

Lifestyle Factors & Dementia

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Seventh leading cause of Death in US

Clinical trials of drugs – almost uniformly unsuccessful

Potential contributors: inflammation, chronic pathogens, trophic withdrawal, insulin resistance, vascular compromise, toxins

1. Heart disease: 696,962
2. Cancer: 602,350
3. COVID-19: 350,831
4. Accidents (unintentional injuries): 200,955
5. Stroke (cerebrovascular diseases): 160,264
6. Chronic lower respiratory diseases: 152,657
7. **Alzheimer's disease: 134,242**
8. Diabetes: 102,188
9. Influenza and pneumonia: 53,544

Dementia Prevention and Reversibility(?)

Basic Science and/or Animal studies	Observation/Association	Longitudinal Epidemiology	RCT
- Lithium Orotate 5-10 mg/dy - Metabolic Profiling - Zinc	- No smoking - Physical activity - Sleep 7-9 hours per night - Healthy Eating - Avoid inactivity - Metabolic Profiling - Zinc supplementation	- Healthy eating - Mediterranean, DASH, Plant based, healthy plant based - Physical exercise - Cognitive activity - Social contact - no Alcohol - no Smoking - High calories incr risk Fat>CHO - Avoid sugary drinks - Increase potassium	- Speed processing - Moderate-high intensity aerobic exercise - Resistance Exercise - Fruit and vegetable Whole grain low fat milk, limit glucose, low fat milk and meat, fish twice a week, Whole grain cereal, limit saturated fat, whey powder supplement - Range of motion and stretching exercise - Zinc supplement up to 40 mg - Magnesium Threonic acid - ClariMem twice a day \$34/month for 12 weeks - Vitamin E supplement - 2000 IU /dy

Health Behaviors – Risk of Alzheimer's & Related Disorders - ADRD

Southern Community Cohort Study

2/3 self-reported Black and primarily low-income Americans

ADRD per claims data (85% sensitivity, 89% specificity)

Enrolled in Medicare for at least 12 consecutive Months After 65

**Controlled: Age, time from enrollment to starting follow up, years
start to follow up claims, gender, Race, education, income,
marital status, enrollment source (CHC vs gen pop),
cardiometabolic disease, depression**

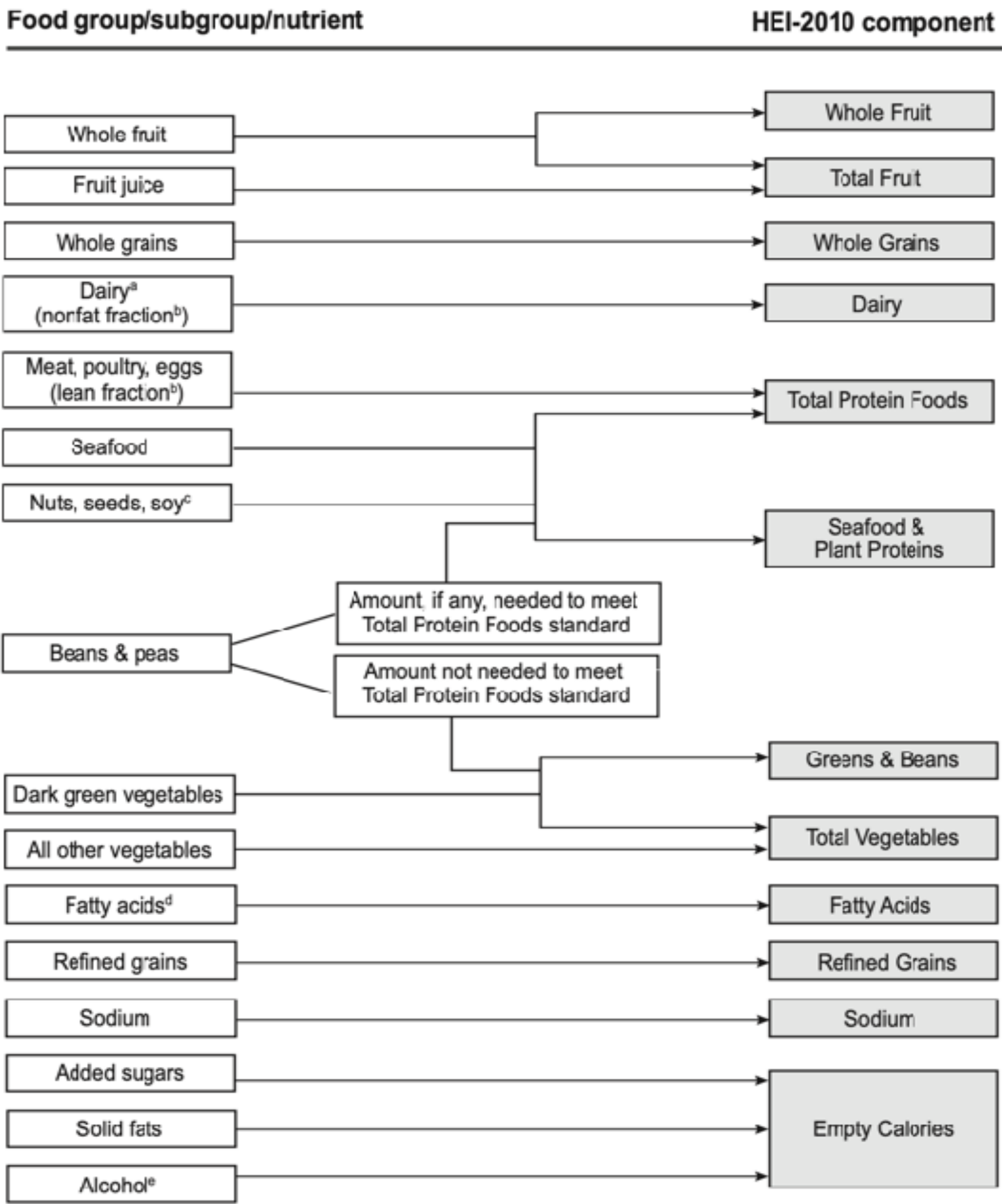
Health Behaviors – Risk of Alzheimer’s & Related Disorders

Behavior	HR
Current vs Never smoked	0.87
0 vs ≥ 8.3 METs Physical Activity per day	0.89
≥ 9 vs 7-9 hours sleep per night	0.75
<7 vs 7-9 hours sleep per night	0.79
Healthy Eating Index (tertiles)	0.85
Composite Lifestyle score (quartiles)	0.68

Health Eating Index – Risk of Alzheimer’s & Related Disorders

The Healthy Eating Index (HEI) -diet quality - the 2010 Dietary Guidelines for Americans.

- (a) it has 12 components, 9 adequacy and 3 moderation components;
- (b) density approach eg, per 1,000 calories or as % of calories
- (c) least-restrictive standards; ie, those that are easiest to achieve among recommendations that vary by energy level, sex, and/or age.



Guenther PM, Casavale KO, Reedy J, et al. Update of the Healthy Eating Index: HEI-2010. *J Acad Nutr Diet*. 2013;113(4):569-580. doi:10.1016/j.jand.2012.12.016

Speed of processing training

- RCT Healthy older adults
N=2808
- Randomized to Memory, reasoning, speed of processing
- 10 training sessions over 6 weeks – booster training at 11 months (up to four) and 35 months (up to 4)
- 10 year follow up

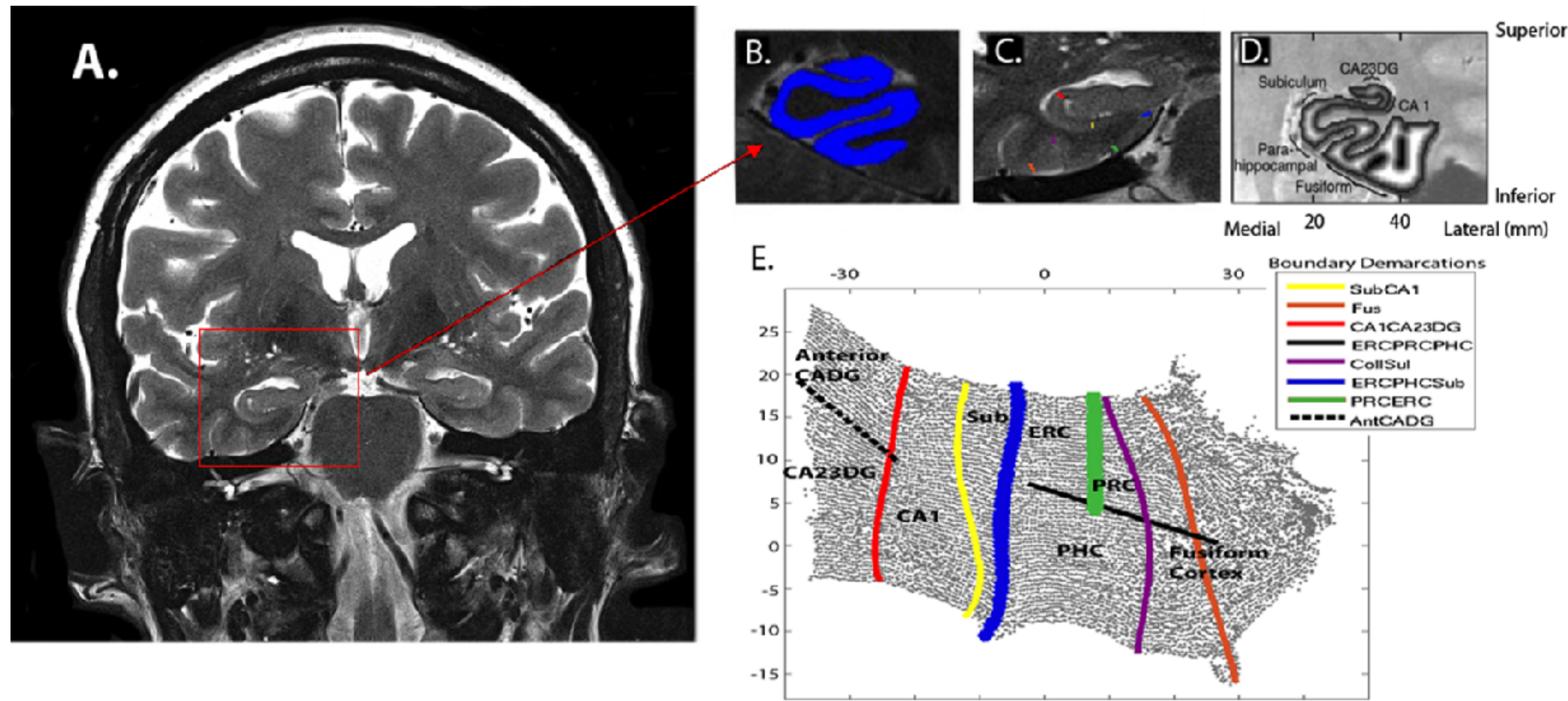
Training Modality	Hazard Ratio	P
Memory	0.79 (CI 0.57 – 1.11	0.177
Reasoning	0.79 (CI 0.56-1.10)	0.163
Speed of Processing	0.9 (CI 0.85 – 0.95)	<0.001

Inactivity

Self-reported activity levels middle-aged and older adults

Sedentary time (sitting) decreased temporal lobe hippocampal volume

Increased activity did not increase volume



Siddarth P, Burggren AC, Eyre HA, Small GW, Merrill DA (2018) Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. PLoS ONE 13(4): e0195549. <https://doi.org/10.1371/journal.pone.0195549>

Exercise and Dementia – Review 2020

Moderate and high intensity exercise beneficial

Demonstrated neuroprotective effects

Antioxidant enzymes increase - superoxide dismutase, e-NOS

Growth factors increase - BDNF, nerve growth factors, insulin-like growth factors vascular endothelial growth factor

Reducing the production of ROS

Sustained attention, visual memory, and frontal cognitive function in mild to moderate severe AD

EXERT study – 2025

(Exercise in Adults with Mild Memory Problems)

- Blinded RCT in YMCA
- Moderate-high intensity **aerobic training vs low-intensity stretching/balance/range of motion** for 18 months.
- 12 month supervision
- ADAS-Cog-Exec every 6 months
- High adherence
- Both may stall decline in adults with amnestic MCI

Resistance exercise to reduce risk of falls in people with Alzheimer's disease (RCT 2025)

- Main outcome measure: Main outcome measure: risk of falls (Short Physical Performance Battery).
- Secondary outcomes: muscle strength (hand dynamometry), neuropsychiatric symptoms (Neuropsychiatric Inventory Questionnaire), fear of falling (Activities-Specific Balance Confidence Scale) and ability to perform activities of daily living (Lawton Instrumental Activities of Daily Living Scale).
- **Resistance exercise** effectively reduces the risk of falls, fear of falling and neuropsychiatric symptoms, and improves muscle strength in people with AD in both the short and medium term

Cámara-Calmaestra R, et al. Resistance exercise to reduce risk of falls in people with Alzheimer's disease: a randomised clinical trial. *Physiotherapy*. 2025 Mar;126:101440. doi: 10.1016/j.physio.2024.101440. Epub 2024 Oct 28. PMID: 39689408.

Diet and Dementia – 2019

- 20 year **prospective cohort** study - Singapore Chinese Health Study
- 16,948 men and women aged 45–74 y at baseline (1993– 1998)
- Reinterviewed at the **third** follow-up visit (2014–2016), ~20 y later
- Singapore-modified MMSE at 20 years
- 5 predetermined **healthful dietary patterns** were assessed for risk of cognitive impairment in the Singapore Chinese population
- OR and 95% CI of cognitive impairment – education-specific cut offs

Wu J, Song X, Chen GC, et al. Dietary pattern in midlife and cognitive impairment in late life: a prospective study in Chinese adults. *Am J Clin Nutr*. 2019;110(4):912-920. doi:10.1093/ajcn/nqz150

Diet and Dementia – 2019

- Diet Quality – Structured **semiquantitative FFQ** incorporating 165 dietary items frequently used in the Population of Singapore – 8 frequency categories and 3 portion sizes
 - Alternate Mediterranean diet (aMED)
 - Dietary Approaches to Stop Hypertension (DASH) diet
 - Alternative Healthy Eating Index (AHEI)-2010
 - Plant-based diet index (PDI)
 - Healthful plant-based diet index (hPDI)

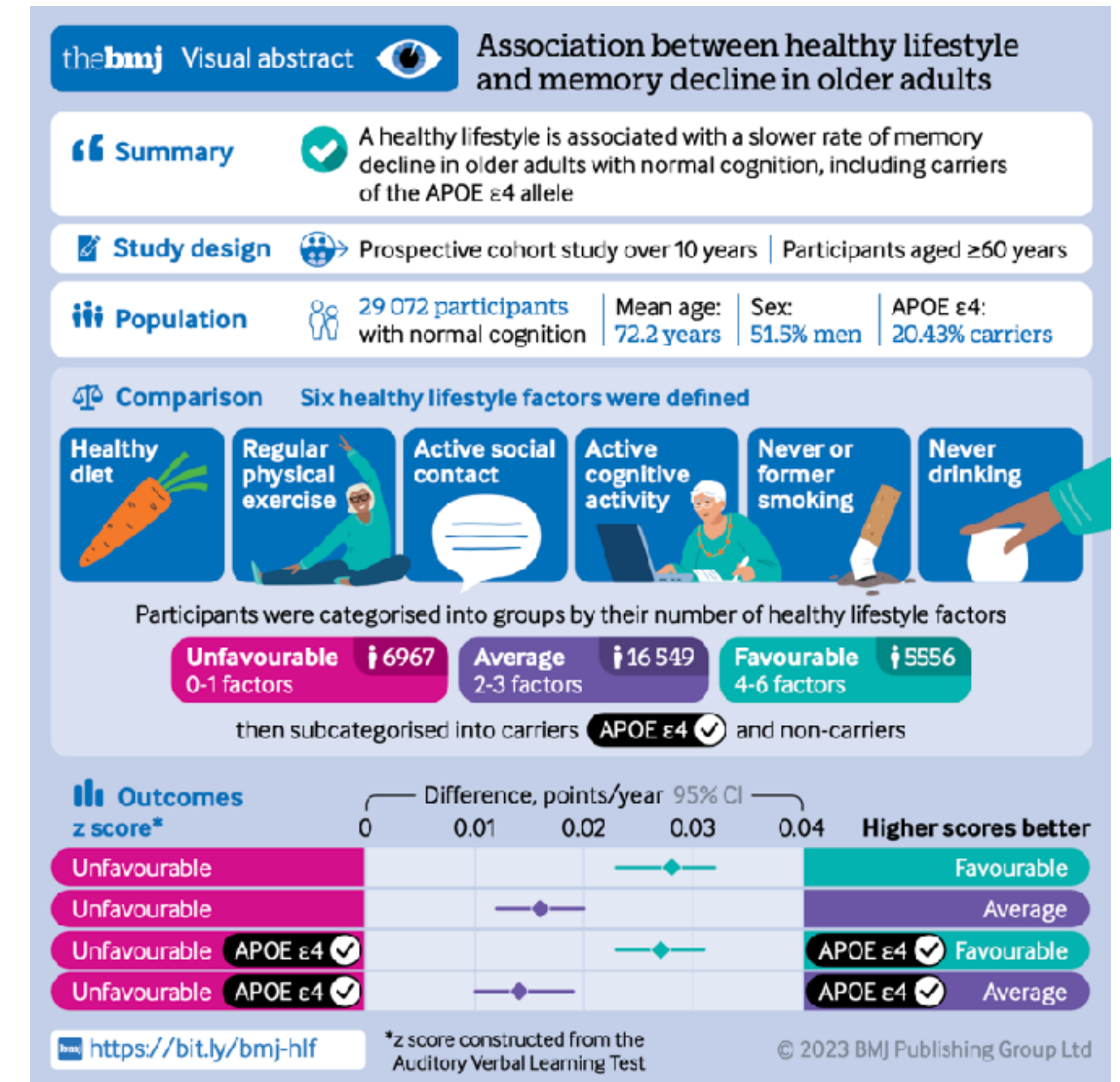
Dietary Patterns Quartiles and Dementia

Dietary Pattern – highest vs lowest Quartile – p for trend <0.001	OR
Alternate Mediterranean diet (aMED)	0.67
Dietary Approaches to Stop Hypertension (DASH)	0.71
Alternative Healthy Eating Index (AHEI)-2010	0.75
Plant-based diet index (PDI)	0.71
Healthful plant-based diet index (hPDI)	0.78

Wu J, Song X, Chen GC, et al. Dietary pattern in midlife and cognitive impairment in late life: a prospective study in Chinese adults. *Am J Clin Nutr*. 2019;110(4):912-920. doi:10.1093/ajcn/nqz150

Lifestyle and Memory Decline - 2023

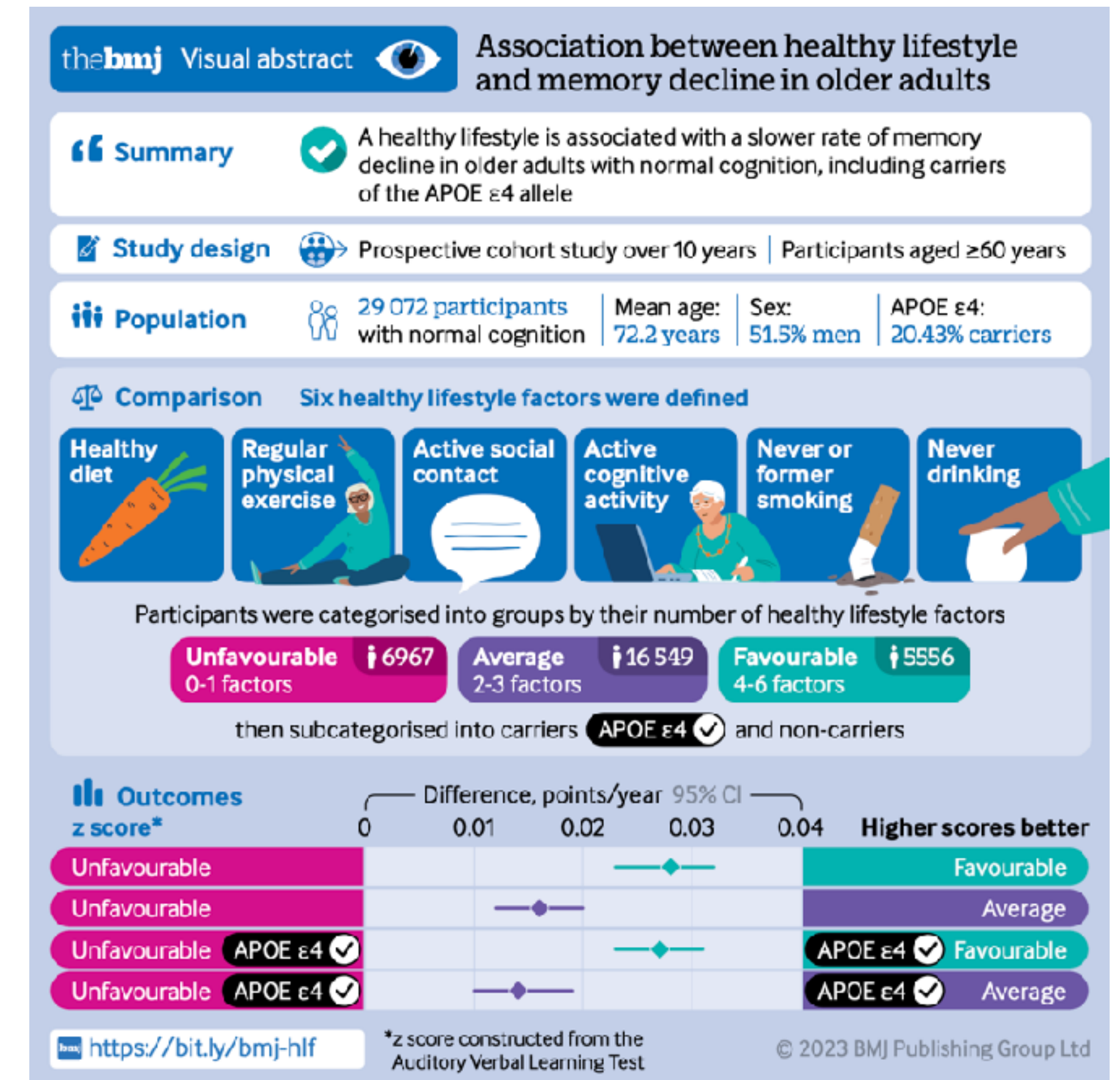
- China - Population-based cohort study -29,000 people ages 60 and older between 2009 and 2019.
- Physical exercise: Doing at least 150 minutes of moderate or 75 minutes of vigorous activity per week.
- Diet: Eating appropriate daily amounts of at least seven of 12 food items (fruits, vegetables, fish, meat, dairy products, salt, oil, eggs, cereals, legumes, nuts and tea).



Jia J, Zhao T, Liu Z, et al. Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study. *BMJ*. 2023;380:e072691. Published 2023 Jan 25. doi:10.1136/bmj-2022-072691

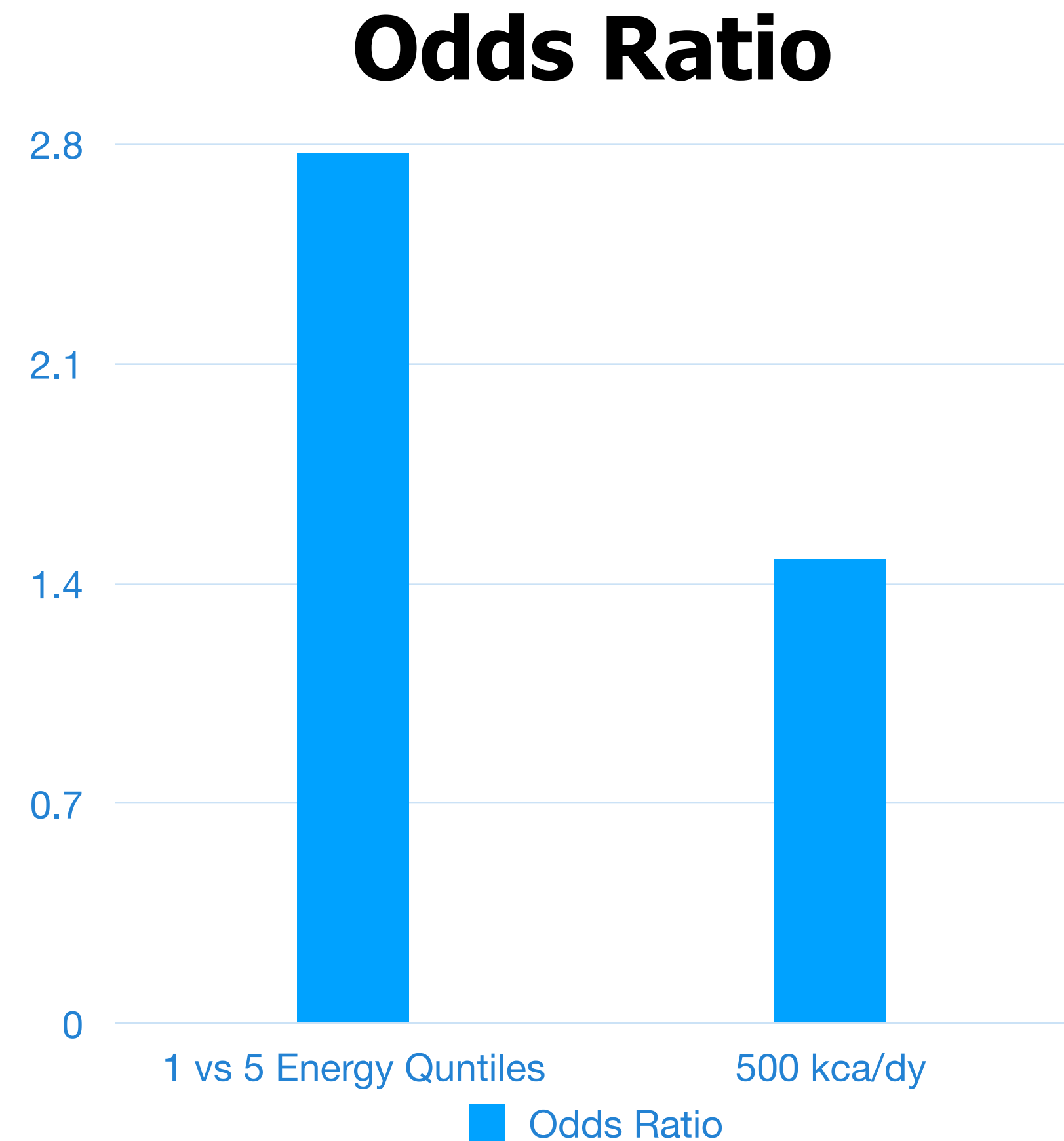
Lifestyle and Memory Decline - 2023

- Alcohol: Never drank or drank occasionally.
- Smoking: Never having smoked or being a former smoker.
- Cognitive activity: Exercising the brain at least twice a week (by reading and playing cards or mah-jongg, for example).
- Social contact: Engaging with others at least twice a week (expl: attending community meetings or visiting friends or relatives).
- With or without APOE-4 Similar Results



Long-term total energy and fat - 2022

- Prospective Epidemiologic - Subjective Cognitive Decline (SCD)
- Nurses' Health Study (49,493) & Health Professionals Follow-up Study (27,842)
- 20 years, Validated SFFQ,
- Highest vs lowest Quintiles
- 3-unit increment in Subjective Cognitive decline
- Fat calories > CHO calories



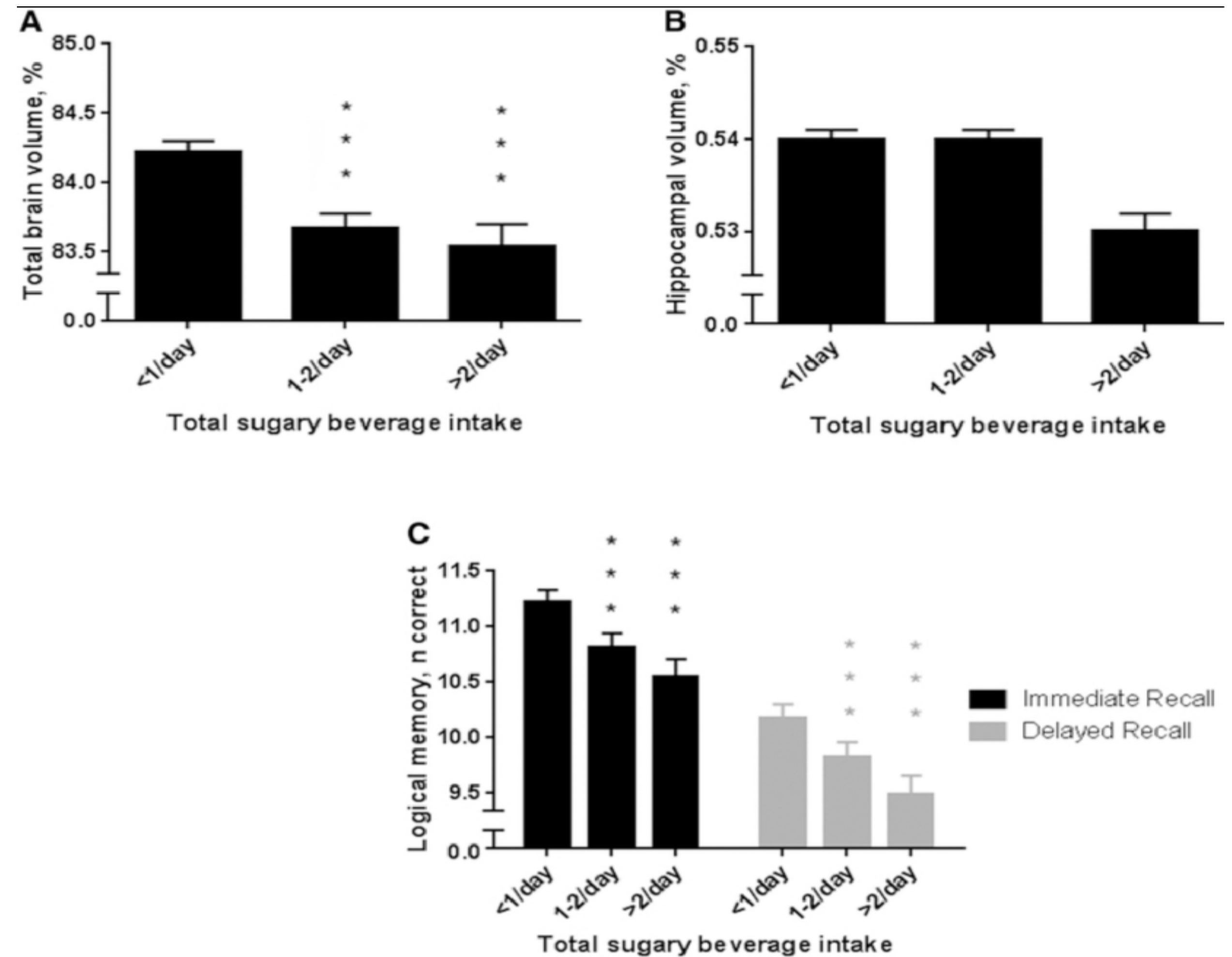
Effect of a 12-mo intervention with whey protein powder on cognitive function in older adults with mild cognitive impairment - 2025 RCT

- Whey protein powder rich in MFGM proteins, taurine, and B vitamins improved cognitive function in mice.
- **Human trial** #53 intervention, #54 control
- 15 grams/day of whey powder
- - Primary endpoint: MoCA
- Secondary outcomes: Digit Symbol Substitution Test score,
- Mean difference between groups in the ITT analysis was 2.72 (95% CI: 0.20, 5.23)

Li F, et al. Effect of a 12-mo intervention with whey protein powder on cognitive function in older adults with mild cognitive impairment: a randomized controlled trial. Am J Clin Nutr. 2025 Feb;121(2):256-264. doi: 10.1016/j.ajcnut.2024.11.019. Epub 2024 Nov 20. PMID: 39571910.

Sugary Drinks & Alzheimer's – 2017 Cross-sectional **association**

- Cross-sectional association
- Framingham Heart Study – Neuropsychological and MRI testing
- Food frequency Questionnaire
- Sugary Drink
- Fruit Juice



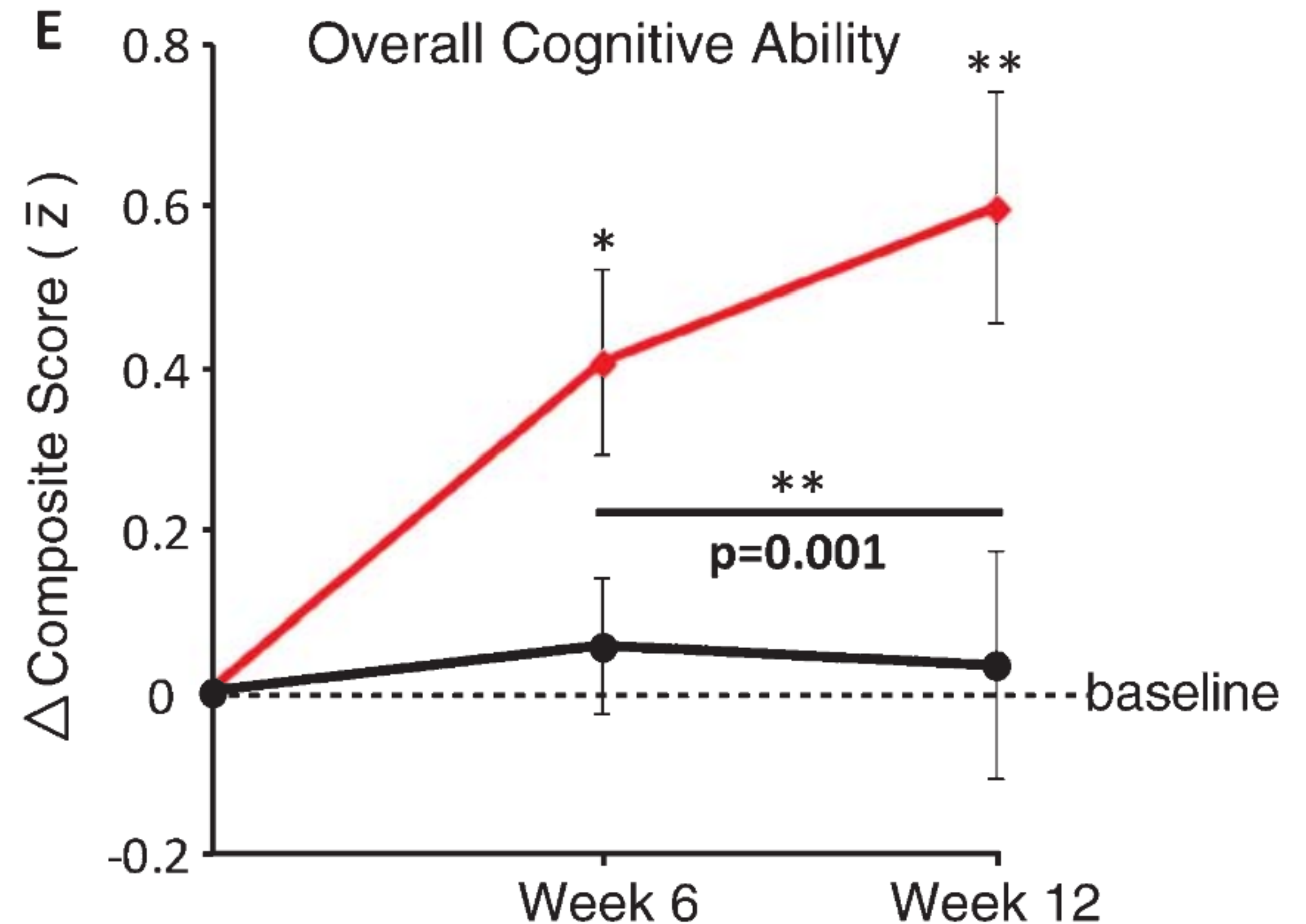
Pase MP, Himali JJ, Jacques PF, et al. Sugary beverage intake and preclinical Alzheimer's disease in the community. *Alzheimers Dement.* 2017;13(9):955-964. doi:10.1016/j.jalz.2017.01.024

Na⁺, K⁺, Na⁺ /K⁺, & Salt & Dementia 2022

- Prospective Cohort (**association**): 1997-2006 China Health and Nutrition Survey, 4,213 ≥ 50 years at baseline.
- High Na⁺ → decreased cognitive function
- Higher K⁺ → higher cognitive function
- Higher Na⁺ /K⁺ → decreased cognitive function
 - Higher self-reported 12-month deterioration
- Cardiovascular and cerebrovascular disease mediated
- Replacing 1000 mg of Na⁺ with K⁺ increased cognitive score by 1 point

Magnesium Threonic Acid - 2016

- 12 wk parallel RCT double blind placebo controlled.
- Placebo vs L-Threonic acid Magnesium salt (brand:Clarimem)
- Four measures of cognitive function.
- Cognitive TMT-B; DigitSpan (consecutive #'s); Flanker; Face-Name; Composite



Vitamin E supplementation – RCT 2014

- Double-blind, placebo-controlled, parallel-group RCT
- 613 patients with mild to moderate AD initiated in 8/2007 - 9/2012 at 14 VA's
- 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152).
- Mild to moderate AD, vit E alone → slower functional decline & decreasing caregiver burden.

Copper and Zinc - 2012

- Excess Copper causes neuronal Toxicity
- Zinc Deficiency causes neuronal damage
- Zinc Supplementation vs Placebo RCT beneficial on cognitive measures

Zn - Cognitive Impairment & Aging - 2022

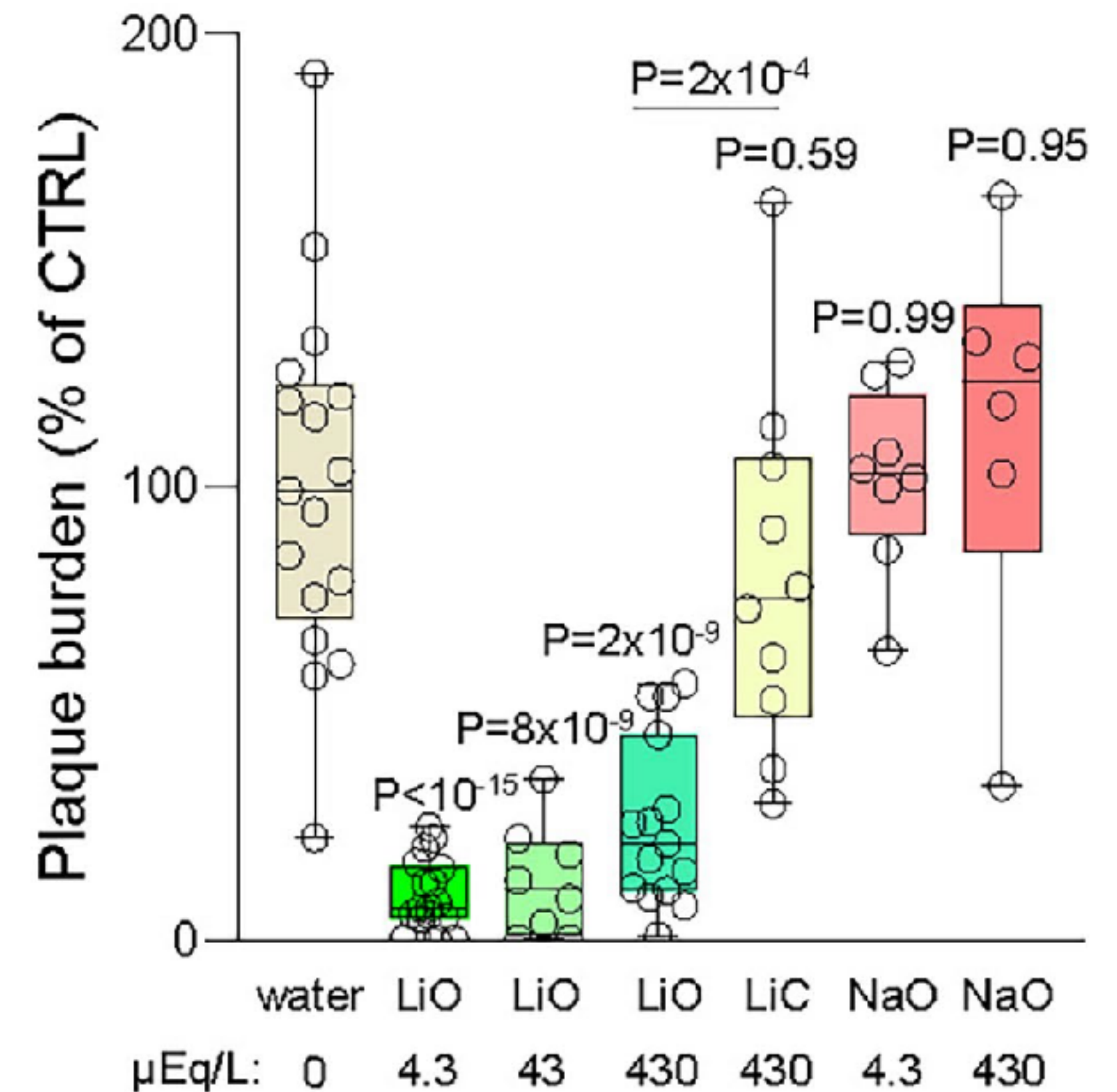
- Review article
- zinc is not redox-active under physiological conditions, and is present in the body in three main forms: free zinc, vesicular zinc, and protein-bound zinc
- Zinc in the brain
 - important for development – 10 times higher in brain than serum
 - decreases with age
 - Intracellular Zn regulated: 14 Zn-Fe transporter-like & 10 transporters+
 - Excess can increase plaque – increase synaptic zinc (with glutamate)
 - Deficit can increase plaque – replacement increases neurogenesis
 - Deficit increases immune aging, inflammation

Lithium deficiency and the onset of Alzheimer's disease - 2025

Preclinical (animal) Research

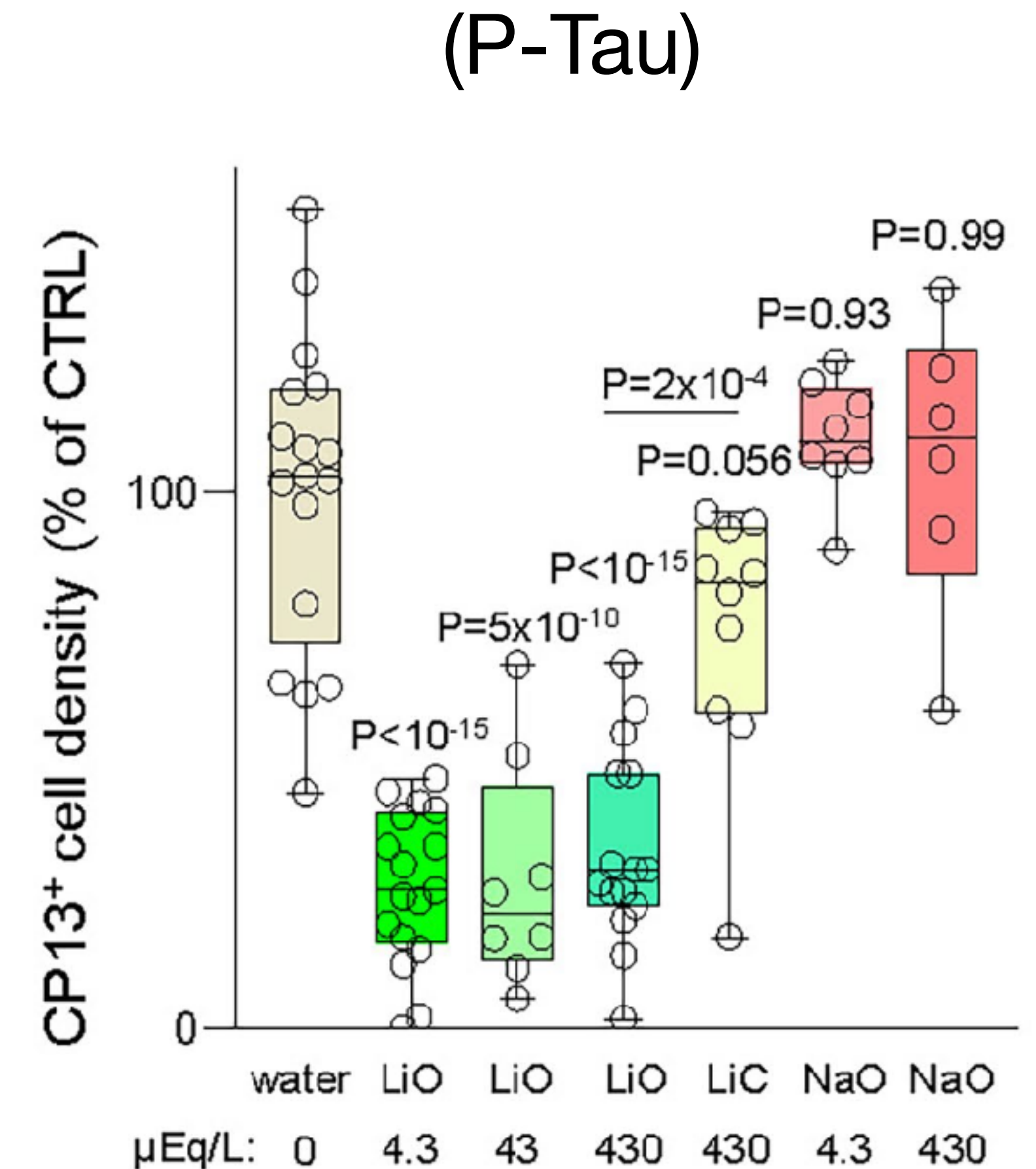
In mice Lithium orotate exhibits reduced conductivity and A β binding compared to lithium carbonate

Reducing endogenous cortical Li by approximately 50% markedly increased the deposition of amyloid- β and the accumulation of phospho-tau, and led to pro-inflammatory microglial activation, the loss of synapses, axons and myelin, and accelerated cognitive decline. Effects were mediated by kinase GSK3 β .



Lithium deficiency and the onset of Alzheimer's disease - 2025

- Single-nucleus RNA-seq showed that Li deficiency gives rise to transcriptome changes in multiple brain cell types that overlap with transcriptome changes in AD.
- Replacement therapy with lithium orotate reduces amyloid binding, prevents pathological changes and memory loss in AD mouse models and ageing wild-type mice.
- Disruption of Li homeostasis may be an early event in the pathogenesis of AD. Li replacement with amyloid-evading salts is a potential approach to the prevention and treatment of AD.
- This is preclinical (animal) research and not a recommendation for lithium use in patients.



FINGER Study - RCT

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

- Study to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population
-
- 2 years Between Sept 7, 2009, and Nov 24, 2011,
- Screened 2654 individuals - age 60 to 77
- 1260 were randomly assigned intervention (631) vs control (629)
- (93%) participants completed the 12 month assessments - (88%) at 24 months

Control:

- Study nurse gave all advice on healthy diet and physical, cognitive, and social activities beneficial for management of vascular risk factors and disability prevention.
- Blood tests at 6, 12, and 24 months, results mailed to all participants, with general information regarding clinical significance & advice to contact PCP if needed.

Ngandu T, et al. 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. *Lancet*. 2015 Jun 6;385(9984):2255-63. doi: 10.1016/S0140-6736(15)60461-5. Epub 2015 Mar 12. PMID: 25771249.

FINGER Study - RCT

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

- Intervention - Exercise, Diet, Cognitive training, vascular risk Monitoring
- Nutritionists - 3 individual & 7-9 group sessions).
 - 10–20% of daily energy from **proteins**,
 - 25–35% daily energy from fat
 - <10% SFA & Trans fats, 10–20% MUFA, and 5–10% from PUFA (including 2.5–3 g/day of omega-3 fatty acids)
 - 45–55% CHO (<10% from **refined sugar**)
 - 25–35 g/day **dietary fiber**
 - < 5 g/day of **salt**
 - <5% daily energy from **alcohol**
 - Energy intake facilitating **5–10% reduction** in bodyweight per BMI, health status, age, and diet of the participant.

Ngandu T, et al. 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. Lancet. 2015 Jun 6;385(9984):2255-63. doi: 10.1016/S0140-6736(15)60461-5. Epub 2015 Mar 12. PMID: 25771249.

FINGER Study - RCT

- Intervention (Cont)
- Dietary goals were achieved by recommendation of high consumption of **fruit and vegetables**, consumption of **wholegrain cereal products** and **low-fat milk and meat products**, limiting of **sucrose** intake to less than 50 g/day, use of vegetable margarine and rapeseed oil instead of butter, and **fish** consumption at least two portions per week.

NTB = Neuropsychological Test Battery

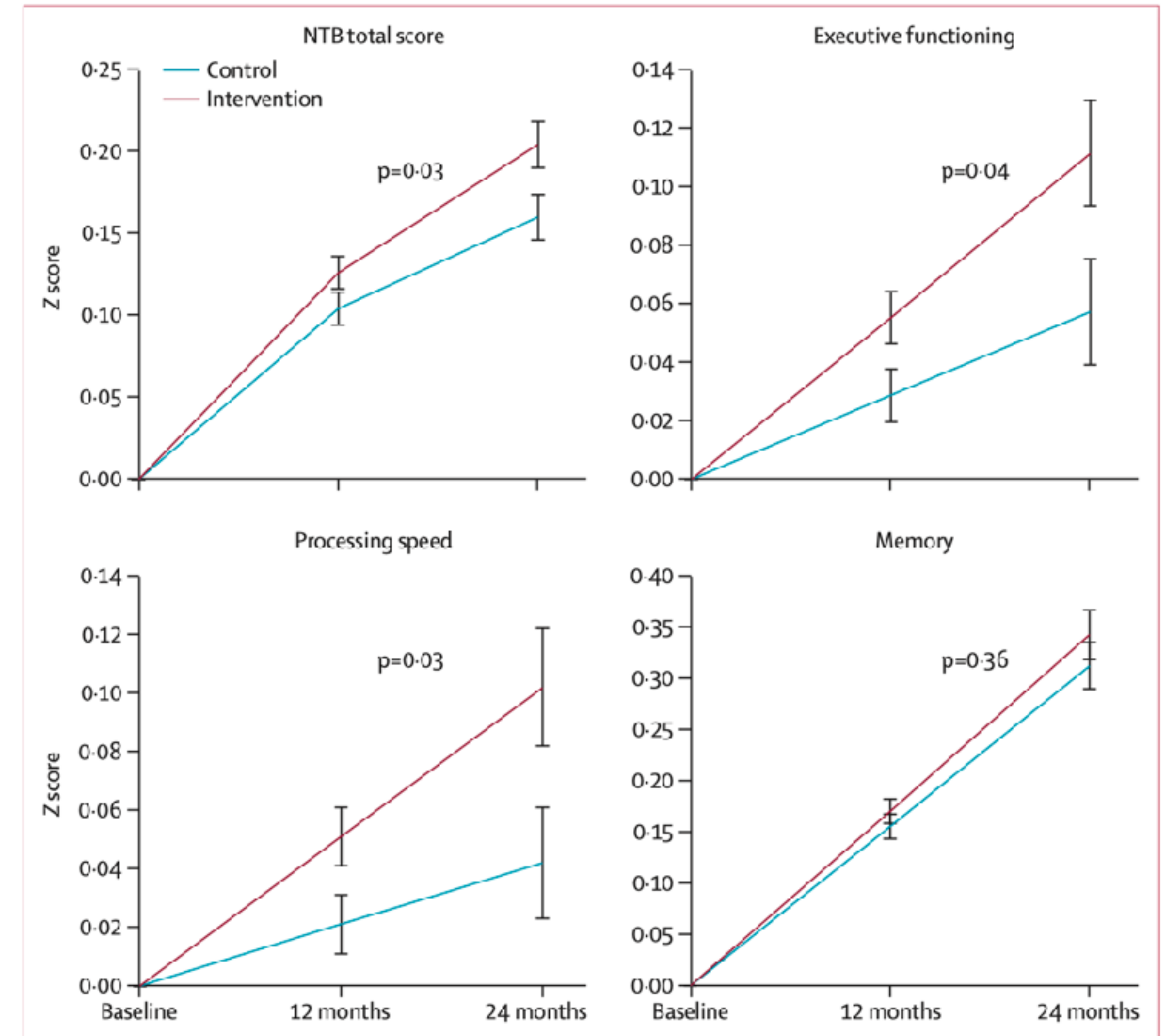


Figure 2: Change in cognitive performance during the 2 year intervention

Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

Alz Dz– Metabolic Profiling - 2015

- Subtypes postulated:
 - Inflammatory: markers such as hs-CRP and globulin:albumin ratio are increased.
 - Non-inflammatory: inflammatory markers are not increased, but other metabolic abnormalities are present.
 - Cortical: affects relatively young individuals, early non-amnestic features such as dyscalculia and aphasia, typically affects ApoE4-negative individuals, Zinc Deficiency related
- **Mono-therapeutic, monophasic approach likely to be suboptimal.**
Personalized, multiphasic programs based on individual's genetics and biochemistry

Patient	ApoE	Sx	Dx	Evaluation	F/u	Comment
80) 80F	3/3	Amnestic, exec	AD		MoCA 18→24	Memory much improved
81) 61F	3/3	Exec	AD	FDG-PET: temp hypometab	NCI 33→79%ile; exec 1→77%ile; cog flex 1→77%ile	Marked subjective improvement
82) 54F	3/3	Amnestic, exec	AD	FDG-PET+	MoCA 19→21	Reading, navigating again; earlier f/u reported [4]
83) 78F	3/4	Amnestic, exec, praxis	AD	MRI: HC vol <1%ile	MoCA 0→3	Striking change: speaking, dressing, dancing, biking, emailing, kayaking all returned
84) 74M	3/4	Amnestic	AD	FDG-PET+	CVLT-IIB 3→84%ile	Improvement sustained at 4.5 yr; f/u to initial report [4]
85) 69F	3/4	Exec	AD	MRI: cerebral atrophy	MoCA 18→27	Driver's license returned; follows recipes again; nurse asked, "What happened?!"
86) 68M	3/4	Amnestic	MCI	Am-PET+; FDG-PET+	HC vol 17→75%ile	Sustained improvement 4 yr; f/u to initial report [4]
87) 56M	3/3	Amnestic, exec, calc	MCI	FDG-PET+		Improved math, memory, able to play poker at high level again
88) 54F	4/4	Amnestic	MCI		NP: cog assessment 35→98%ile	Sustained improvement 6 yr; f/u to [4]
89) 57F	4/4	Amnestic	MCI	NP	NCI 16→73%ile	Sustained improvement 2y; f/u to [4]
90) 76M	4/4	Amnestic	AD	FDG-PET+	MMSE 23→30	Declined when DC'd protocol, improved back on; f/u to [4]

*Uncontrolled case series; cannot prove effectiveness

Bredesen DE, Sharlin K, Jenkins D, Okuno M, Youngberg W, et al. (2018) Reversal of Cognitive Decline: 100 Patients. J Alzheimers Dis Parkinsonism 8: 450. DOI: [10.4172/2161-0460.1000450](https://doi.org/10.4172/2161-0460.1000450)

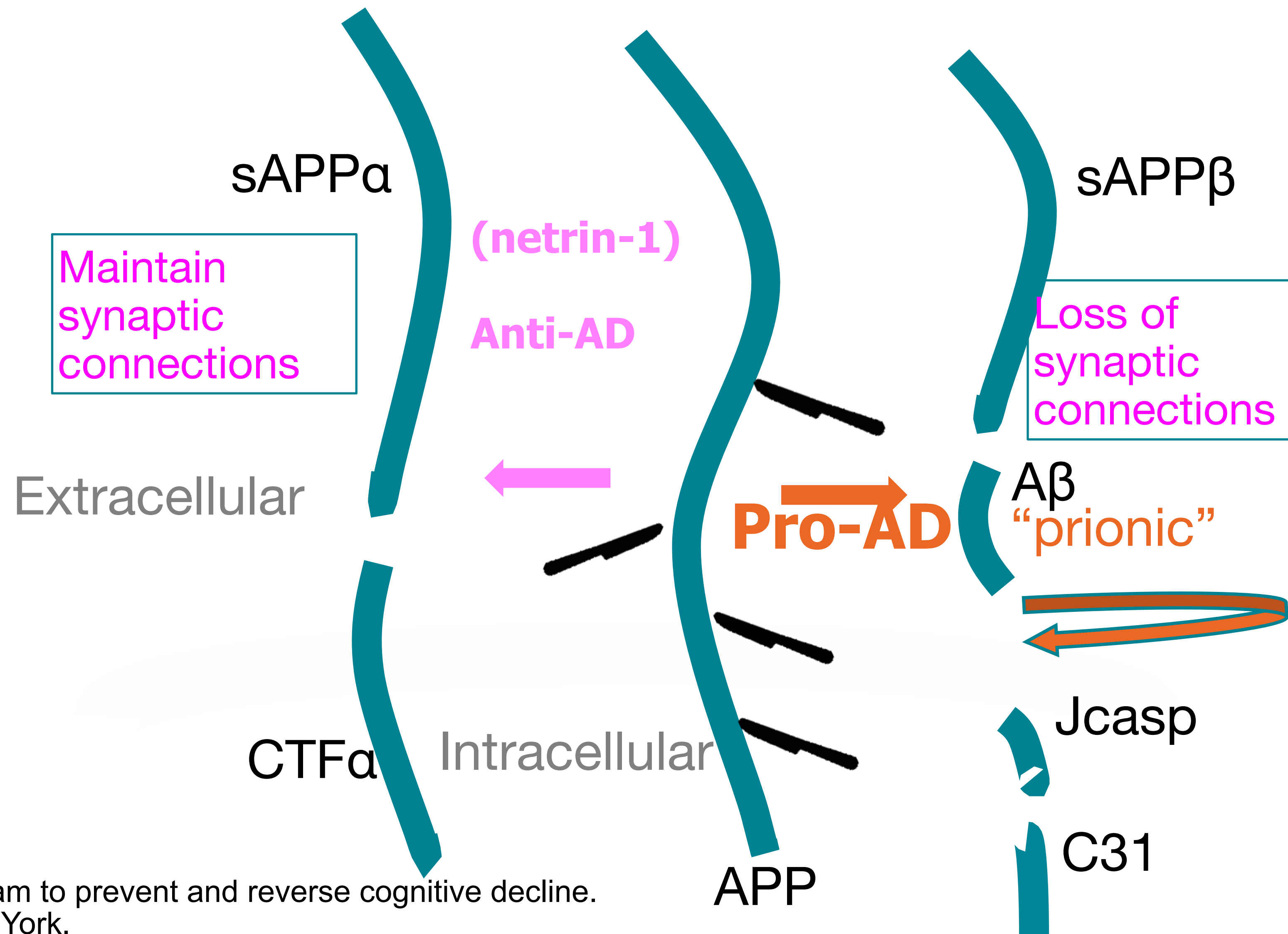
Patient	ApoE	Sx	Dx	Evaluation	F/u	Comment
91) 56F	4/4	Amnestic, exec, word finding	MCI		Composite memory 32→61%ile	F/u to [4]
92) 48F	3/4	Amnestic	MCI		MoCA 23→30	Marked symptomatic improvement
93) 72M	ND	Amnestic, behavioral	AD			Improved memory, writing, reduced anxiety
94) 73F	3/4	Exec	MCI		MoCA 23→27	
95) 70M	3/4	Amnestic, VS	MCI	Am-PET+	NP 30→50%ile	Improved memory, navigation
96) 67F	4/4	Amnestic, exec, calc, behavioral	AD		SAGE 0	Return of addition, subtraction, multiplication, division; holding conversations again
97) 63M	3/4	Amnestic, exec, calc	AD	MRI: gray matter atrophy	MoCA 17→29	Able to return to work
98) 74F	4/4	Amnestic, exec	AD	MRI: HC vol 18%ile, cortical atrophy	MoCA 14→21	
99) 79M	3/3	Amnestic	AD	MRI	MoCA 11→15; MSQ 47→34	
100) 78M	4/4	Amnestic	AD	MRI	MoCA 20→23; MSQ 40→10	

Bredesen DE, Sharlin K, Jenkins D, Okuno M, Youngberg W, et al. (2018) Reversal of Cognitive Decline: 100 Patients. J Alzheimers Dis Parkinsonism 8: 450. DOI: [10.4172/2161-0460.1000450](https://doi.org/10.4172/2161-0460.1000450)

Amyloid Precursor Protein - APP

APP
695 amino acids
Made by neurons
Cut by proteases
“Dependence receptor”

Amyloid β -
Accumulates
Near synapses
Reduces
connections
40-42 AA



Bredesen DE (2017) The end of Alzheimer's: The first program to prevent and reverse cognitive decline. (1stedn), Avery, an imprint of Penguin Random House, New York.

Plasticity Balance

APP-Master Dependency receptors

Estrogen

Testosterone

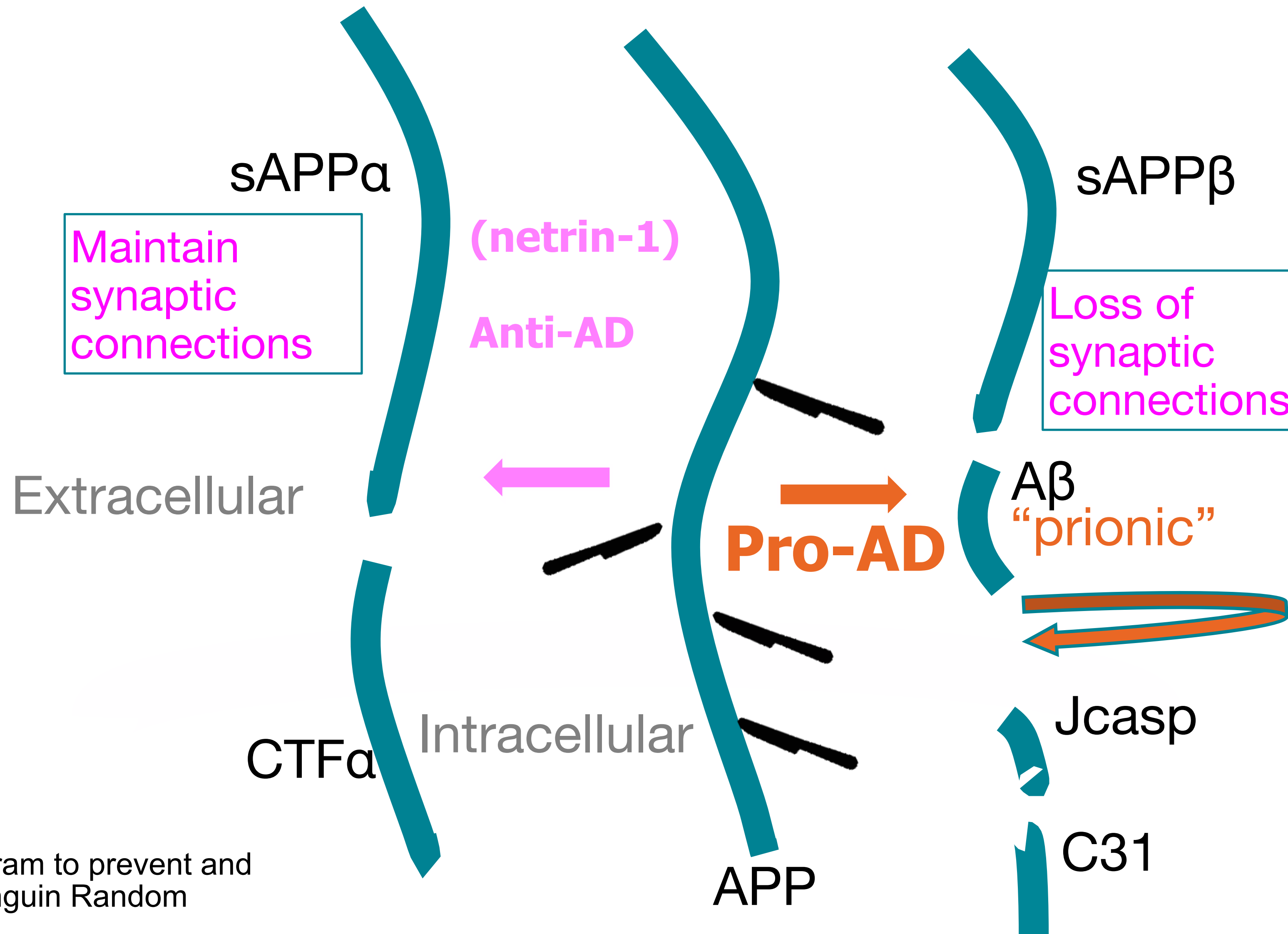
Thyroid

NF- κ B

Sirtuin SirT1 (resveratrol activated longevity molecule)

Vitamin D

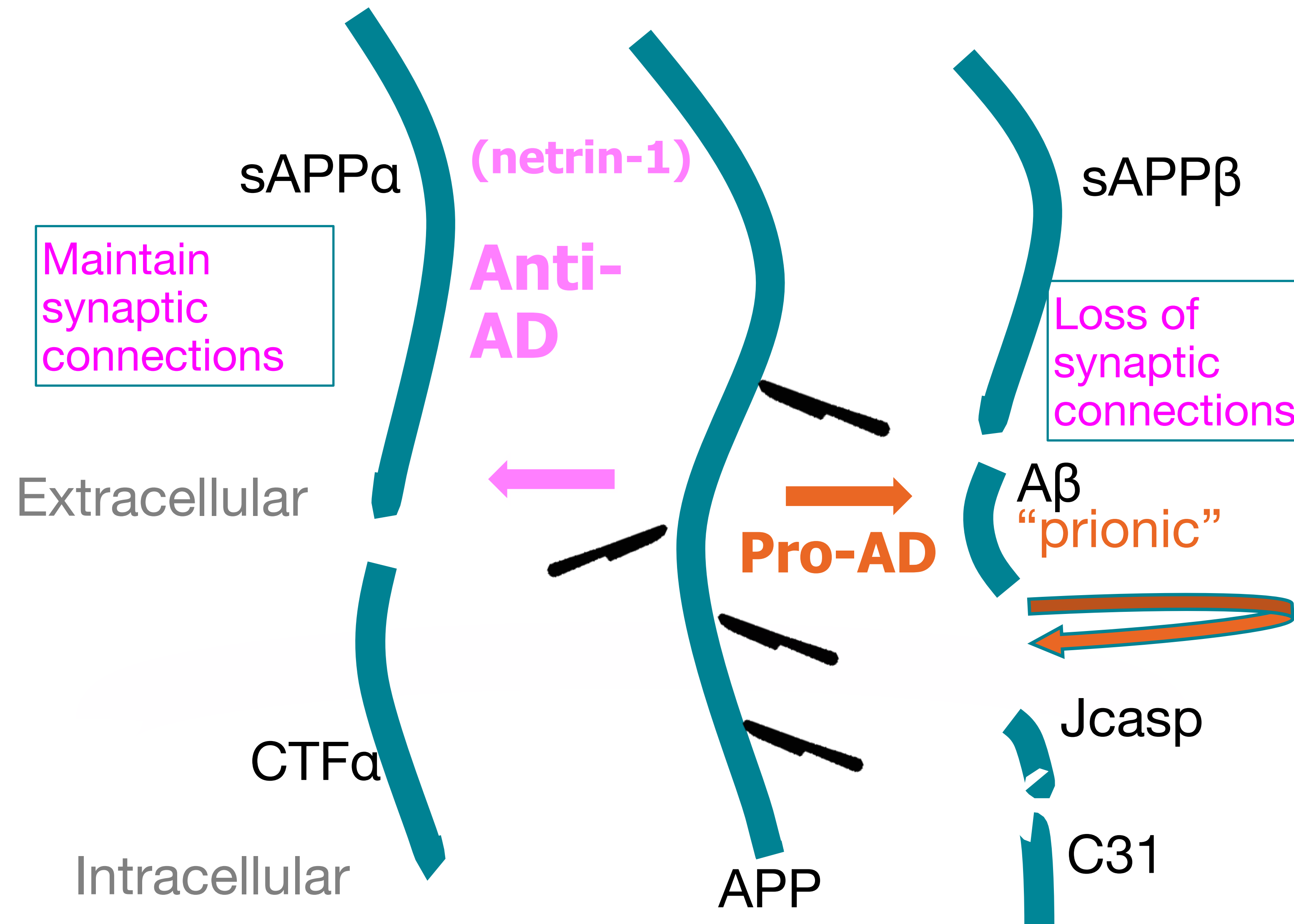
Each with its own dependency receptor



Bredesen DE (2017) The end of Alzheimer's: The first program to prevent and reverse cognitive decline. (1stedn), Avery, an imprint of Penguin Random House, New York.

Apo E4

Increases production of amyloid Beta
Decreases clearance
Binds to DNA in Nucleus – 1700 genes
inactivates SirT1 Sirtuin
Activates NF- κ B
Risk of Dementia - increase
Homozygous + 50%
Heterozygous + 30%



#36 “Holes in the Roof” Approach

- The following approaches are investigational and not a standard of care or guideline-recommended.

#36 “Holes in the Roof” Approach

- Genetics- Apo E4 & others
- Inflammation – CRP <0.9 mg/dl, IL-6 <3 pg/ml, TNFα <6.0 pg/ml, Ω6/Ω3 0.5-6, AG ratio ≥1.8
- Infections – HSV-1, Borrelia, fungi
- Homocysteine - < 6 mmol/L – B6 >110 nmol/L, Folate 10-25 ng/ml, B-12 >500 pg/ml, MMA
- Fasting Insulin – AGE Receptor – **Insulin supports neuron survival** Fasting insulin <4.5 microlU/ml; glucose ≤90 mg/dl; A1C <5.6 --
- Hormone Status – **Vit D** 50-80 ng/ml; **Thyroid** – TSH <2 microlU/ml, Free T3 3.2-4.2 pg/ml, Free T4 1.3-1.8 ng/dl, Free T3 x 100/Reverse T3 >20; **Estrogen** (α-secretase →single cleavage protective.) Estradiol 50-250 pg/ml, **Progesterone** 1-20 ng/ml, **Estradiol:progesterone** 10:100; **Testosterone** 500-1000 ng/dL, **free testosterone** 6.5-15 ng/dL; **Cortisol** AM 10-18 mcg/dL, **pregnenolone** 50-100 ng/dL, **DHEA-s** 350-430 mcg/dL women & 400-500 mcg/dL men.

#36 “Holes in the Roof” Approach

- Zinc/Copper: Copper:Zinc ratio 0.8-1.2, Red Cell zinc 12-14 mg/L, Copper – (3 x ceruloplasmin) ≤ 30
- Magnesium – RBC Mg -5.2-6.5 mg/dL
- Selenium (association) 110-150ng/ml; glutathione 5.0-5.5 micromolar
- Toxic exposures –
- Mercury Tri-Test (Brand Quicksilver)– (fish vs dental amalgams) < 50th %; <5mcg/L blood levels
- Lead <2 mcg/L
- Arsenic – chicken, water, rice < 7mcg/L
- Cadmium – yellow and red paints < 2.5 mcg/L

#36 “Holes in the Roof” Approach

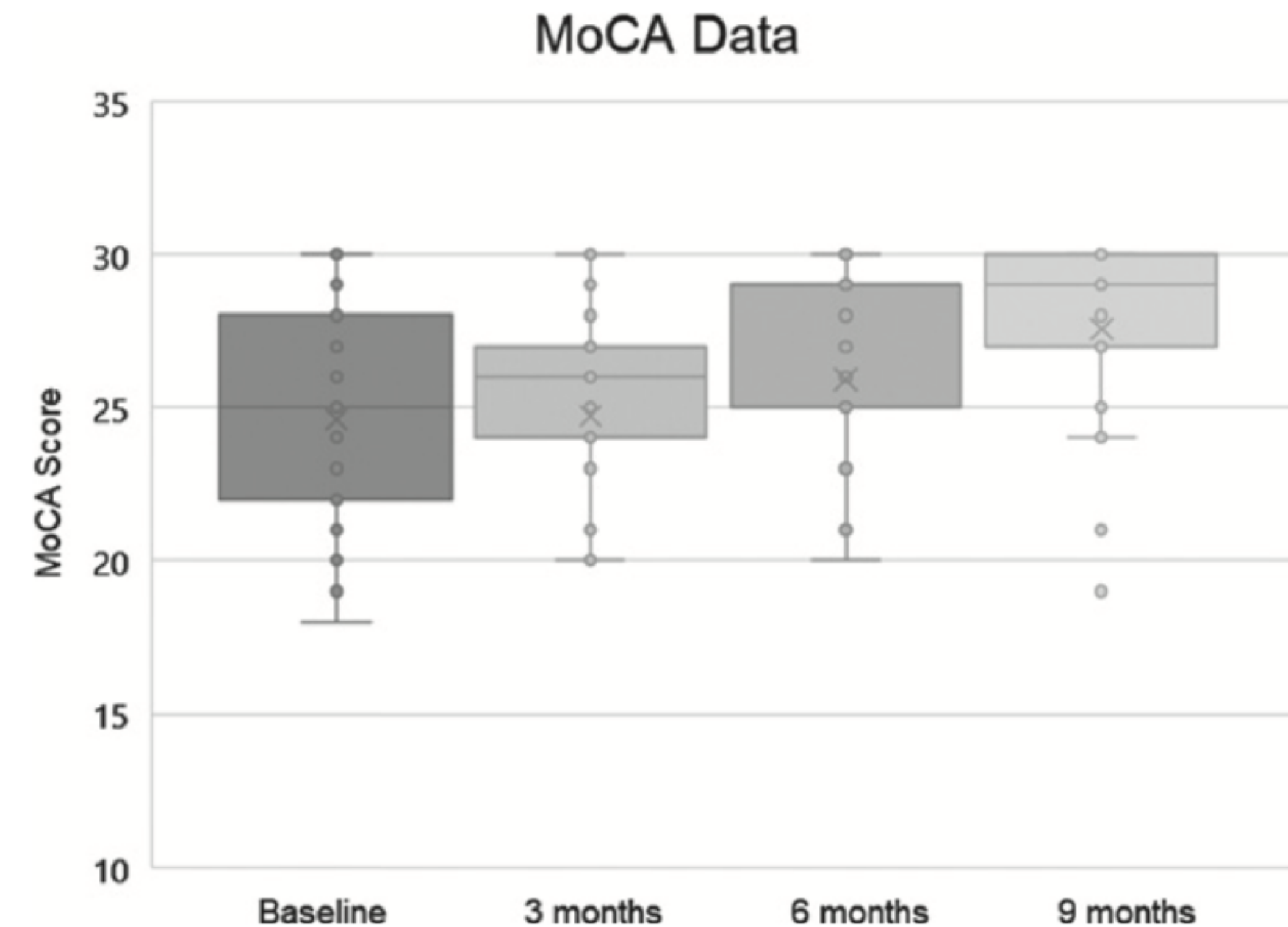
- Sleep – decreased amyloid associated – increased CA and Mg flux – glymphatic flushing – autophagy, incr “debris out” – Apnea- Hypopnea index < 5
- Lipids:LDL-p 700-1000; sdLDL<20 ng/dL, oxidized cholesterol ,60 U/l, TC >150 mg/dl
- Vit E – alpha tocopherol 12-20 mcg/ml
- Thiamine 20-30 nmol/l or RBC thiamine pyrophosphate 100-150 ng/ml
- GI permeability – IGG Cyrex Array #2 negative
- Gluten Sensitivity – tissue transglutaminase Ab negative, Cyrex Array 3 (gluten) or 4 (Rye, barley, sesame, oats, rice) negative

#36 “Holes in the Roof” Approach

- Blood brain barrier permeability –Porphyromonas gingivalis, Fusibacterium nucleatum, Prevotella intermedia, HSV, Treponema pallidum, Borrelia burdorferi, Babesia, bartonella - Cyrex #20 array negative
- Autoantibodies – Cyrex Array 5 negative
- Statins – simvastatin incr APP-C31
- Volumetrics – Generalized type 3, hippocampal – type 1&2
- Targeted Treatment

Precision Medicine Approach - 2022

- Clinical Pilot - 25 patients with dementia or mild Cognitive impairment (50-76 yrs)
- MoCA scores ≥ 19
- inflammation, chronic infection, dysbiosis, insulin resistance, protein glycation, vascular disease, nocturnal hypoxemia, hormone insufficiency or dysregulation, nutrient deficiency, toxin or toxicant exposure, and other biochemical parameters associated with cognitive decline.
- MRI volumetrics, Neuro vital signs
- Improved both APOE+ and APOE- individuals
- No reported untoward effects.



Precision Medicine for Alzheimer's: Pilot to RCT

PREPRINT —
NOT PEER-REVIEWED

A follow-up randomized controlled trial (EVANTHEA) tests the approach from Toups et al.'s 2022 pilot study

From Pilot to RCT

1

2022 — Pilot Study

Toups et al., 25 patients, uncontrolled. J Alzheimers Dis 88(4):1411–1421

2

2023 — Rationale for a Trial

Bredesen, Toups et al. make the case for controlled testing. J Alzheimers Dis 96:429–437

3

2026 — EVANTHEA RCT Results

NCT05894954 · Toups (PI), Bredesen (sr. advisor) · Multi-site, randomized

Also reported: improvements in blood pressure, weight, cholesterol, and HbA1c (metabolic markers).

RCT Key Findings

73



patients completed the multi-site RCT

>1 SD



improvement on CNS Vital Signs cognition score, treatment vs. control (statistically significant)

2:1



randomization — precision-medicine protocol vs. standard-of-care control

p=0.154



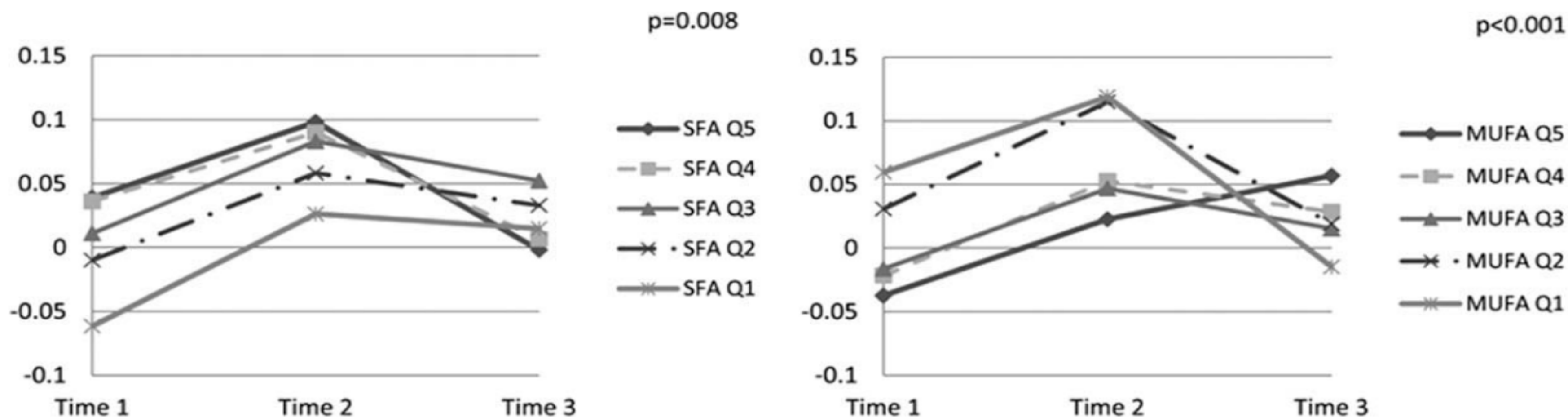
MoCA showed an improvement trend but did not reach statistical significance

Growing with the Evidence

- Complexity of the system
- Drugs are not working – only “slowing”
- Basic Science evidence – observational and RCT
- Epidemiologic Evidence
- Randomized controlled trials
- Actionable? — “False Hope” vs “False Hopelessness”
- Guidelines – Levels of Evidence
 - Medical Professional Recommendation
 - Patient’s Choice

Saturated Fat and Cognition - 2012

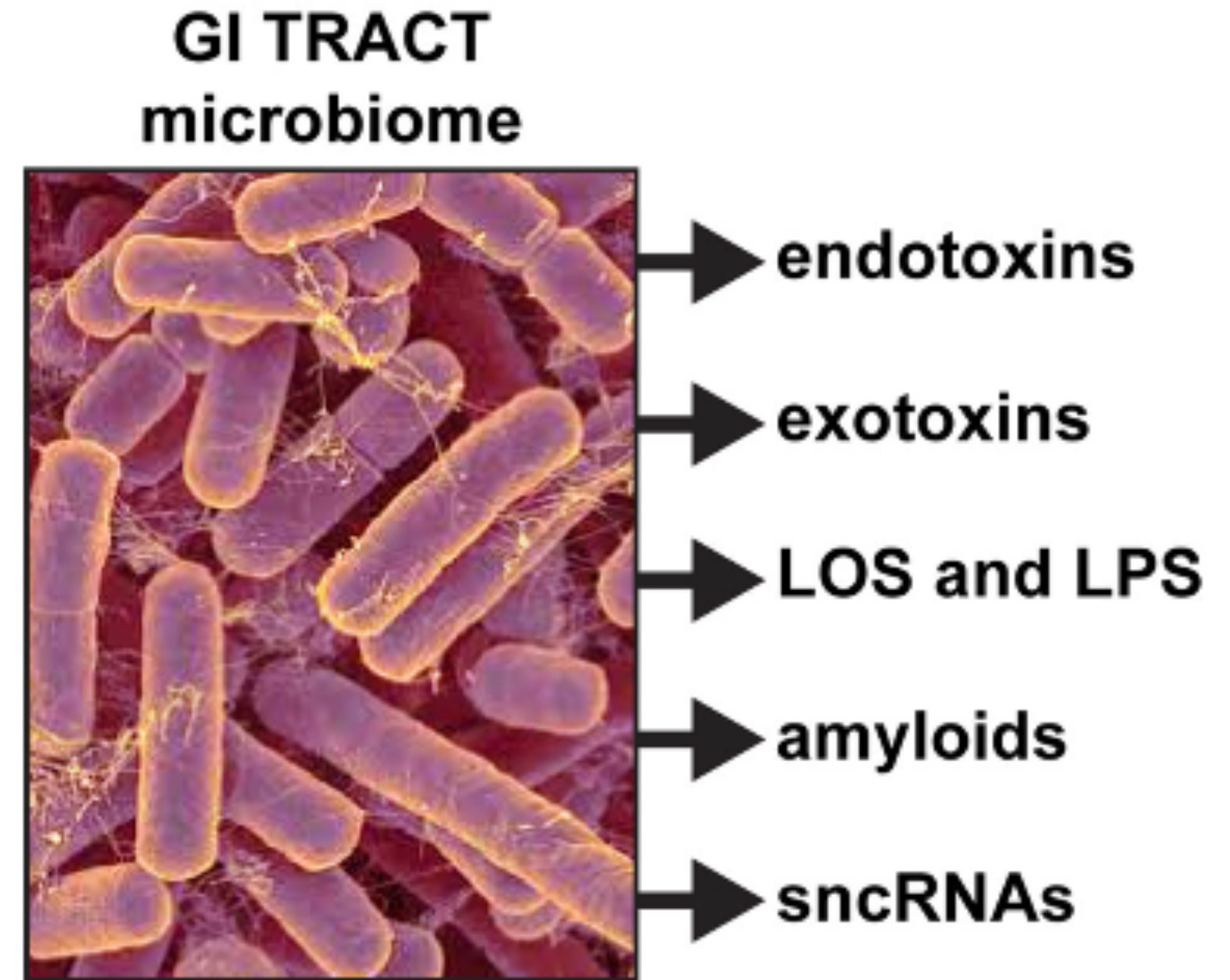
- Women's Health Study 6,183 older females (**association**)
- SFA, MUFA, PUFA, trans-PUFA
- Serial cognitive testing 4 years beginning 5 years after dietary assessment – **Global cognition** (general + verbal + semantic fluency) and verbal memory



Multivariate-adjusted least-squares mean global cognitive scores over 4 years are shown by quintiles of fat types (n=6,172).

Microbiome impact on Alzheimer's Dz - 2017

- Endotoxins – heat stable from outer membranes
- Exotoxins – soluble polypeptides produced inside – death-lysis release
- LOS & LPS – secreted by B fragilis & E Coli – pro-inflammatory to neurons
- Amyloids - Secretory
- Small non-coding RNA - exuded

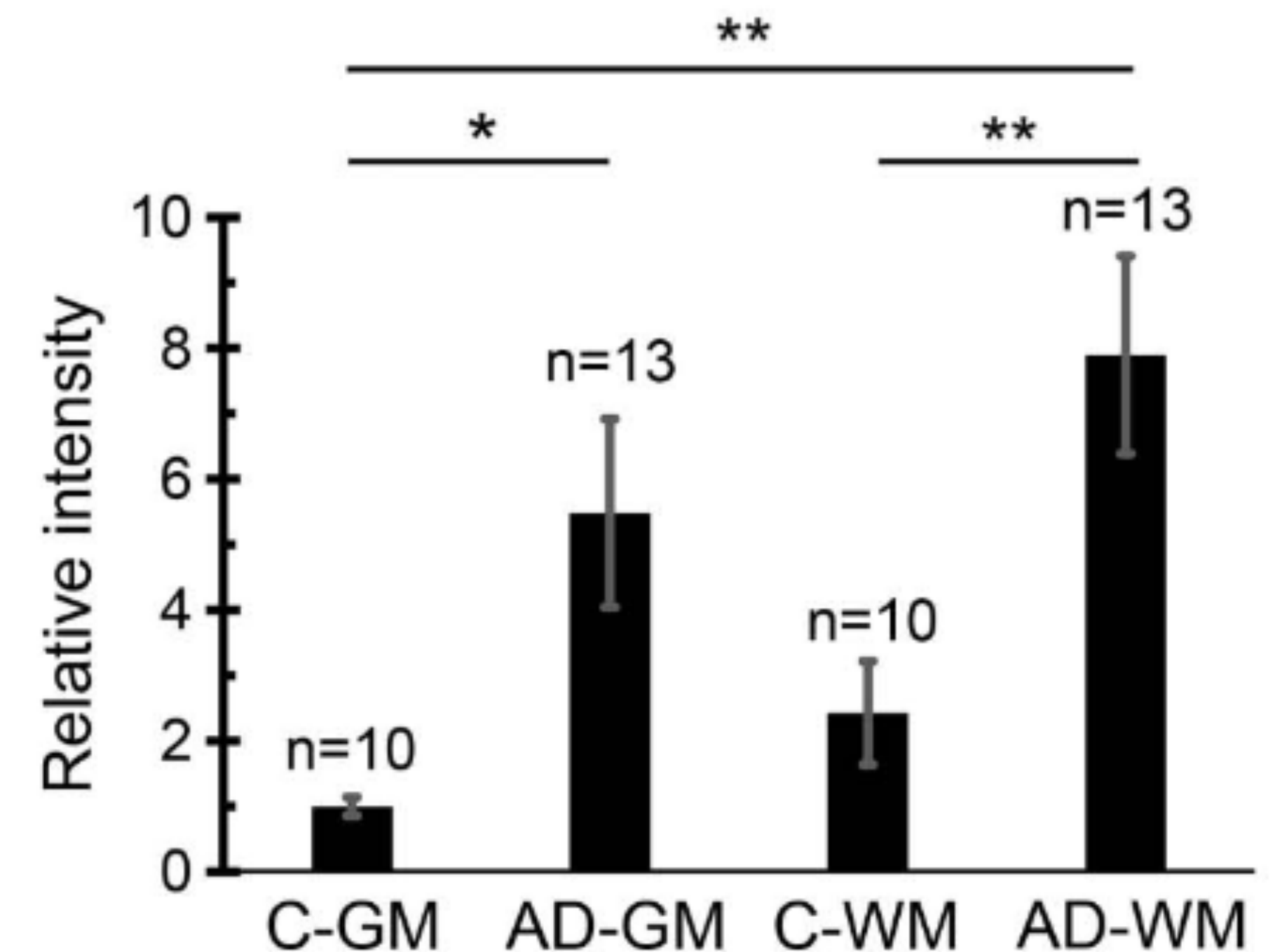


•*Zhao Y, Jaber V, Lukiw WJ. Secretory products of the human gi tract microbiome and their potential impact on alzheimer's disease (Ad): detection of lipopolysaccharide (Lps) in ad hippocampus. Front Cell Infect Microbiol. 2017;7:318.

Gram-negative bacterial molecules associated with Alzheimer pathology - 2016

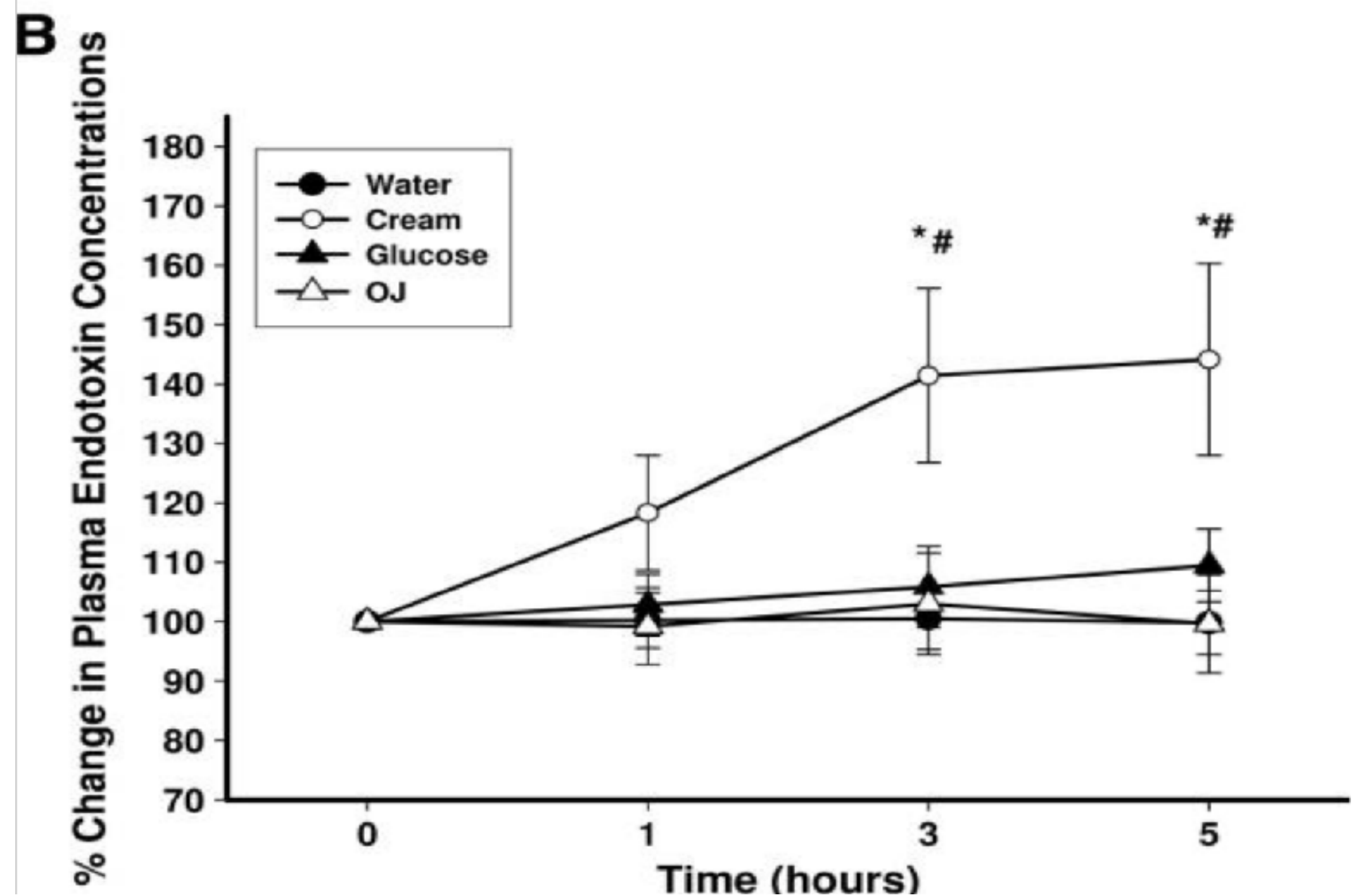
- We demonstrate Gram-negative bacterial LPS, E coli K99 pili protein, and DNA in control (N=18) and AD (N=24) brains. K99 and LPS levels were greater in AD compared to control brains.
- LPS co-localized with A β 1-40/42 in amyloid plaques and with A β 1-40/42 around blood vessels in AD brains. These data suggest that Gram-negative bacterial molecules are associated with AD pathology.

C. *E coli* K99 accumulation in aging brains



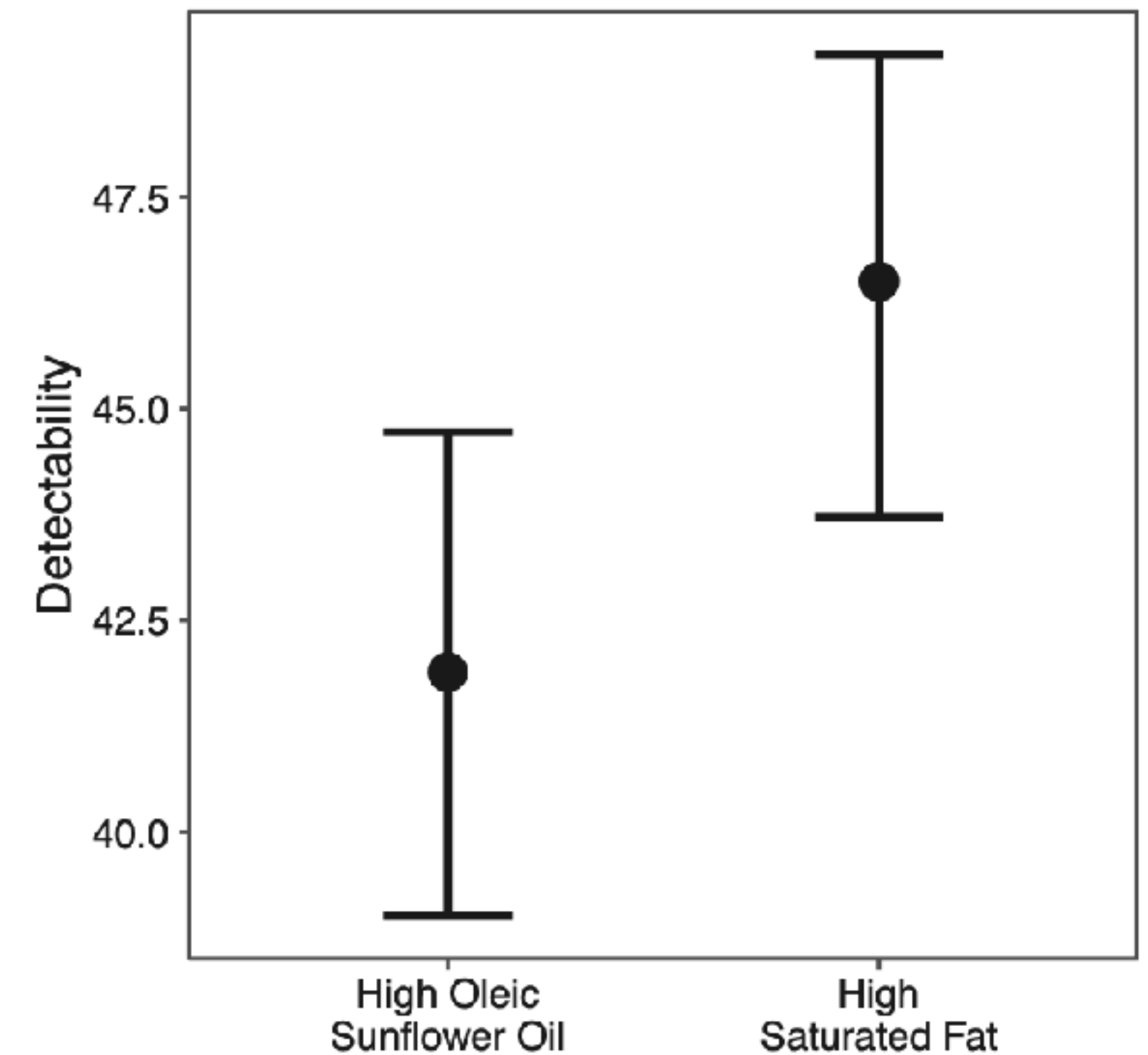
Toll-Like Receptor-4 & LPS Expression response to Saturated Fat Ingestion - 2010

Indexes of inflammation including nuclear factor- κ B (NF- κ B) binding, and the expression of SOCS3, tumor necrosis factor- α (TNF- α), and interleukin (IL)-1 β in MNCs, increased significantly after glucose and cream intake, but **TLR-4 expression** and **plasma LPS concentrations increased only after cream intake**. The intake of orange juice or water did not induce any change in any of the indexes measured.



RCT - High saturated-fat meal and endotoxemia on Post Meal attention - 2020

- Double Blind Randomized crossover trial (N=58)
- SFA (palmitic) vs high-oleic meal
- 930 kcal 60 g fat, 60 g CHO, 37g protein
- Single meal Endpoints:
 - Common Performance Test
 - endotoxemia



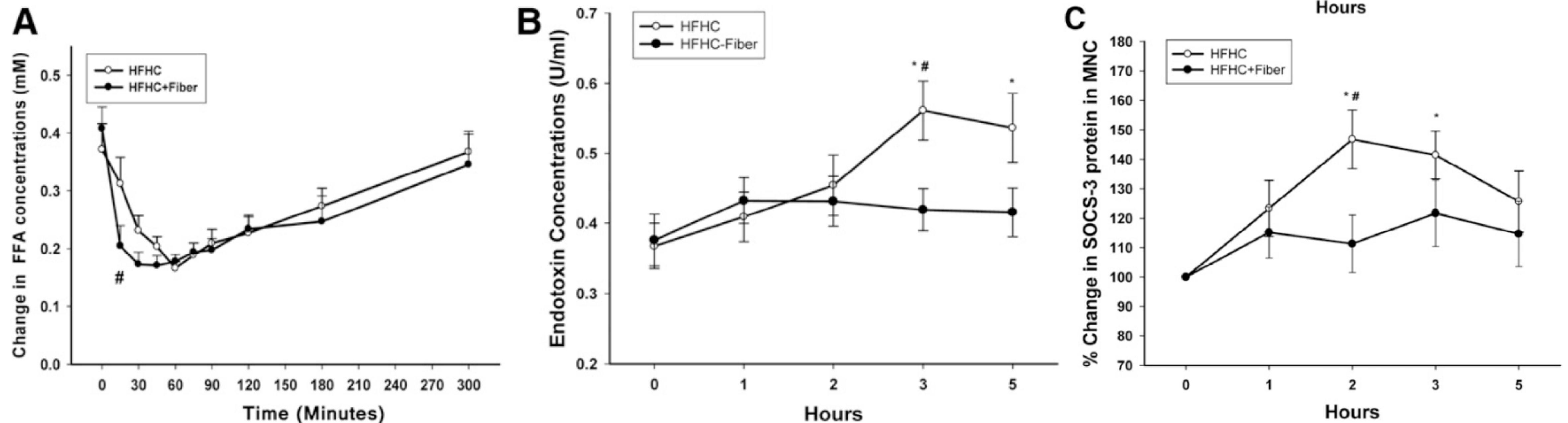
Higher scores (worse) in those on SFA meal especially in those with lower baseline endotoxemia measures (< 23th percentile, $p < 0.001$)

Fiber decreases post meal inflammation

- Single-center, prospective, open-label, randomized, crossover study
- High fat High Calorie meal with and without 30 grams of fiber – 5 hour measures
- HFHC w/o fiber - increases in lipopolysaccharide (LPS) concentrations, MNC ROS generation, interleukin (IL)-1b, tumor necrosis factor a (TNF-a), Toll-like receptor (TLR)-4, and CD14
- HFHC w fiber –no increase in LPS,
 - blunted the rise in ROS generation, IL-1b, TNF-a, TLR-4, and CD14.
 - increased Suppressor of cytokine signaling (SOCS)-3, protein tyrosine phosphatase 1B (PTP-1B) messenger RNA, and protein levels

Fiber decreases post meal inflammation

- Addition of fiber to an HFHC meal reduced the magnitude of increase of glucose, increased insulinogenesis, and reduced endotoxemia and oxidative and inflammatory stress. The increase in DPP IV concentrations was also reduced.



Case

- Pleasant 82 year-old female seen first – 2/21/2022
- Bethanechol, losartan, Omega 3, Vit C, Vit D3
- Lives with husband, 12/2021 Hip replaced – using a walker out of house
- Dementia – decreased cooking – sandwiches & soups – weight loss - BMI 20 kg/m²
- Neighbor/friend of 40+ years doing finances for her, shopping assistance
- HBG 10.2, FBS 99 mg/dl, high homocysteine, low magnesium, low zinc, menopausal s/p Hysterectomy (Estrogen total 70 pg/ml, n=40-244 for post menopausal with hx of hysterectomy)
- Taking “ReCode supplements” – added estradiol 0.5 mg per day
- *This is an illustrative case and does not establish causality or generalizability

Case

- follow up– 1/26/23
- 9 month lab follow up pending
- Taking: Vit b-12, Vit D, zinc, estradiol, magnesium
- Improved:
 - Weight up to 123 lb BMI-19.26
 - Improved kitchen skills
 - Thrift store experience

Dementia Prevention and Reversibility(?)

Basic Science and/or Animal studies	Observation/Association	Longitudinal Epidemiology	RCT
• Lithium Orotate 5-10 mg/dy • Metabolic Profiling • Zinc	• No smoking • Physical activity • Sleep 7-9 hours per night • Healthy Eating • Avoid inactivity • Metabolic Profiling • Zinc supplementation	• Healthy eating - Mediterranean, DASH, Plant based, healthy plant based • Physical exercise • Cognitive activity • Social contact • no Alcohol • no Smoking • High calories incr risk Fat>CHO • Avoid sugary drinks • Increase potassium	• Speed processing • Moderate-high intensity aerobic exercise • Resistance Exercise • Fruit and vegetable Whole grain low fat milk, limit glucose, low fat milk and meat, fish twice a week, Whole grain cereal, limit saturated fat, whey powder supplement • Range of motion and stretching exercise • Zinc supplement up to 40 mg • Magnesium Threonic acid - ClariMem twice a day \$34/month for 12 weeks • Vitamin E supplement - 2000 IU /dy

Practice Recommendations

- Complexity of Dementia is not solvable by medication
- Evidence that Dementia may be reversible to a degree - Research continues
- Nutrition Matters –
- Supplements may be helpful based on physiologic testing
- Resources available:
 - <https://www.apollohealthco.com/cognoscopy/>
 - Referenced articles
 - “normal” levels slides

