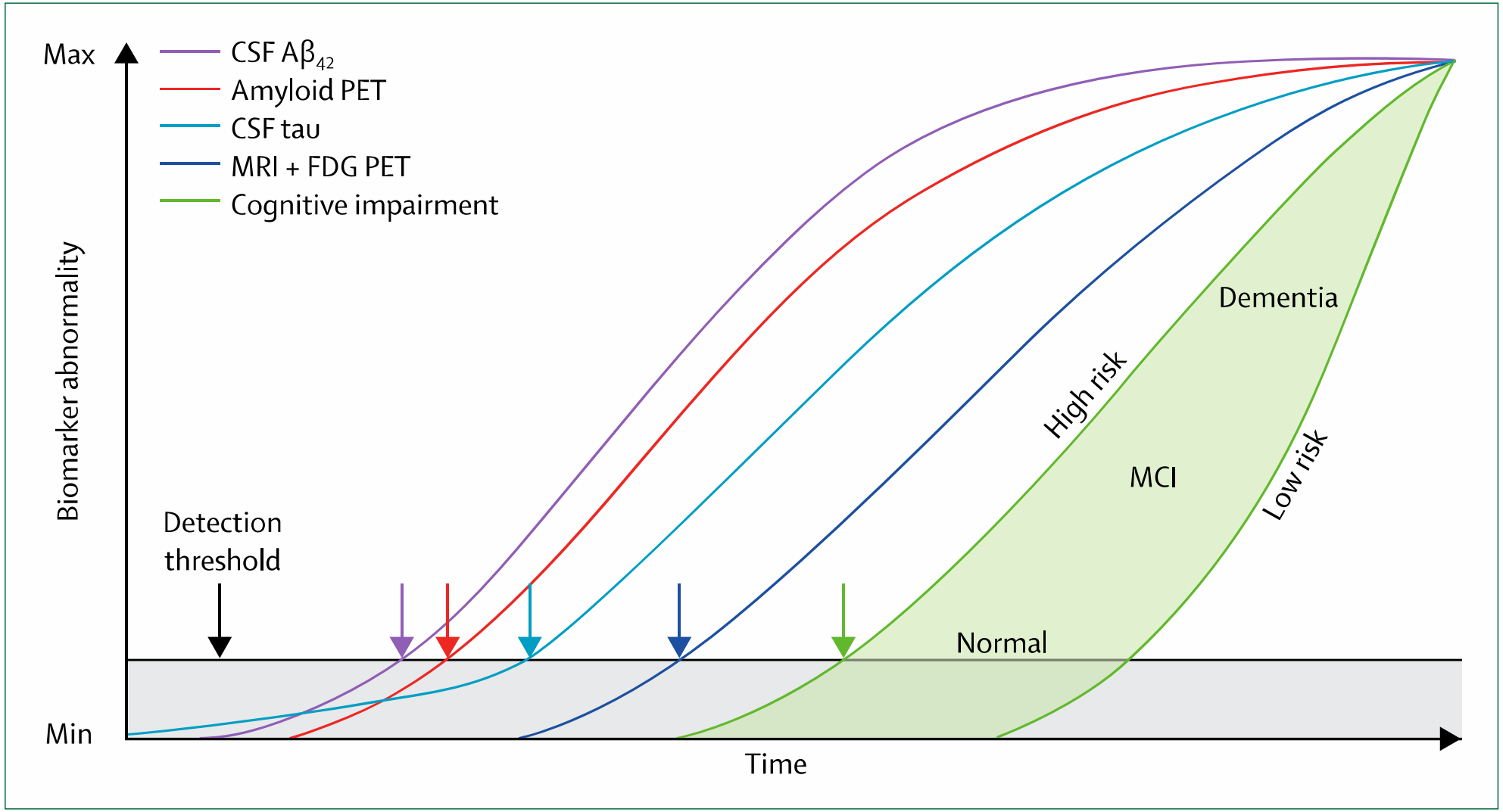


Ruthirakuhan M et al, Alzheimers Dementia, 2023.

Behavioral symptoms are important prognostic features

…that require further evaluation to inform possible treatment options

Dynamic Biomarkers in AD



Jack CR et al, Lancet, 2013.

New Diagnostic Criteria for Alzheimer's Disease

Defining diseases biologically rather than as syndromes.

AD is a biological process that begins with measurable AD neuropathologic changes (ADNPC) while asymptomatic.

Do not recommend testing for these biomarkers in cognitively normal individuals.

Received: 7 February 2024 | Revised: 21 March 2024 | Accepted: 4 April 2024

DOI: 10.1002/alz.13859

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

TABLE 1 Categorization of fluid analyte and imaging biomarkers.

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

AD Biomarkers

- **CORE 1**: Change early / early diagnosis
- **CORE 2**: Change late / staging disease severity or symptom progression
- Fluid Aβ42-based assays may become abnormal slightly before amyloid PET, the two are usually highly concordant.
- P-tau become abnormal around the same time as amyloid PET and before tau PET.

AD Biomarkers

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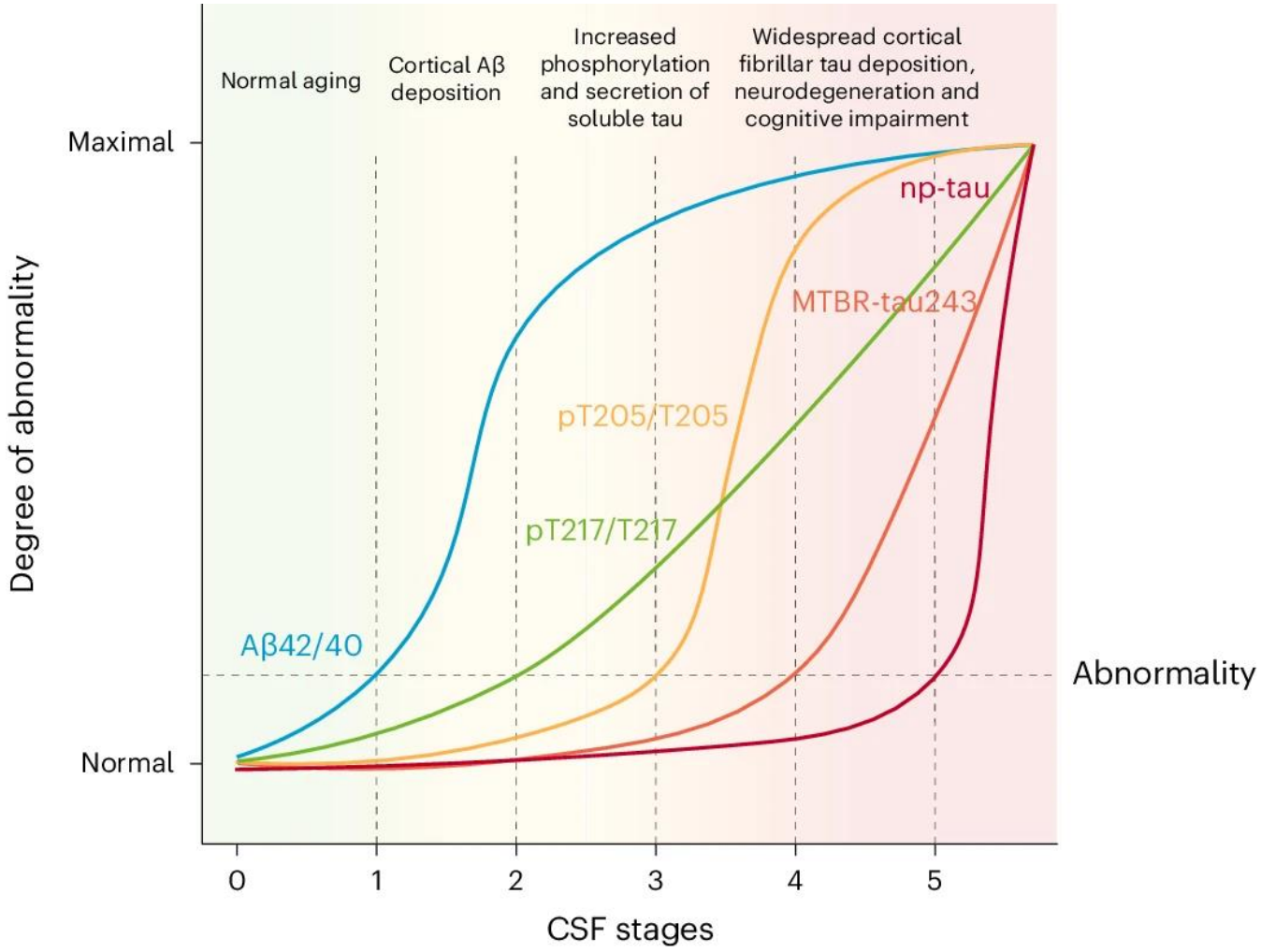
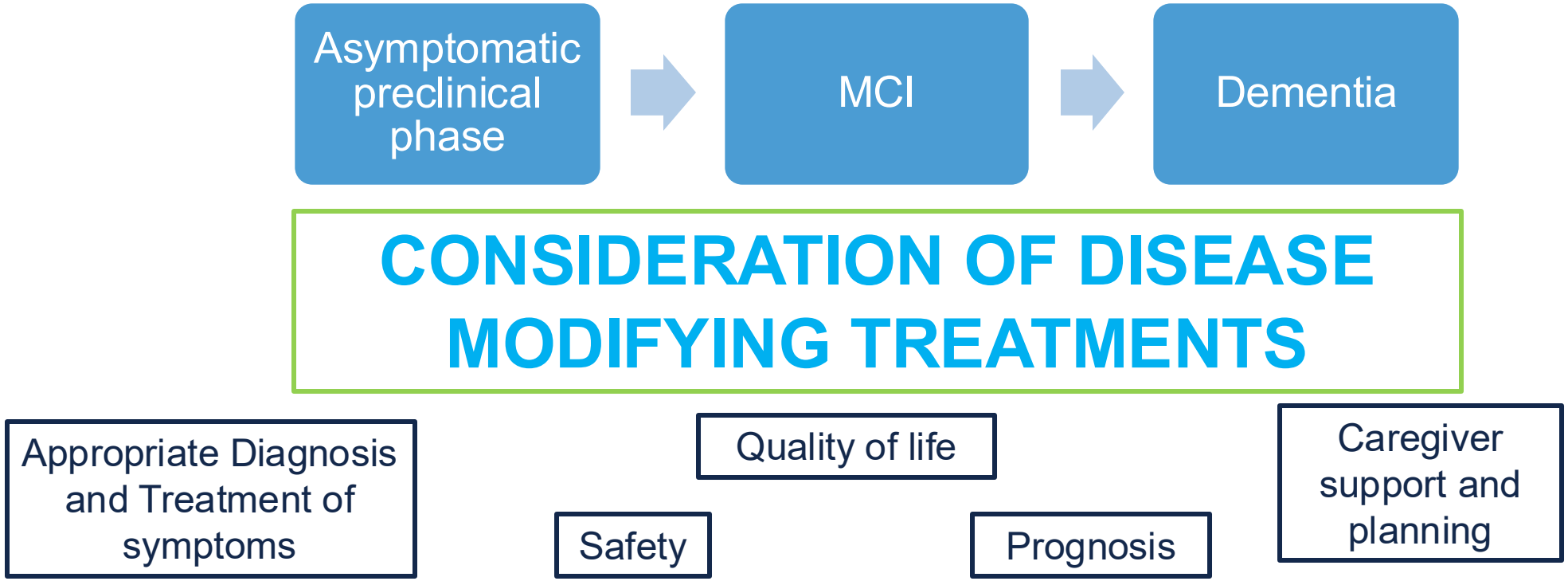
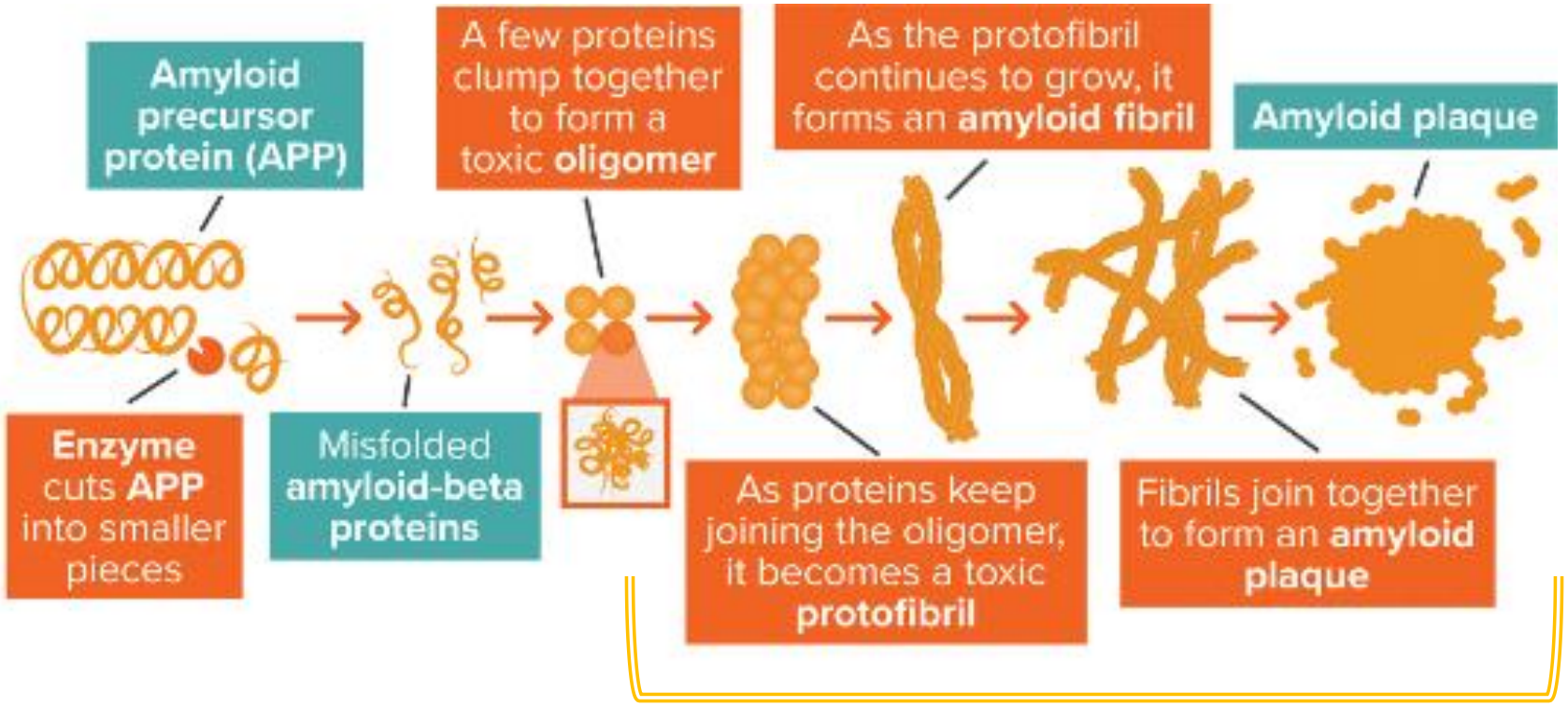


Salvado G, et al. Nature Aging, 2024.

Why is early diagnosis important?



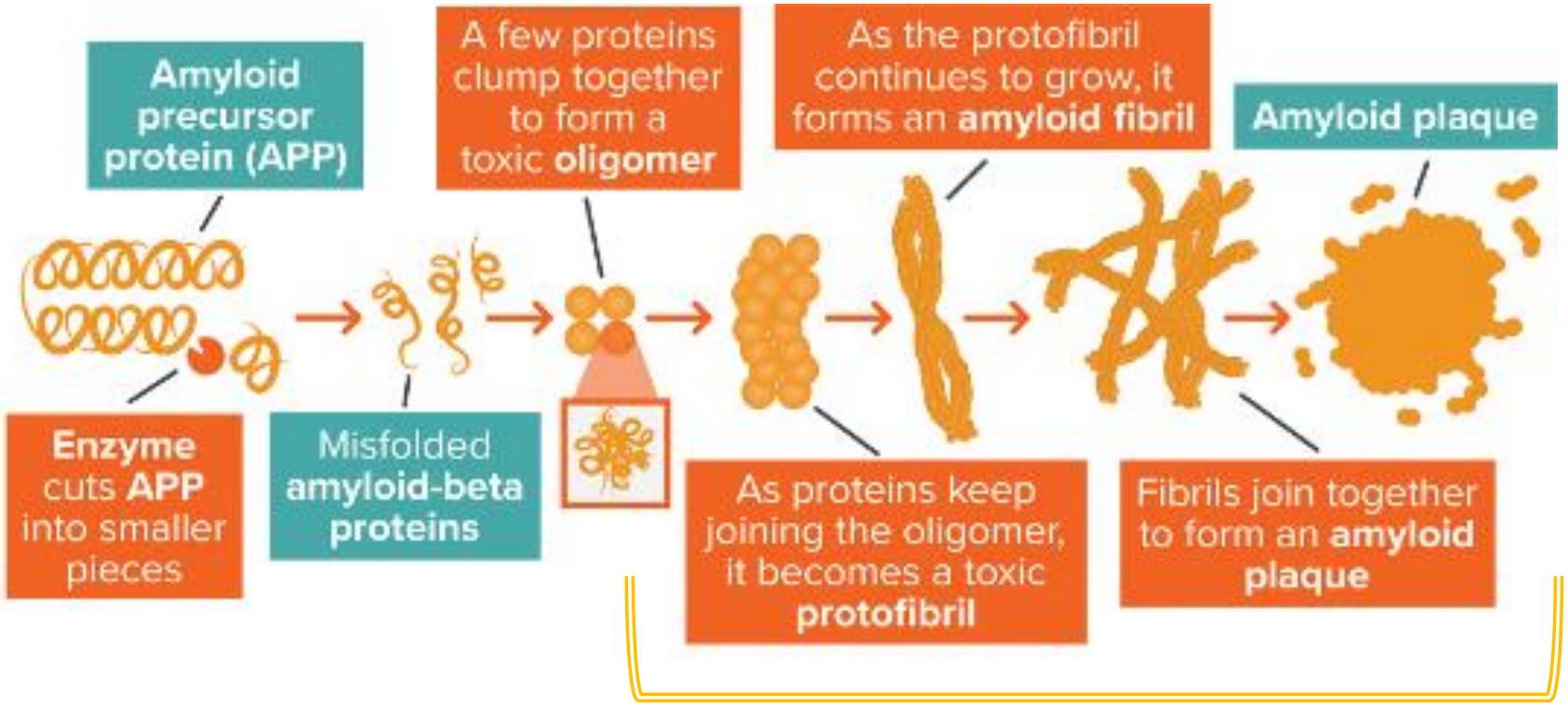
Anti-Amyloid Treatment



Aducanumab

- Accelerated approval 2021
- Benefit contested
- Highest risk of side effects
- Discontinued 2024

Anti-Amyloid Treatment



Lecanemab

- IV infusion every 2 weeks
- Efficacy: slowed cognitive decline and daily functional impairment in clinical trials

Donanemab

- IV infusion every 4 weeks
- Efficacy: slowed cognitive decline in clinical trials

Both

- Reduce cognitive decline
- Comparable rates of serious adverse events

Su CH, et al. Clinical Medicine, 2025

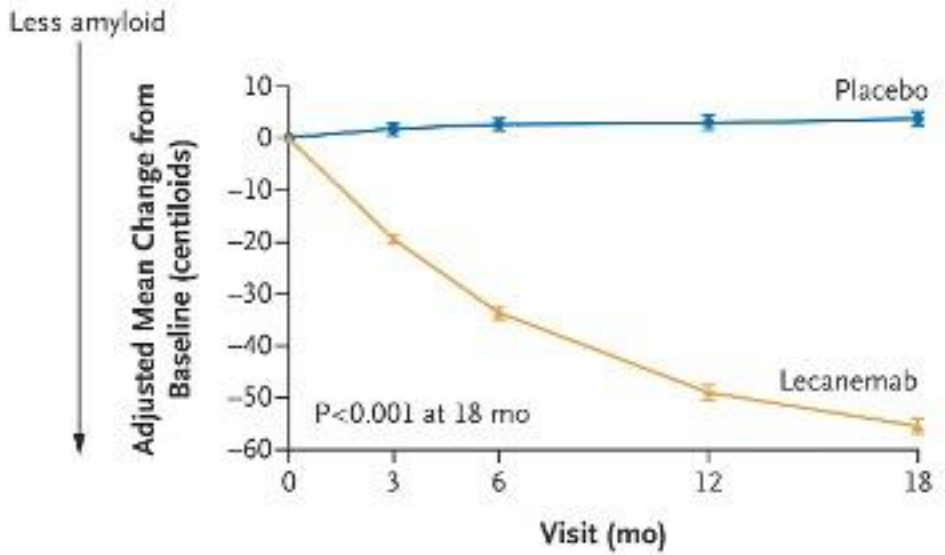
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

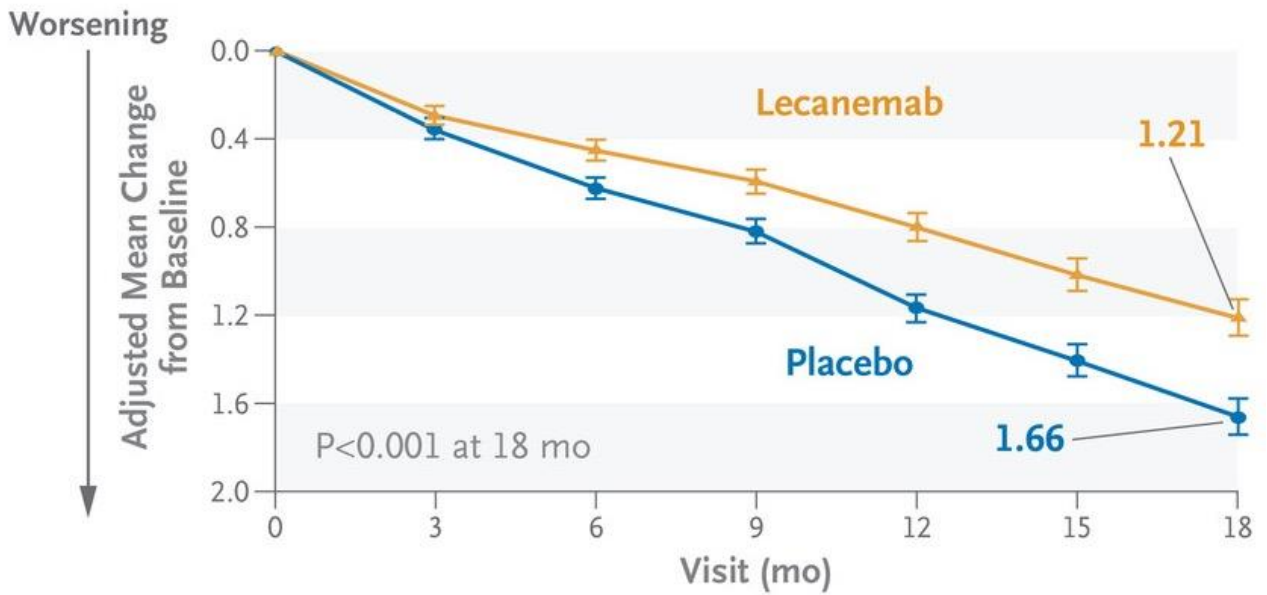
B Amyloid Burden on PET



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

Change in CDR-SB Score (Range 0–18)

Difference in least-squares mean change, −0.45 (95% CI, −0.67 to −0.23)

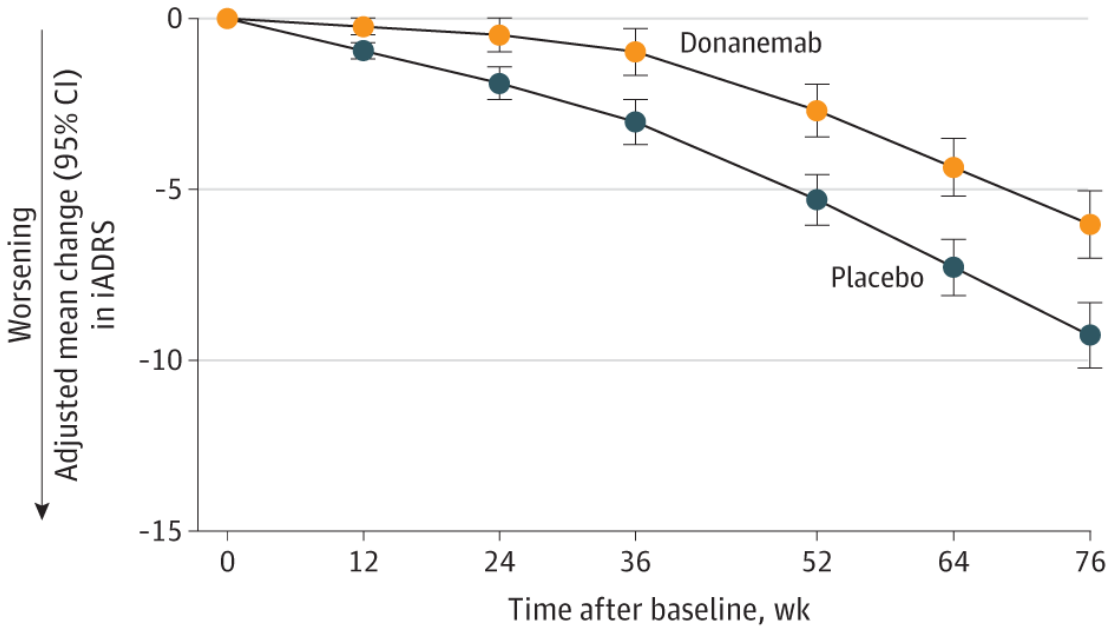


JAMA Network™

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

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

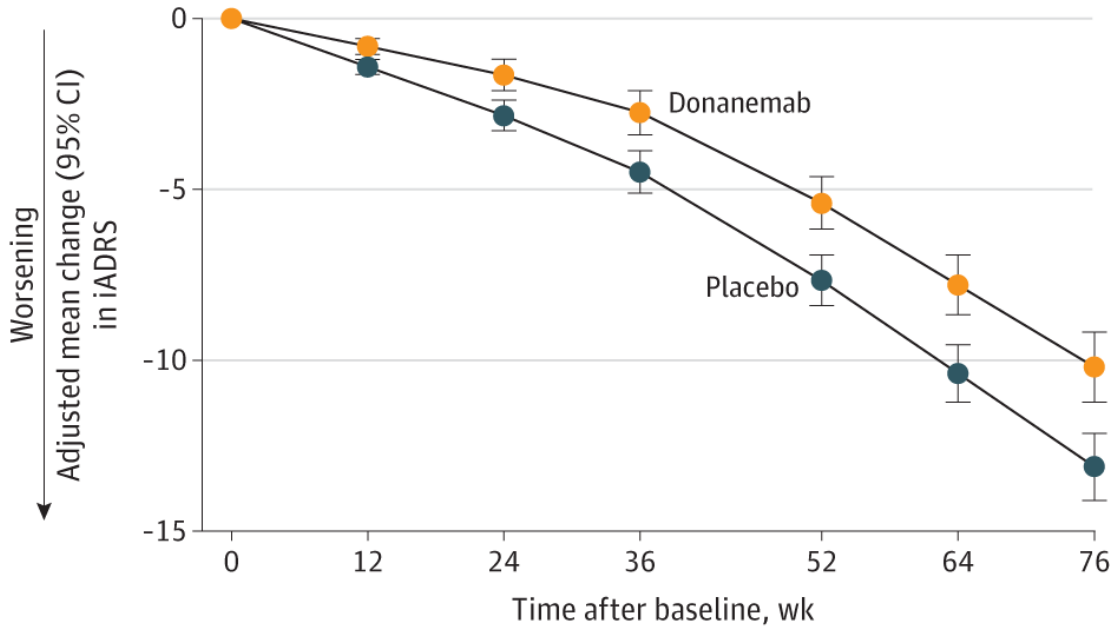
A iADRS in low/medium tau population



No. of participants

Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

B iADRS in combined population



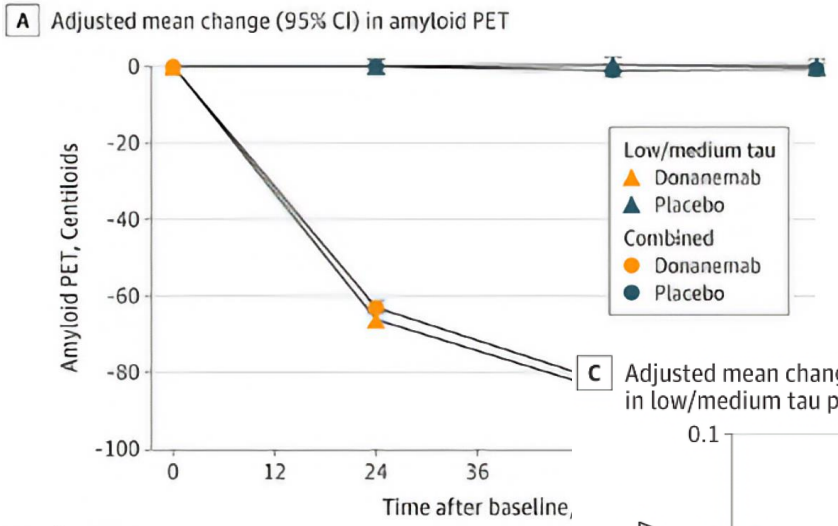
No. of participants

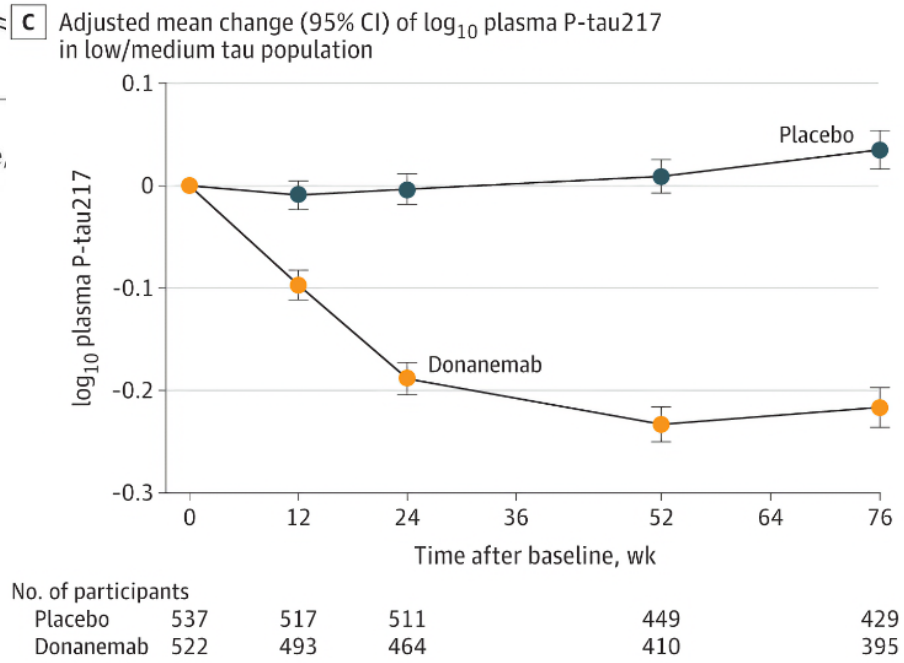
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

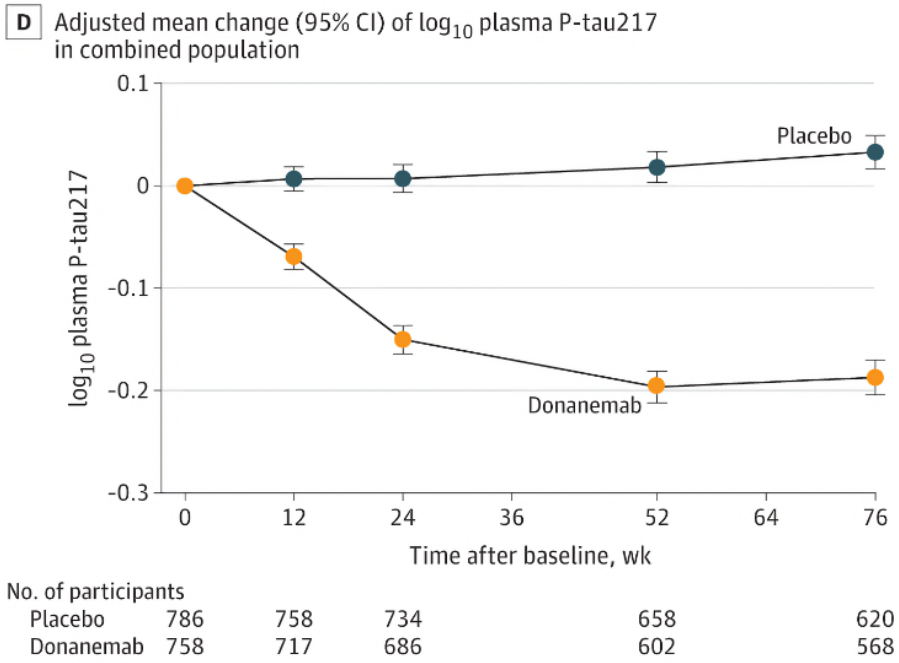
JAMA Network™

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

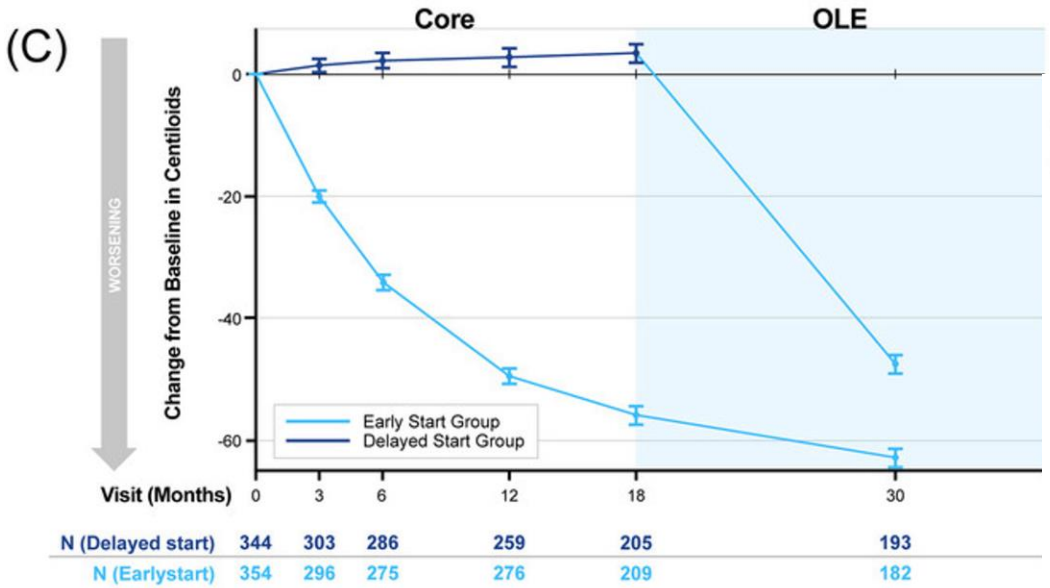
JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239

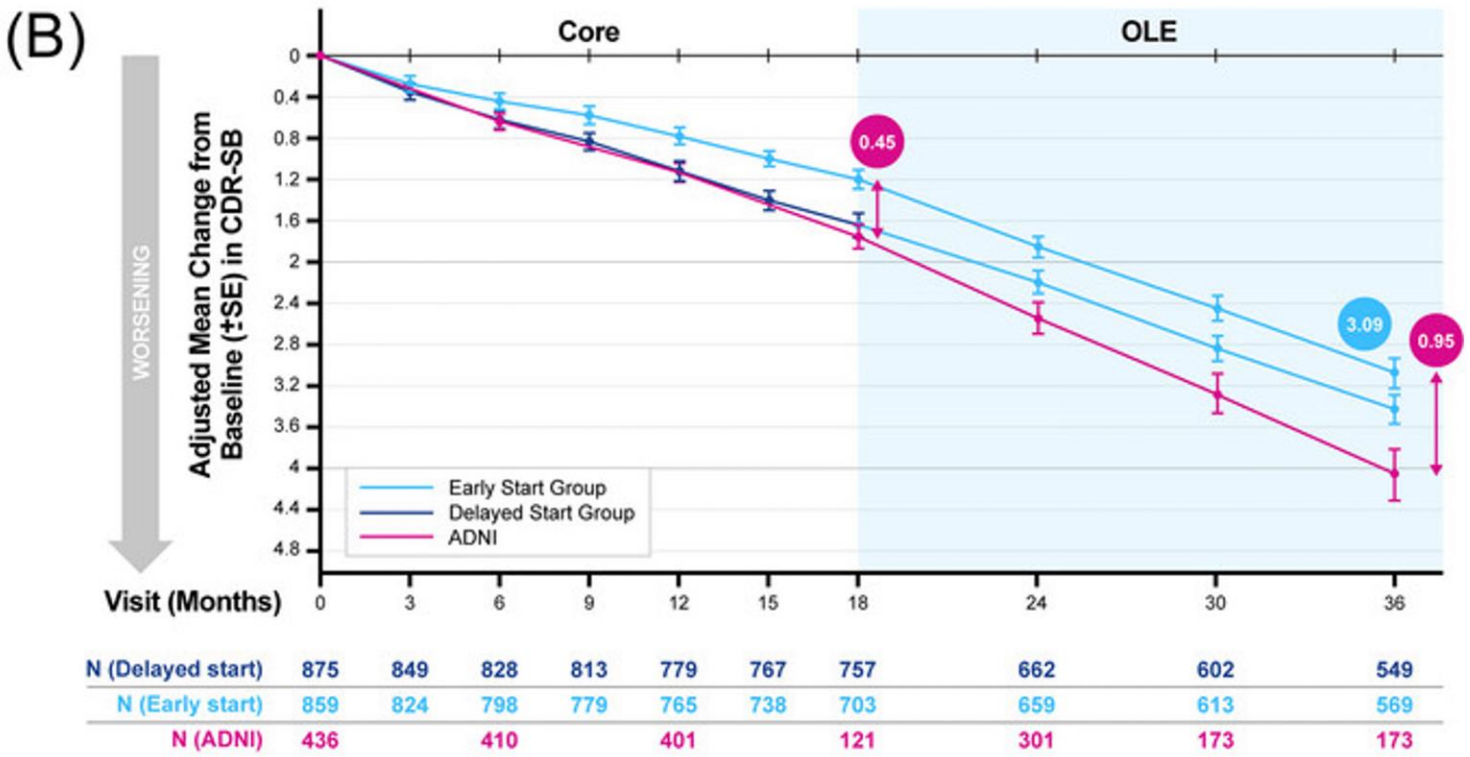






Importance of Early Treatment Initiation: Results from Open-Label Lecanemab Extension

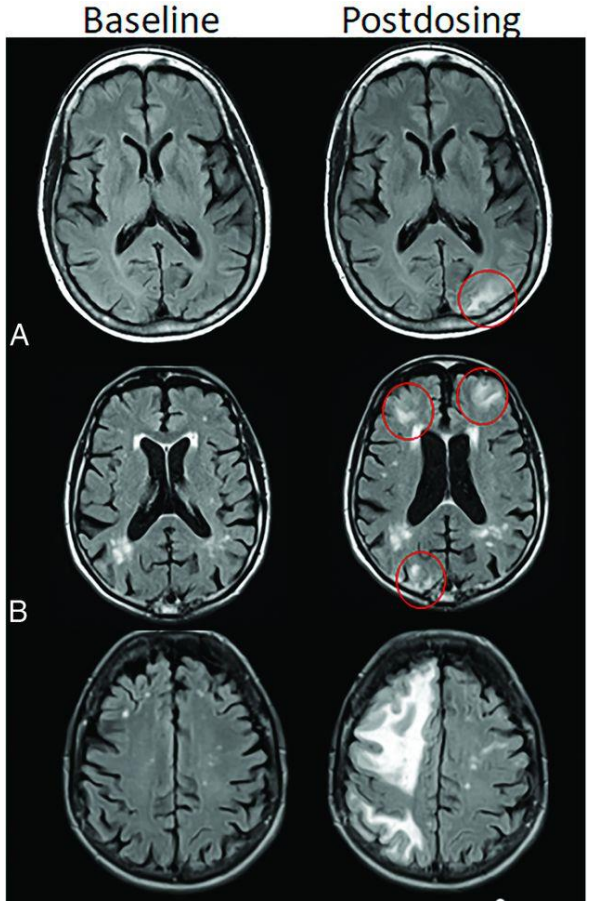




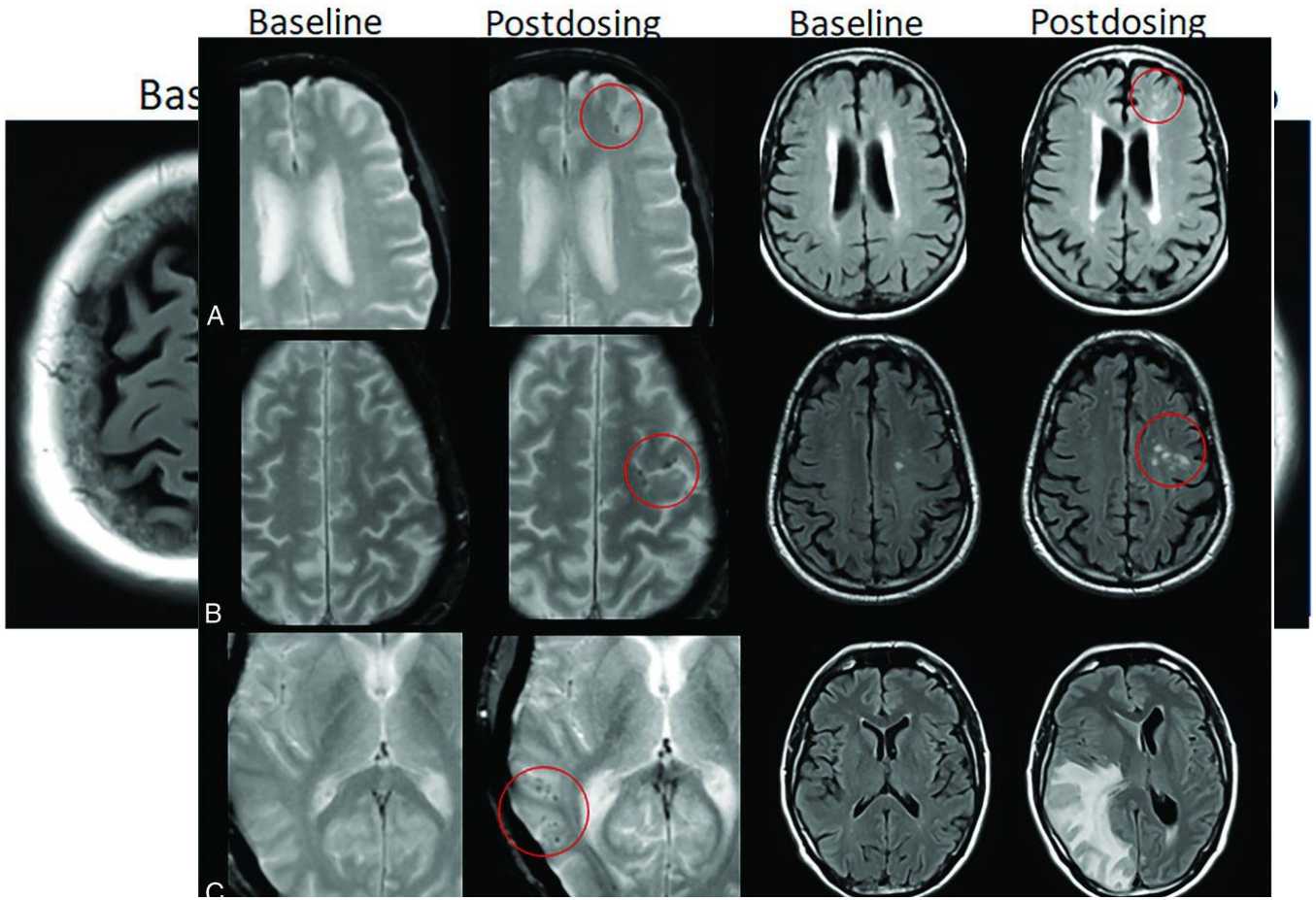
Van Dyck CH, et al. Alzheimer's & Dementia, 2025.

RISKS: Amyloid-Related Imaging Abnormalities (ARIA)

ARIA-E (Edema, Effusion)



ARIA-H (Hemorrhage - microinfarcts)



Cogswell PM, et al. AJNR, 2022

RISKS: Amyloid-Related Imaging Abnormalities (ARIA)

More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel; or other major intracranial pathology

Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD

J Prev Alzheimers Dis. 2023 ; 10(3): 362–377. doi:10.14283/jpad.2023.30.

Lecanemab: Appropriate Use Recommendations

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

Amyloid-Related Imaging Abnormalities (ARIA)

- Risk Factors for ARIA
  - *APOE-e4* carrier, pretreatment microhemorrhages
  - Most incidences occur early in treatment course
  - About 3-5% of ARIA –E symptomatic, 1% of ARIA-H
    - < 1% serious

	Lecanemab	Donanemab
ARIA-E	12.6%	24.4%
ARIA-H	17.3%	31.4%

- Requires regular monitoring by MRI
  - Lecanemab: MRIs after 2nd, 4th, 6th and 13th infusion.
  - Donanemab: MRIs after 1st, 2nd, 3rd, and 6th infusion.

Filippi M et al. JAMA Neurology, 2022; Sims JR et al, JAMA 2023. van Dyck CH, et al. N Engl J Med, 2023.
Merkel J, et al. Alzheimer's Research and Therapy, 2026.

Potential side effects

Symptomatic ARIA

- Headache
- Confusion
- Visual changes
- Dizziness / gait difficulty
- Potential serious
  - Seizures
  - Encephalopathy

Infusion Reactions

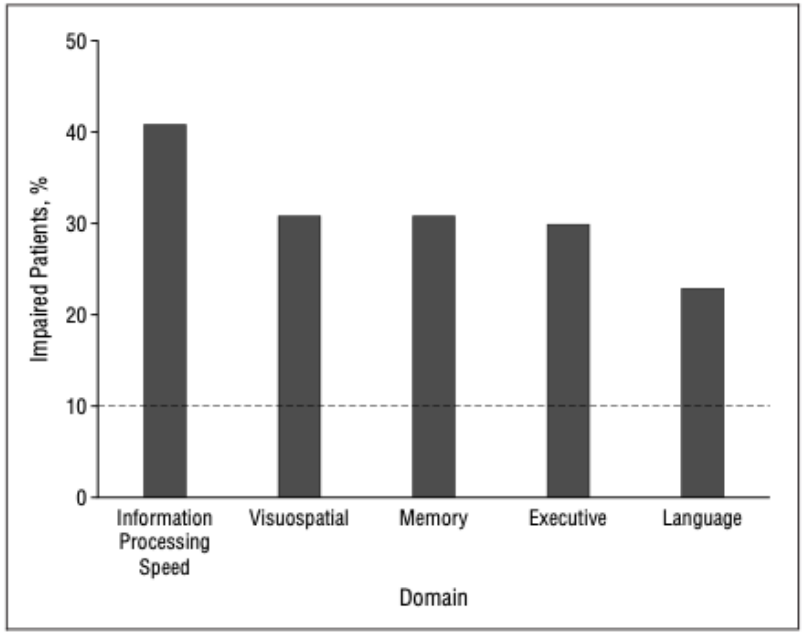
- Fever
- Flu-like symptoms
- Nausea
- Shortness of breath
- Changes in heart rate, blood pressure

What treatment options do we have for patients with LLD without Alzheimer's Disease?

Reminder about the problem in LLD…

Clinical Features	Depression	Alzheimer's Disease
Speed of onset	Rapid	Insidious in late life
Mood	Sad, irritable	Variable
Attention	Often compromised	Intact simple, impaired complex
Processing Speed	Slowed	Slows with progression
Executive Fxn	Impaired flexibility and initiation	Impaired flexibility and problem-solving
Visuospatial	Intact	Declines with progression
Memory	Variable, intact	Impaired

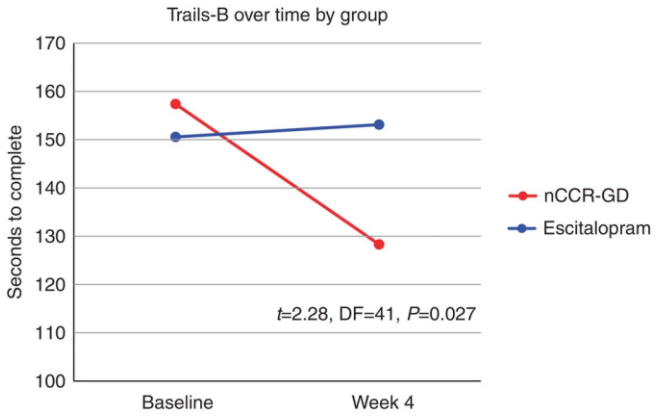
- Not the same pathology or cognitive profiles as AD
- Unknown mechanism
- No current pharmacological treatment options

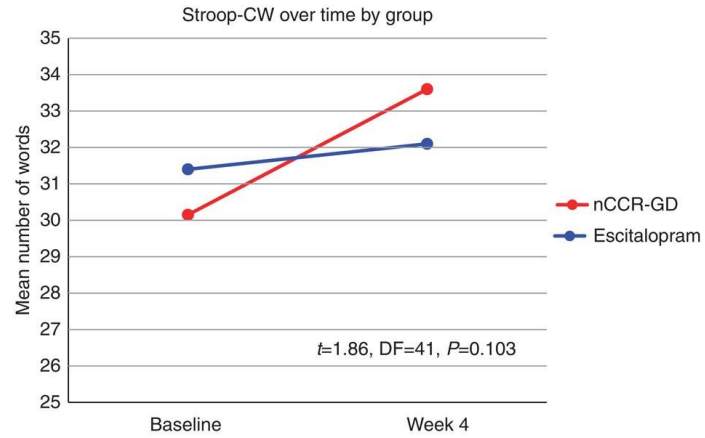


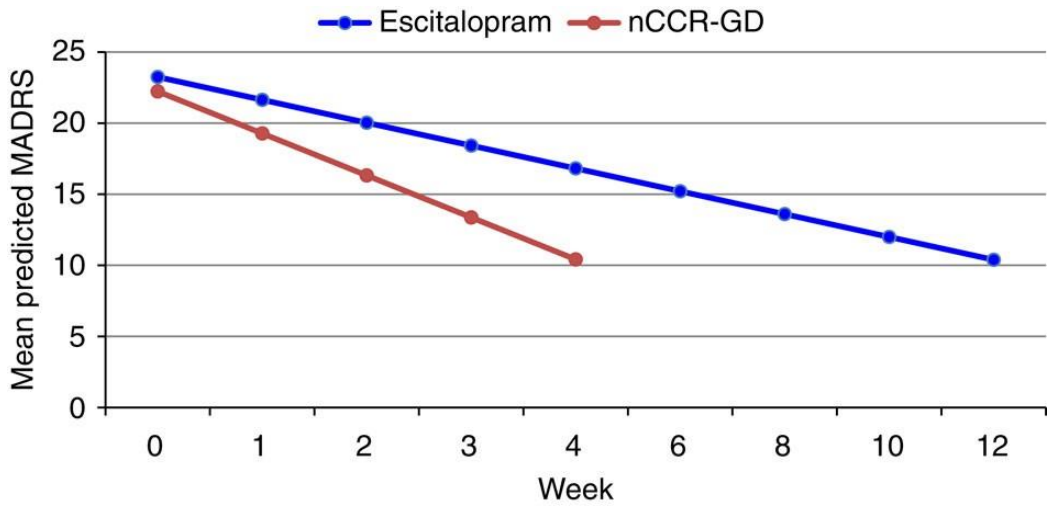
McClintock S & Gregg A, Reversible Causes of Cognitive Impairment and Dementia, 2025; Butters MA et al, Arch Gen Psych 2004

Neuroplasticity-Based Computerized Cognitive Remediation

- "Game-based" interventions
- Targeted to key cognitive processes affected
- Daily practice, 30-60m
- 4+ weeks
- Key findings:
  - Can improve cognitive performance and generalize
  - May also benefit mood symptoms
  - May generalize to other populations with similar cognitive profiles







Morimoto SS, et al. Nat Commun 2014. Also see, Gunning FM et al, Transl Psychiatry 2021.

Combining Cognitive Remediation with Neuromodulation: PACT-MD Study

POPULATION

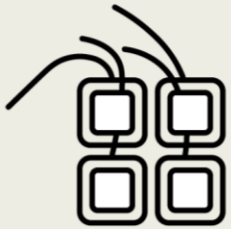
143 Males, 232 Females

Older adults with mild cognitive impairment (MCI) or remitted major depression with or without MCI

Mean (SD) age, 72.2 (6.4) y

INTERVENTION

375 Participants analyzed



188 Active CR and active tDCS
Active cognitive remediation (CR) and active transcranial direct current stimulation (tDCS)

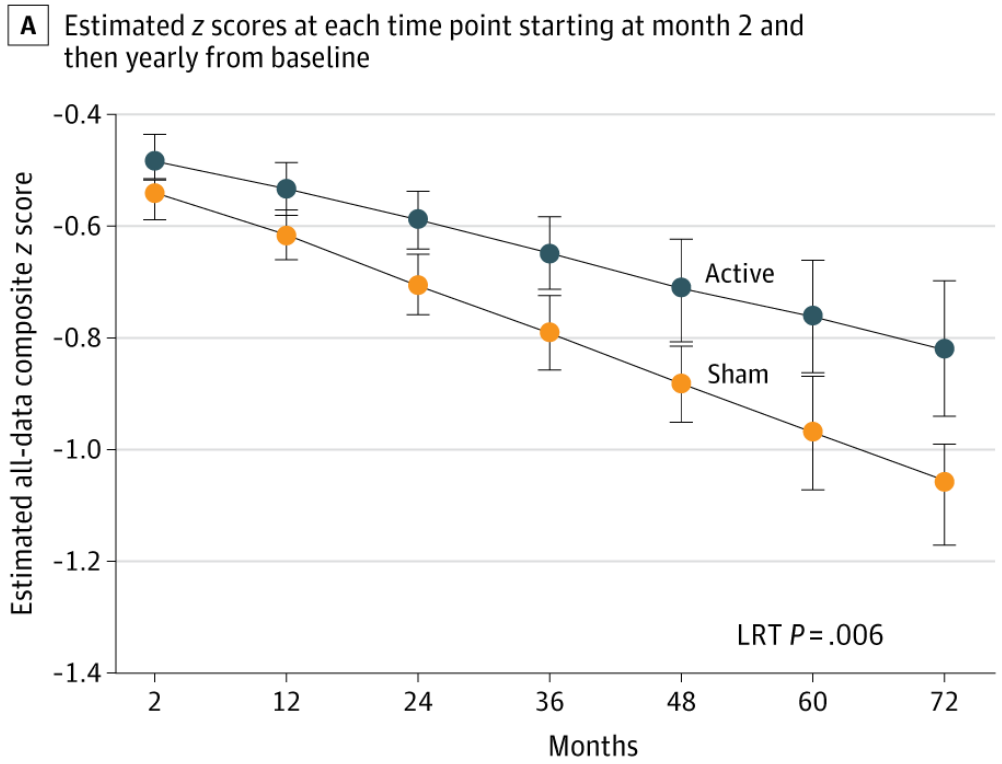
187 Sham CR and sham tDCS

SETTINGS / LOCATIONS

5 Hospitals in Toronto, Ontario, Canada

PRIMARY OUTCOME

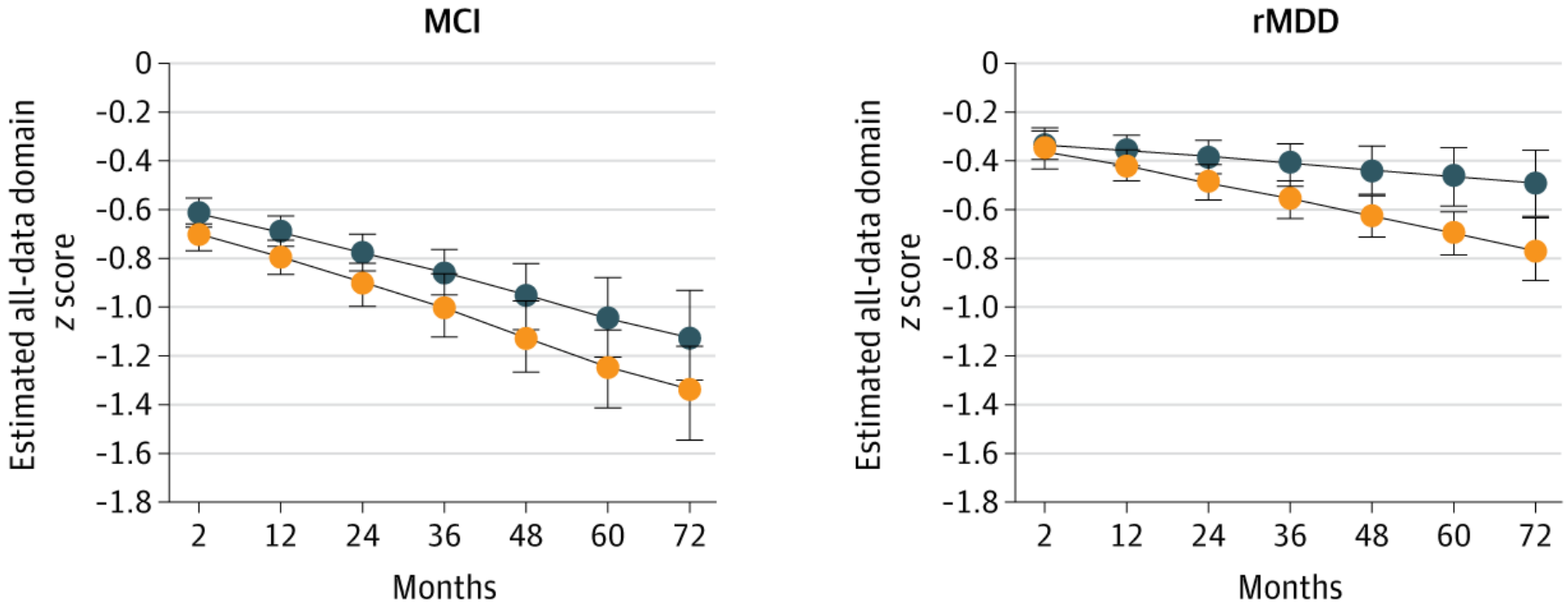
z Score of a composite cognitive score; the more negative the *z* score, the more impaired is global cognition



Tajji TK et al, JAMA Psychiatry, 2025

Combining Cognitive Remediation with Neuromodulation: PACT-MD Study

B Estimated treatment response at each time point starting at month 2 and then yearly from baseline for both diagnostic groups



Tajji TK et al, JAMA Psychiatry, 2025

What else can we do to prevent cognitive decline?

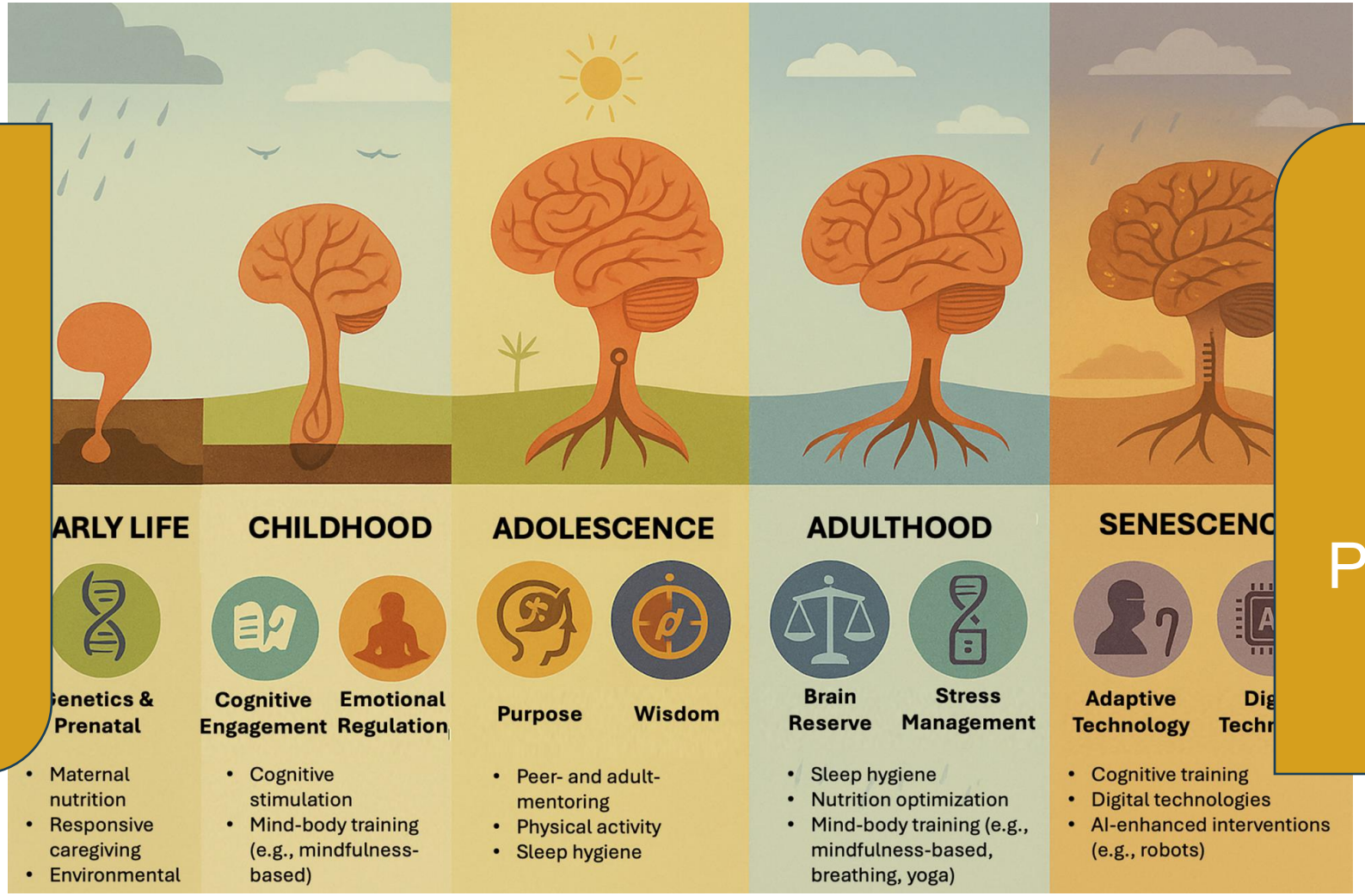
Building resilience and promoting brain health

Developing and sustaining resilience across the lifespan – “Healthy Longevity”

Common Themes:

Social Connection

Physical Activity



Risks:

Isolation, Loneliness

Poor physical health, disability

Lavretsky H et al, Neuropsychopharmacology, 2026.

Interventions to Enhance Resilience Factors

Social Factors:

- Social networks can shrink with aging

Opportunities for Engagement

- Target loneliness
- Enhance support

- Group therapy
- Layperson-delivered interventions

Szymkowicz SM…..Taylor WD. Translational Psychiatry, 2023.

Interventions to Enhance Resilience Factors

Physical Disability: Need for sustainable movement-based interventions

- Slowing, coordination deficits, and balance difficulties common with aging
- Depression leads to sedentary behavior
- Extensive data for benefits of exercise
  - Implementation: ways to facilitate
  - Need ‘dosing’ information
  - Social options – group classes, tai chi
- Role for physical therapy?

Szymkowicz SM…..Taylor WD. Translational Psychiatry, 2023.

Interventions to Enhance Resilience Factors

<u>Sensory Impairment</u>: Can improving sensory function improve other aging outcomes?

- Hearing, vision loss linked to depression & cognitive decline
- May be associated with isolation, but also physical decline and falls risk

- Data support that improving vision & hearing reduces depressive symptoms
- Psychotherapy may benefit individuals with more severe, uncorrectable loss, such as macular degeneration

Szymkowicz SM…..Taylor WD. Translational Psychiatry, 2023.

Final take home points

- Depression's recurrent nature may contribute to brain aging and cognitive decline. Depression does not always herald AD
- When depression and AD coexist, early identification can allow for disease-modifying treatments.
- Efforts to improve cognition in depression outside of AD are ongoing. Enhancing resilience through social and physical interventions can have benefit

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