



A Time of Hope: Advances in Treatment and Modifiable Risk Factors

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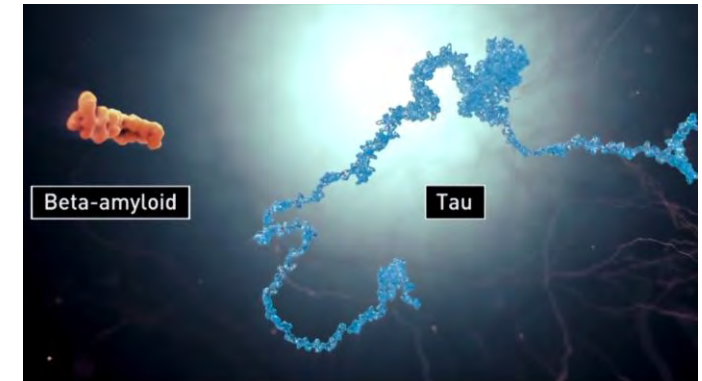
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Disease-modifying treatments: An exciting time!

- Leqembi (lecanemab-irmb) – FDA approved
 - Reduces Alzheimer’s disease-related pathology (brain amyloid burden) and slightly slows cognitive and functional decline (tested for 18 months).
 - Administered intravenously every two weeks.
 - Most effective in the early stages of the disease with mild cognitive symptoms.
- Donanemab – pending FDA review
 - Reduces brain amyloid burden, and slightly slows cognitive and functional.
 - Administered intravenously every month.
 - Most effective in the early stages of the disease with mild cognitive symptoms, and those with low/medium tau pathology.

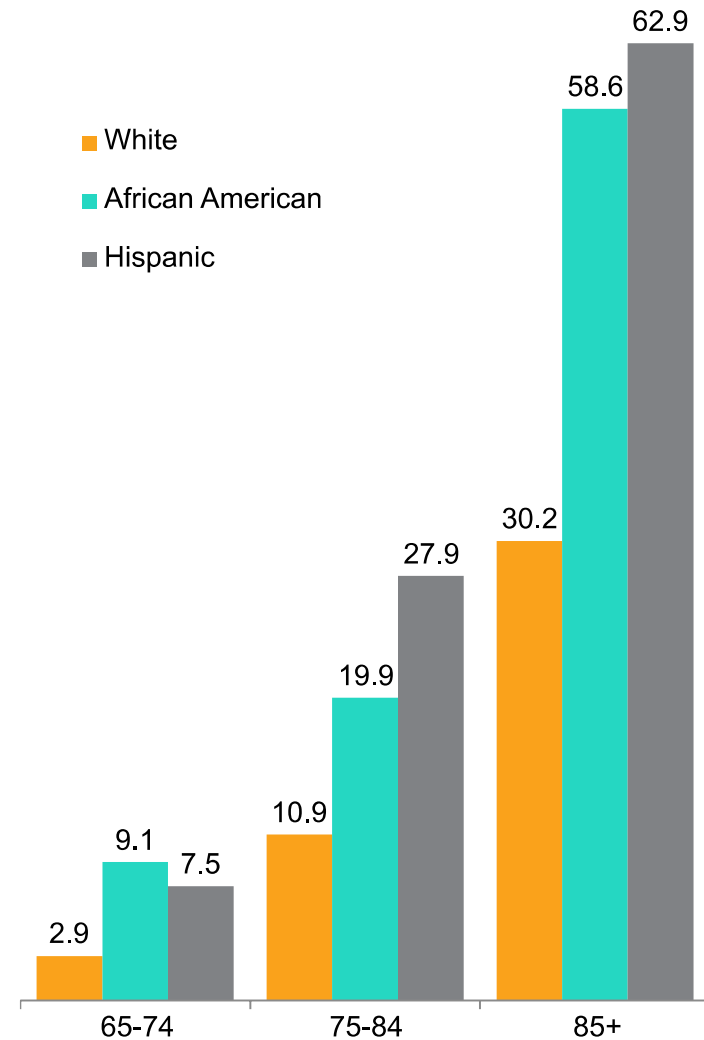


What can we do to avoid Alzheimer's disease?

Some risk factors cannot be modified

- Age
- APOE4 and other genetic risks
- Race/Ethnicity (e.g., Latinos, African-Americans)

Proportion of People Aged 65 and Older with Alzheimer's and Other Dementias
Washington Heights-Inwood Columbia Aging Project



Some risk factors cannot be modified

- Age
- APOE4 and other genetic risks
- Race/Ethnicity (e.g., Latinos, African-Americans)
- Sex

Original Investigation

ONLINE FIRST

April 3, 2023

Association of Age at Menopause and Hormone Therapy Use With Tau and β -Amyloid Positron Emission Tomography

Gillian T. Coughlan, MS, PhD¹; Tobey J. Betthausen, PhD^{2,3}; Rory Boyle, PhD¹; [et al](#)

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Female sex-associated risk

- Women exhibit greater neurofibrillary tangles than men in the context of high amyloid-beta.
 - They have similar cognitive performance up until clinical onset of AD, and then faster decline.
- Greater tau was associated with self-reported younger age at menopause and history of menopausal hormone therapy (in those with high amyloid-beta).
 - Those who initiated hormone therapy at least 5 years after age at menopause showed more tau than those who initiated near their age at menopause.
- Cognition was slightly worse in those with menopause at younger age and who initiated hormone therapy at least 5 years after age at menopause and.

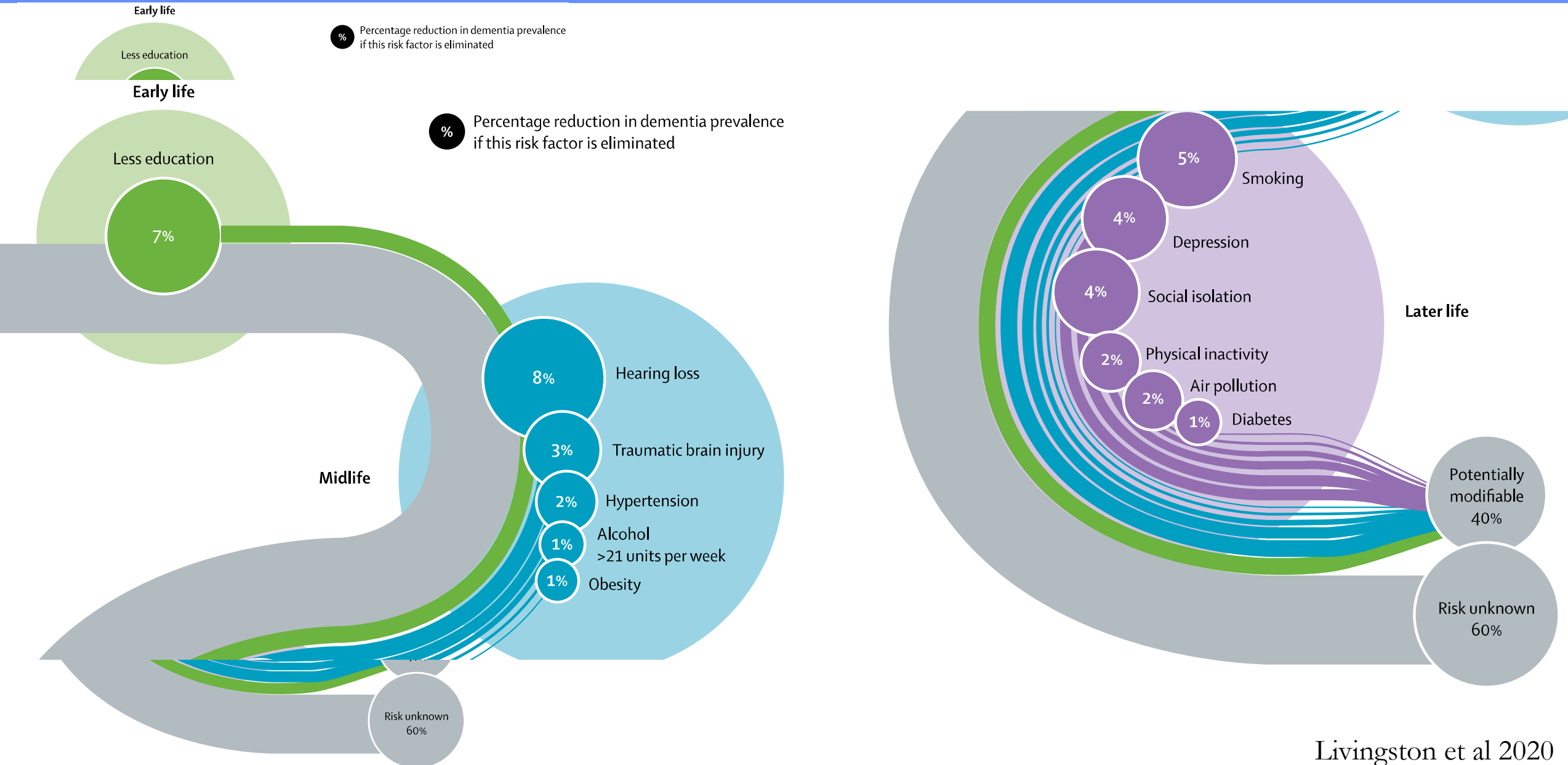
Female sex-associated risk

- Potential clinical guidelines
 - Hormone replacement may be safe when close to menopause onset.
 - Intervening late may significantly increase risk for dementia

We can't cure it (for now), but we can reduce the risk

- It has been estimated that modifying 12 risk factors could prevent, or at least delay, up to 40% of dementias.

We can't cure it (for now), but we can reduce the risk



We can't cure it (for now), but we can reduce the risk

- A 10-25% reduction in the following risk factors could potentially prevent as many as 1·1-3·0 million AD cases worldwide:
 - diabetes
 - midlife hypertension
 - midlife obesity
 - smoking
 - depression
 - cognitive inactivity or low educational attainment
 - physical inactivity

Risk factors

- Formal education
 - Relatively few further gains with education after the age of 20 years, around the time when the brain is highly developed.
- Traumatic brain injury (TBI)
 - Severe TBI has been associated with hyperphosphorylated tau pathology.
 - Risk increases with number of TBIs
- Cognitive engagement
 - Bilingualism

Risk factors

- Obesity
 - Weight loss is associated with better cognition but unknown long-term risks.
- Depression and psychological distress
 - The cause or the result of dementia?
 - Antidepressants do not seem to change the relationship.
- Social contact
 - Data suggests that dementia risk is greater in people who are lifelong single or widowed, compared with married people, even after adjusting for education, sex, etc).
 - Effects of pandemic?

Risk factors

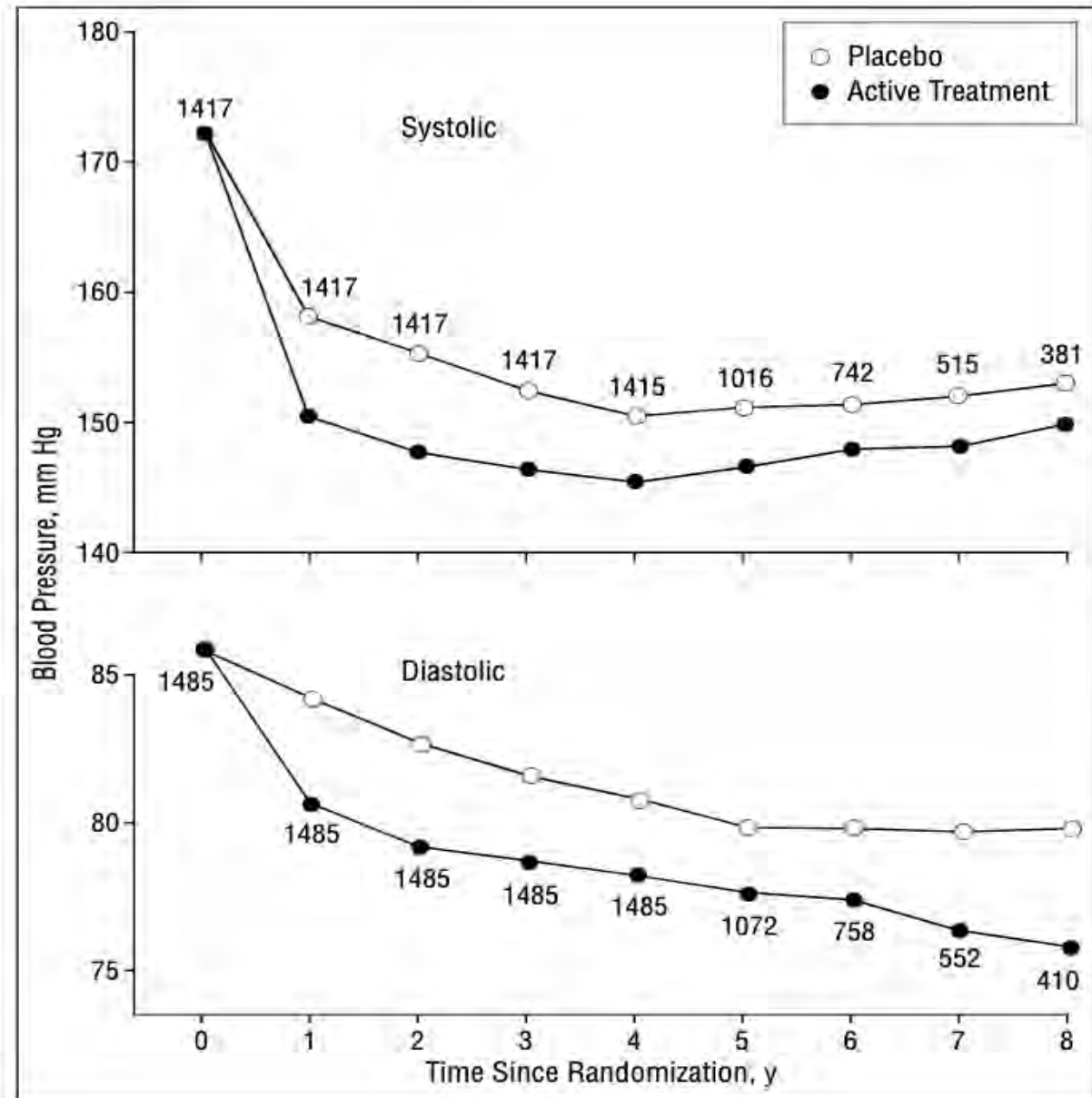
- Hypercholesterolemia
 - Has been associated with amyloid-beta (cholesterol is involved in clearance)
 - APOE4 carrier status is related to increased cholesterol levels.
 - Hypercholesterolemia in mid-life has been associated with an increased risk of AD, but not in late life.
- Diabetes
 - Increased risk in individuals with T2DM, including borderline T2DM (pre-diabetic)
 - Insulin is involved in amyloid-beta clearance from the brain, and higher levels of insulin could disrupt this metabolism.
- Hypertension
 - Persistent hypertension in *mid-life* is associated with greater risk for late-life dementia.
 - Even greater risk if it persists into older age.
 - Anti-hypertensive drugs (any) reduce risk based on randomized controlled trials (not statins – mixed evidence).

Risk factors

- After the double-blind, placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial ended in February 1997, randomized patients were offered active study medication for a further period of observation.

Risk factors

Antihypertensive drugs†
Nitrendipine only
Nitrendipine
Enalapril maleate
Hydrochlorothiazide



Risk factors

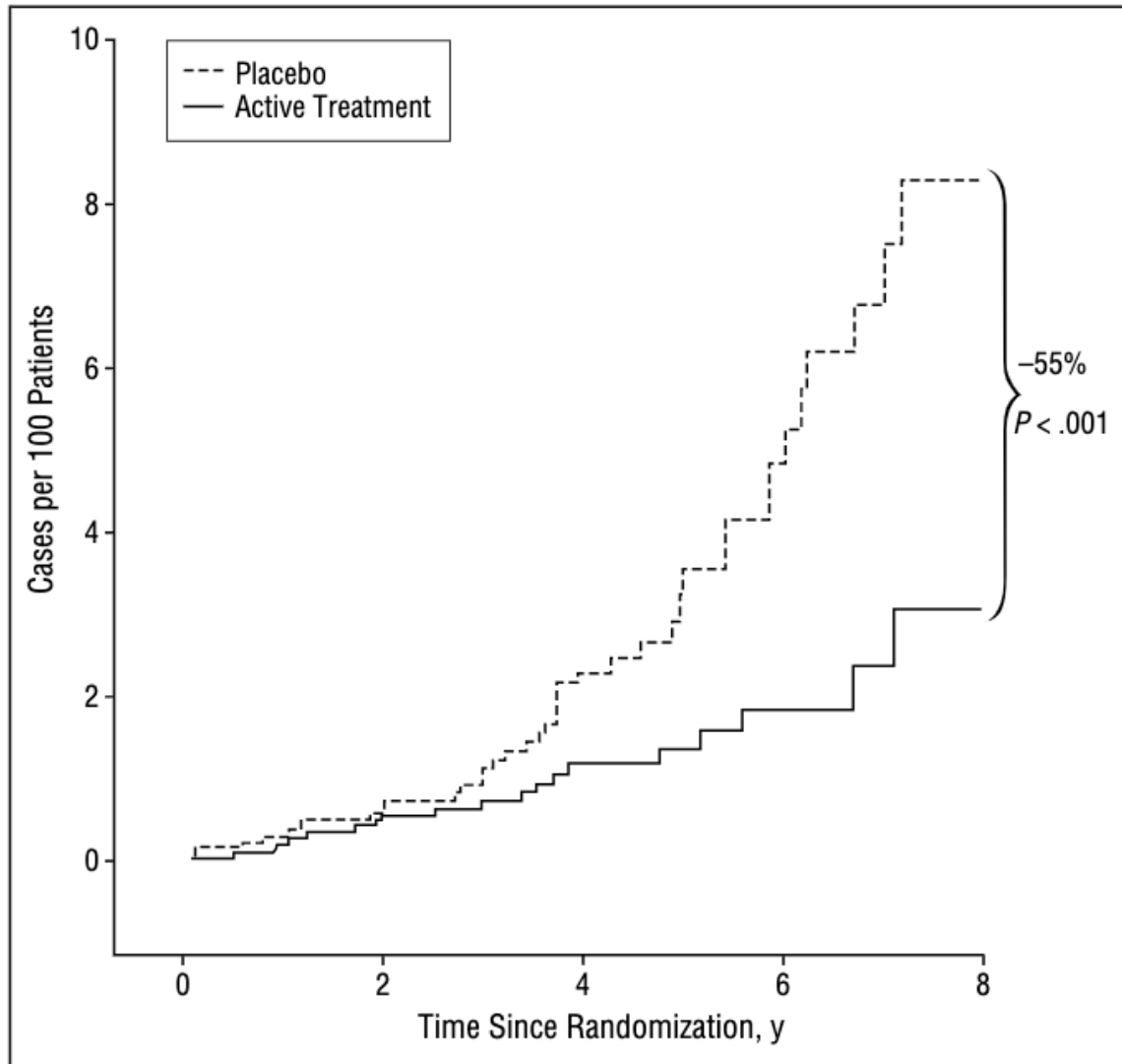


Figure 3. Culmulative rate of dementia by treatment group.

Table 2. Origin of Dementia

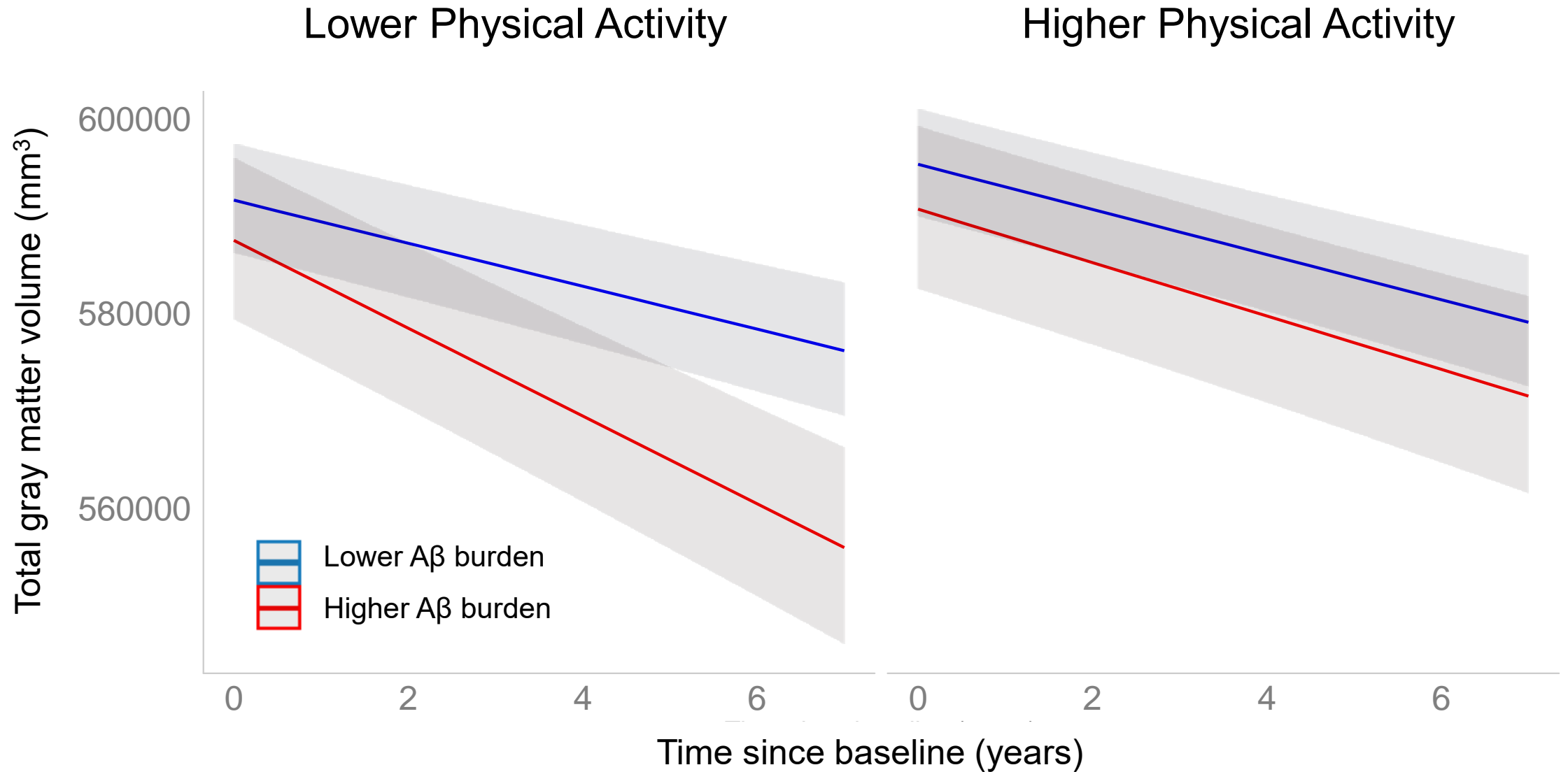
Variable	Control Group	Active Group	All Participants
No. of incident cases			
All causes	43	21	64
Alzheimer dementia	29	12	41
Mixed or vascular dementia*	12	7	19
Origin unknown	2	2	4
Rate, per 1000 patient-years			
All causes	7.4	3.3	5.2
Alzheimer dementia	5.0	1.9	3.4
Mixed or vascular dementia*	2.1	1.1	1.6
Origin unknown	0.3	0.3	0.3

*The cause of dementia was likely to be vascular in 4 control patients and 3 patients randomized to active treatment.

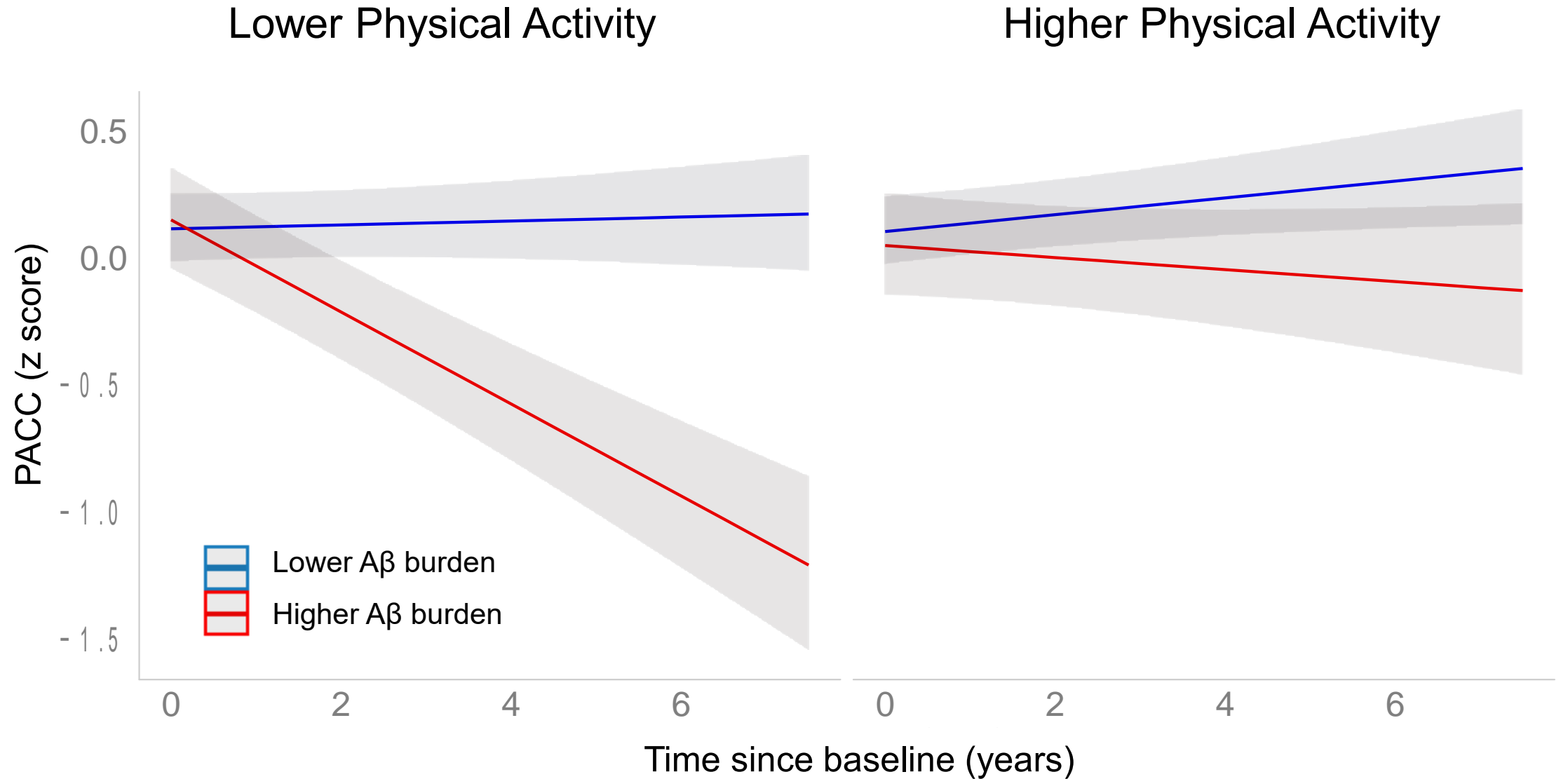
Physical activity/Exercise

- Physical Activity = any bodily movement
- Exercise = physical activity that is planned, structured, repetitive, and purposive.
- Aerobic/Cardiorespiratory Fitness = the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy.

Physical activity



Physical activity



Physical activity/Exercise

- Mostly endurance exercise.
 - Moderate-to-high intensity
- Largest impact when cognitively-healthy and possibly in those with mild cognitive impairment.
- Other benefits: physical performance (e.g., less falls) and functional independence

Potential mechanisms

- Cognitive and brain reserve
- Reduction of cardiovascular risk factors / preservation of vascular health
- Increases long-term potentiation and neurogenesis
- Reduction of Alzheimer's disease pathology
- Promotes production of anti-inflammatory factors
- Increases production of neurotrophic factors (e.g., Brain Derived Neurotrophic Factor)

Diet

WHAT'S ON THE **MIND DIET?**

 **AT LEAST THREE SERVINGS OF WHOLE GRAINS EACH DAY**

AT LEAST ONE DARK GREEN SALAD AND ONE OTHER VEGETABLE EACH DAY



BERRIES AT LEAST TWICE A WEEK

 **AT LEAST A ONE-OUNCE SERVING OF NUTS EACH DAY** 


BEANS OR LEGUMES AT LEAST EVERY OTHER DAY

POULTRY AT LEAST TWICE A WEEK




FISH AT LEAST ONCE A WEEK

If you don't drink alcohol, purple grape juice provides many of the same benefits.

A FIVE-OUNCE GLASS OF RED WINE EACH DAY



NO MORE THAN ONE TABLESPOON A DAY OF BUTTER OR MARGARINE; CHOOSE OLIVE OIL INSTEAD

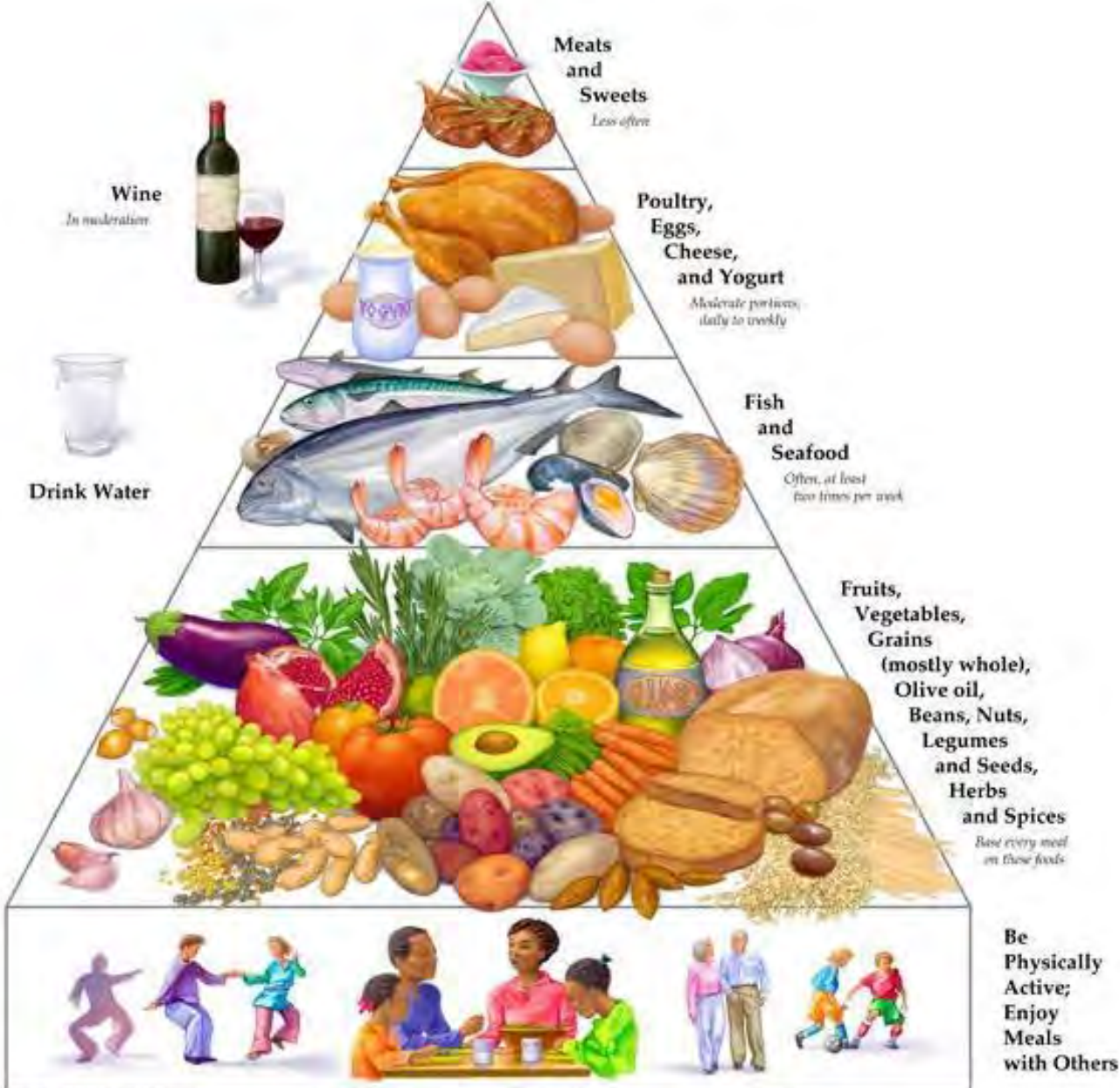


CHEESE, FRIED FOOD AND FAST FOOD NO MORE THAN ONCE A WEEK

PASTRIES AND SWEETS LESS THAN FIVE TIMES A WEEK



Diet



Diet

- A higher MIND diet score as shown by higher intake of foods on the MIND diet has been associated with better cognitive functioning and slower cognitive decline in a cohort of adults 65 and older, even when accounting for those with Alzheimer's disease and other brain diseases.
- Researchers following a cohort of Puerto Rican adults ages 45-75 found after 8 years that those with the highest MIND diet scores had better cognitive function than those with the lowest scores.
 - Greater poverty and less education were strongly associated with lower MIND diet scores and lower cognitive function.
- Some studies suggest that these diets are most effective in people with cardiovascular disease.

The impact of modifiable risk factors in people with genetic risk

- An unhealthy lifestyle and high genetic risk together are associated with higher dementia risk.
- A healthy lifestyle is associated with a lower dementia risk, including among cognitively-unimpaired people with high genetic risk.

Severe COVID-19 is associated with molecular signatures of aging in the human brain

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 Check for updates

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As coronavirus disease 2019 (COVID-19) and aging are both accompanied by cognitive decline, we hypothesized that COVID-19 might lead to molecular signatures similar to aging. We performed whole-transcriptome analysis of the frontal cortex, a critical area for cognitive function, in individuals with COVID-19, age-matched and sex-matched uninfected controls, and uninfected individuals with intensive care unit/ventilator treatment. Our findings indicate that COVID-19 is associated with molecular signatures of brain aging and emphasize the value of neurological follow-up in recovered individuals.

Differences in risk factors between countries

- Prevalence of dementia is increasing faster in low-to-middle income countries compared to higher income countries.
 - Greater life expectancy
 - Greater risk factor burden (also greater opportunity for change!)
- Cardiovascular risk factors may accelerate cognitive decline in Latinos more than for non-Hispanic whites.

What we do then?

- Maintain a healthy blood pressure, and adherence to antihypertensive treatment.
- Protect hearing and encourage use of hearing aids for hearing loss.
- Reduce exposure to air pollution.
- Avoid smoking.
- Prevent head injury.
- Limit alcohol use.
- Encourage obtaining formal education
- Encourage staying cognitively and socially active.
- Maintain a healthy weight.
- Engage physical activity
 - ~150-300 minutes of moderate exercise a week, or 75-150 of vigorous exercise
- Eat well (e.g., MIND diet)



THANK
YOU!

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