THE WINDOW OF OPPORTUNITY: BRAIN HEALTH AND EARLY ALZHEIMER'S DIAGNOSIS

Jonathan Graff-Radford, M.D.
Professor of Neurology

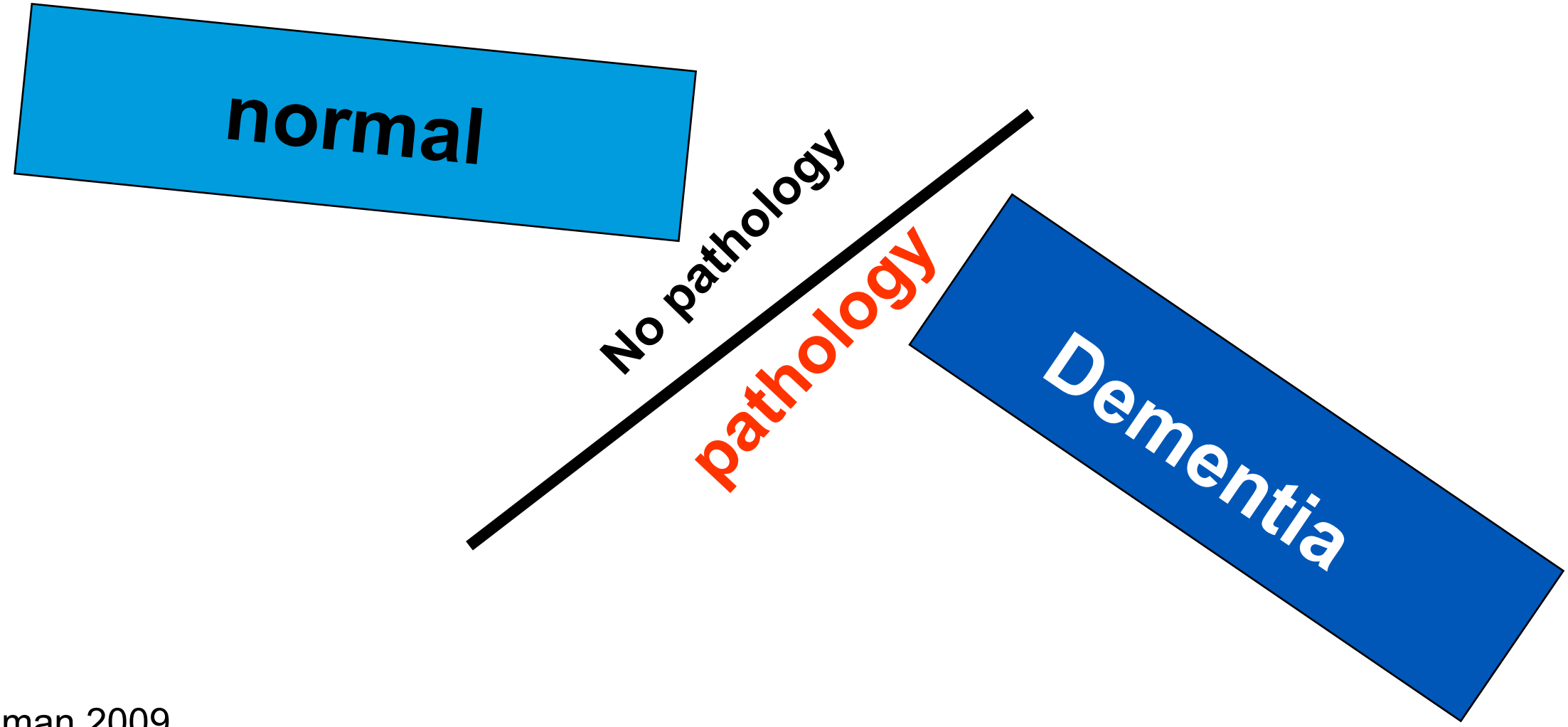
Mayo Clinic, Rochester, MN

OUTLINE

- What is the difference between Alzheimer’s disease and dementia?
- How common is Alzheimer’s disease?
- Risk factors/protective factors
- Treatments
- Early Diagnosis
- Future treatments

Relationship between normal state and dementia

The two state view of early 1980's



D Knopman,2009

ORIGINAL CONTRIBUTION

Mild Cognitive Impairment

Clinical Characterization and Outcome

Ronald C. Petersen, PhD, MD; Glenn E. Smith, PhD; Stephen C. Waring, DVM, PhD; Robert J. Ivnik, PhD; Eric G. Tangalos, MD; Emre Kokmen, MD

Background: Subjects with a mild cognitive impairment (MCI) have a memory impairment beyond that expected for age and education yet are not demented. These subjects are becoming the focus of many prediction studies and early intervention trials.

Objective: To characterize clinically subjects with MCI cross-sectionally and longitudinally.

Design: A prospective, longitudinal inception cohort.

Setting: General community clinic.

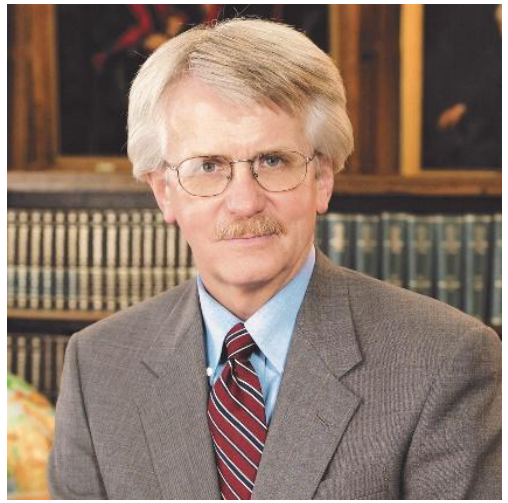
Participants: A sample of 76 consecutively evaluated subjects with MCI were compared with 234 healthy control subjects and 106 patients with mild Alzheimer disease (AD), all from a community setting as part of the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry, Rochester, Minn.

Main Outcome Measures: The 3 groups of individuals were compared on demographic factors and measures of cognitive function including the Mini-Mental State Examination, Wechsler Adult Intelligence Scale–Revised, Wechsler Memory Scale–Revised, Dementia Rating Scale, Free and Cued Selective Reminding Test, and Auditory Verbal Learning Test. Clinical classifications of dementia and AD were determined according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria, respectively.

Results: The primary distinction between control subjects and subjects with MCI was in the area of memory, while other cognitive functions were comparable. However, when the subjects with MCI were compared with the patients with very mild AD, memory performance was similar, but patients with AD were more impaired in other cognitive domains as well. Longitudinal performance demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD.

Conclusions: Patients who meet the criteria for MCI can be differentiated from healthy control subjects and those with very mild AD. They appear to constitute a clinical entity that can be characterized for treatment interventions.

Arch Neurol. 1999;56:303-308



- **Alzheimer's Disease Spectrum**

Normal

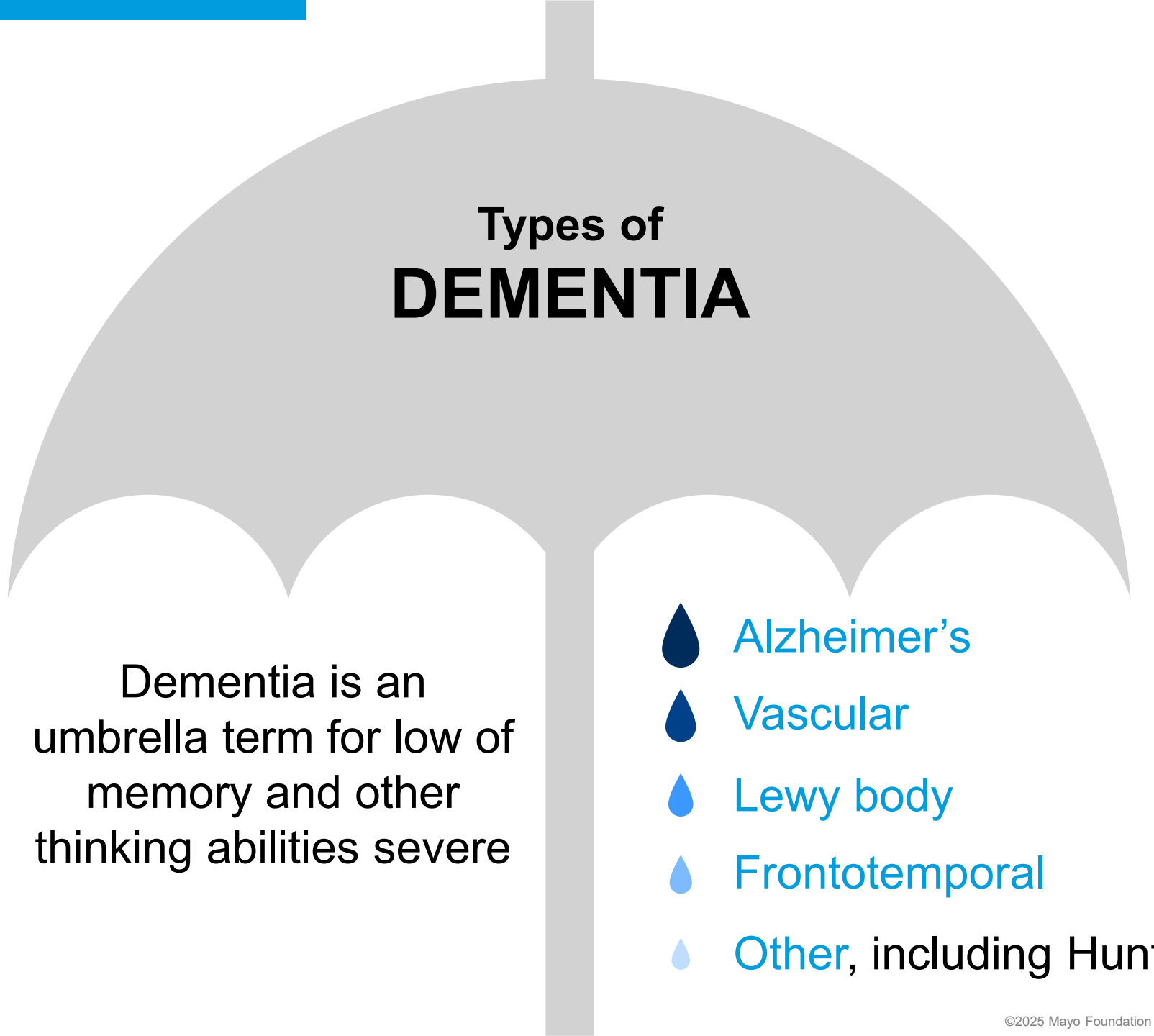
MCI Due to AD

Dementia Due to AD

ALZHEIMER'S DISEASE OR DEMENTIA?

- Dementia is an umbrella term for difficulties with memory, language, problem-solving
- Dementia has several causes
- Alzheimer's disease is most common cause of dementia
- Alzheimer's disease changes include the accumulation of the abnormal proteins and loss of nerve cells

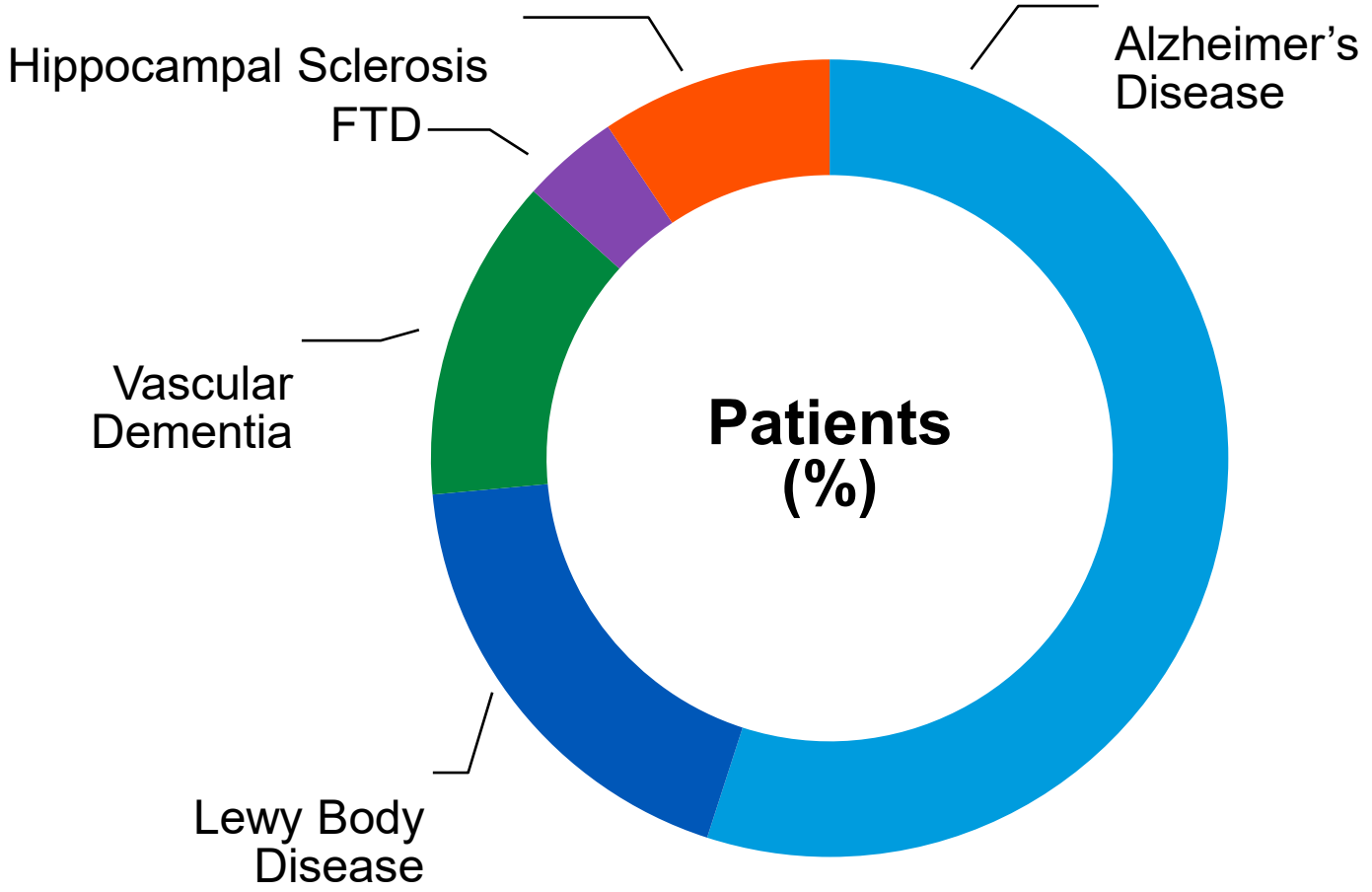
Types of
DEMENTIA



Dementia is an umbrella term for low of memory and other thinking abilities severe

- Alzheimer’s
- Vascular
- Lewy body
- Frontotemporal
- Other, including Huntington's

FREQUENCY OF DIFFERENT PATHOLOGIES IN STATE OF FLORIDA BRAIN BANK



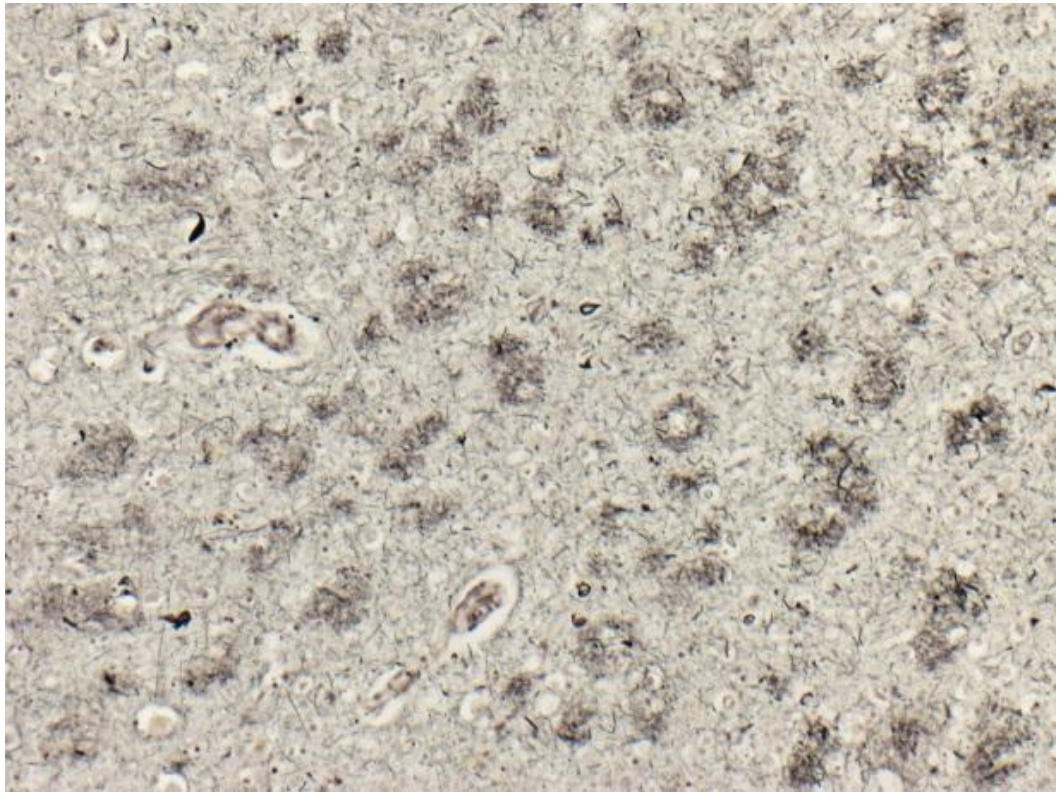
Based on data from Barker et al: Alzheimer disease and associated disorders 16, 203, 2002

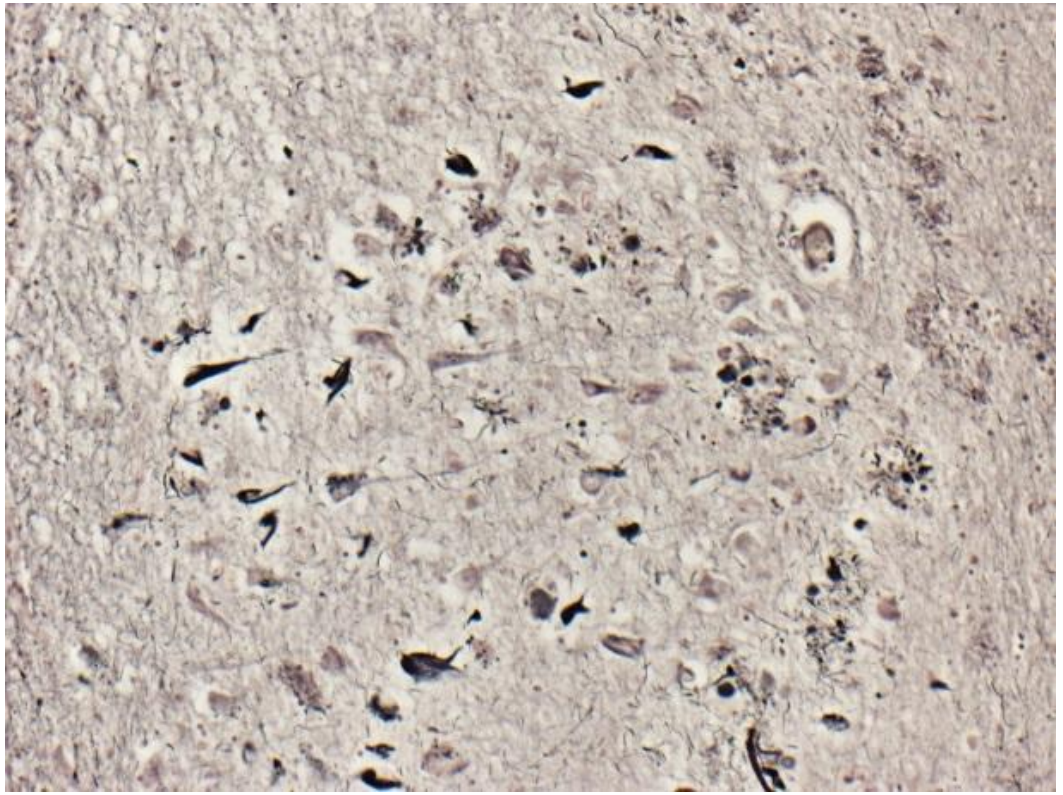
WHAT IS ALZHEIMER'S DISEASE?

- Alzheimer's is the most common cause of dementia (memory and thinking problems)
- It happens when abnormal proteins build up in the brain
- Amyloid – forms sticky plaques between brain cells
- Tau – forms tangles inside brain cells
- These protein buildups lead to damage and death of brain cells over time. The result is problems with memory, thinking, and daily functioning
- Bottom Line:✓ Alzheimer's disease starts with silent changes in the brain, often years before symptoms appear

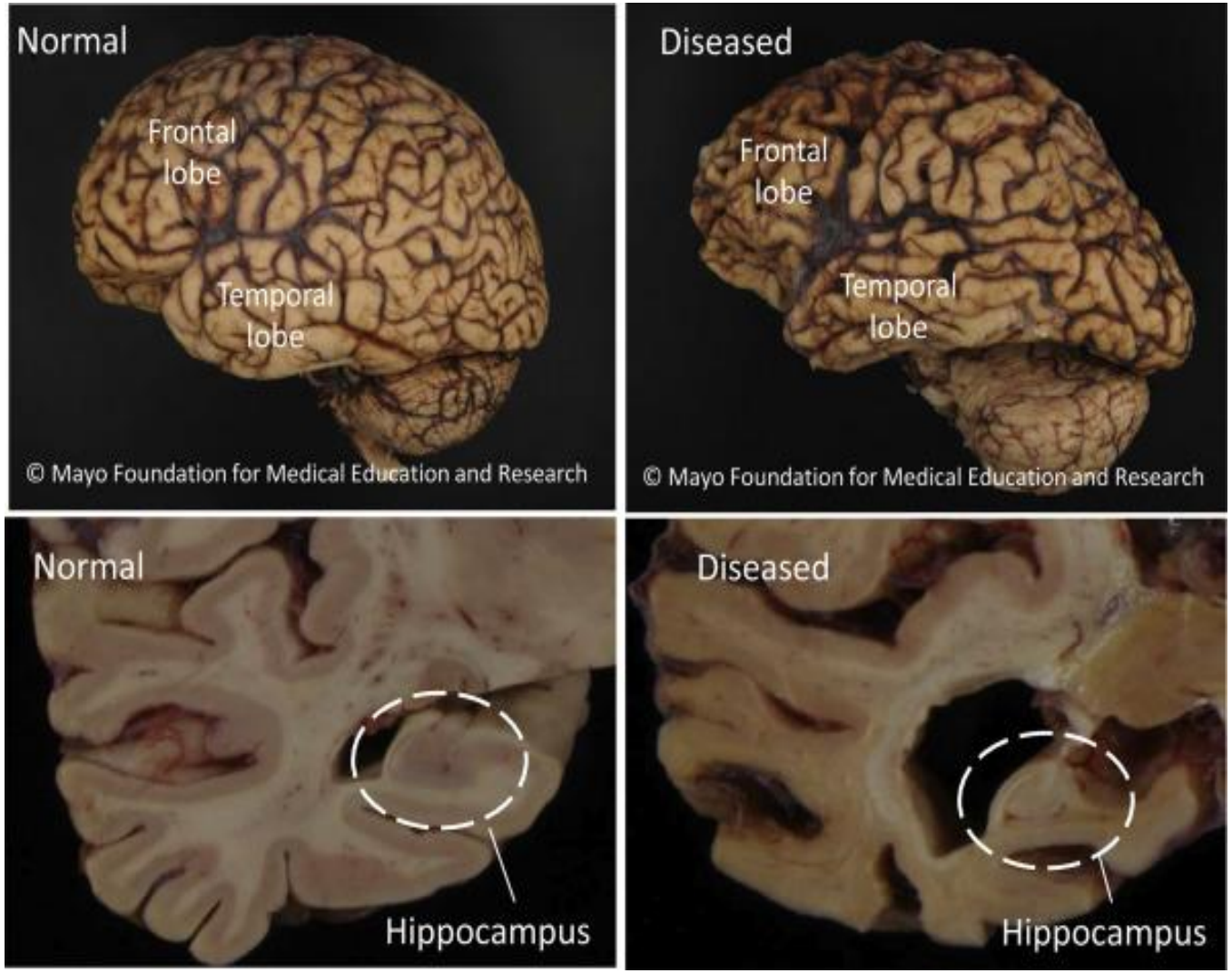
WHAT IS ALZHEIMER'S DISEASE?

- Pathology
- Neuritic plaques and neurofibrillary tangles





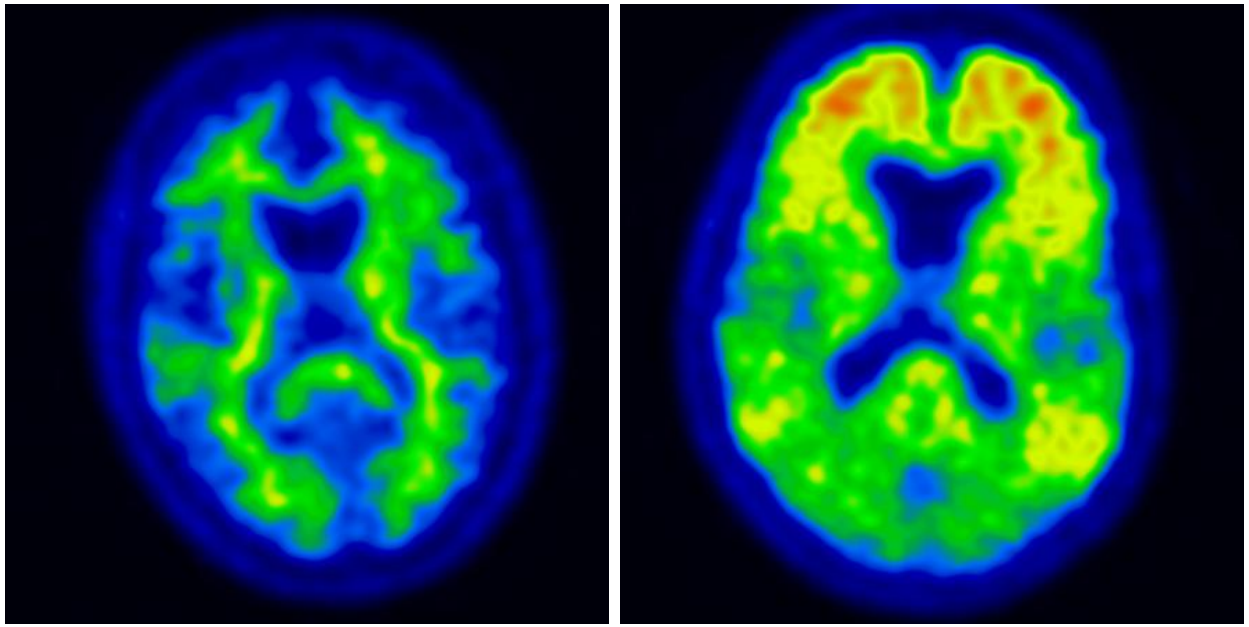
ALZHEIMER'S DISEASE



Mayo Clinic Proceedings 2016 91e117-e118DOI: (10.1016/j.mayocp.2016.06.002)

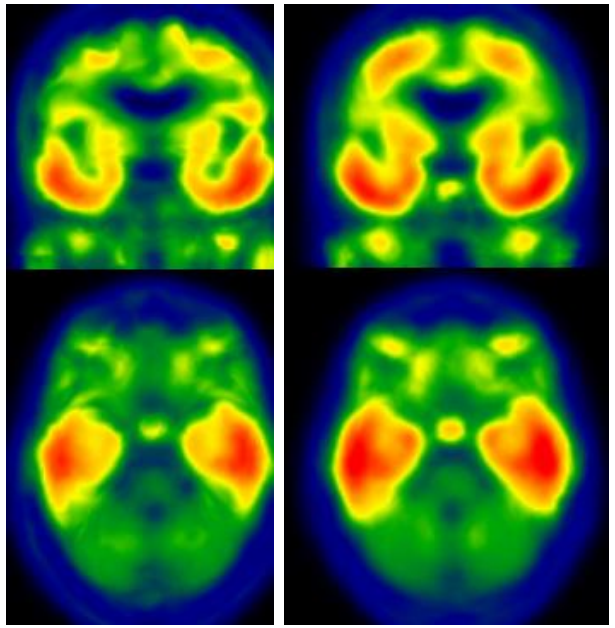
ALZHEIMER'S: NEURORADIOLOGY

Amyloid PET

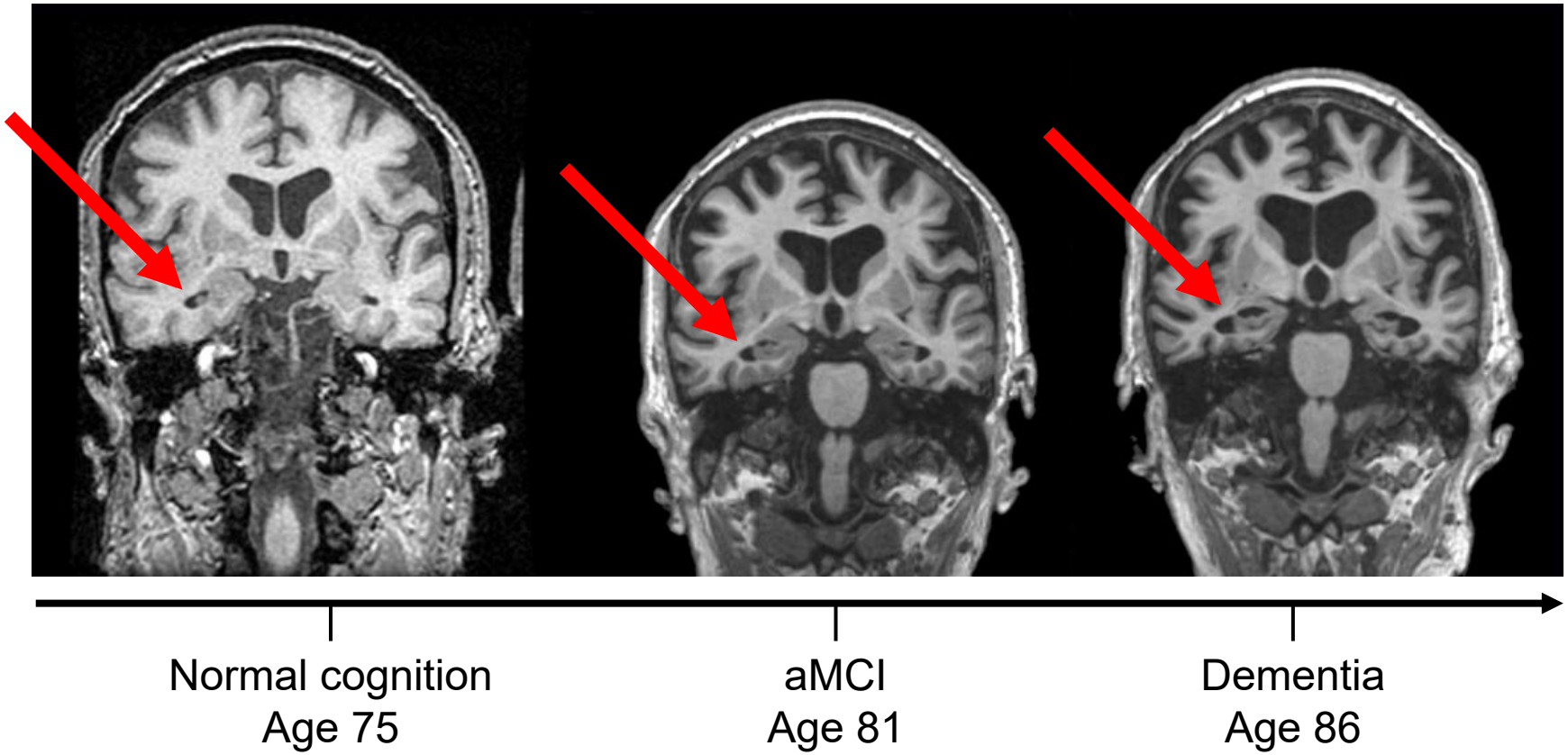


Normal AD

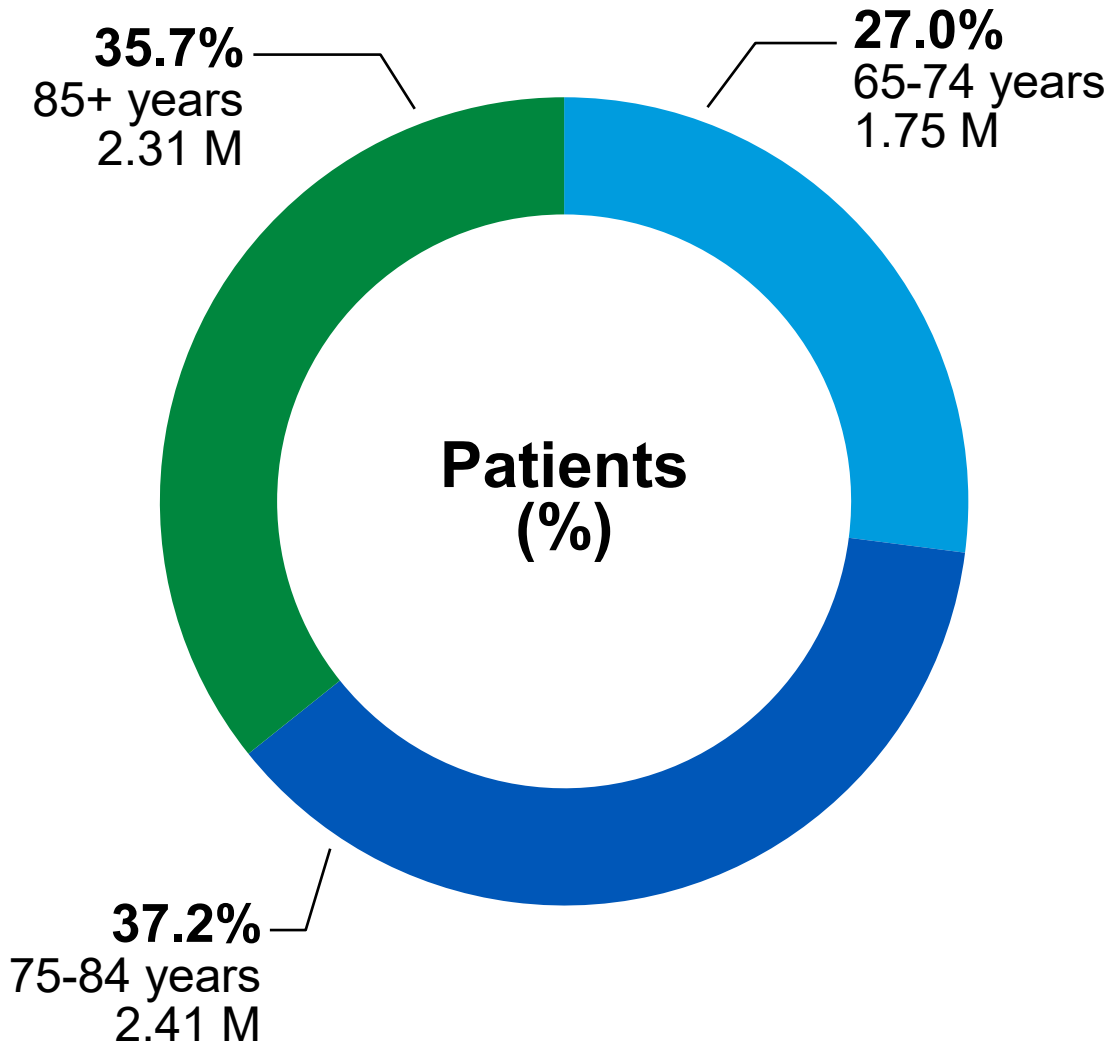
Tau PET



ALZHEIMER'S: NEURORADIOLOGY



NUMBER OF AGES OF PEOPLE 65 OR OLDER WITH ALZHEIMER'S DEMENTIA, 2022*



*Percentages do not total 100 due to rounding;
Created from data from Rajan et al.A2, 224

Alzheimer's Association 2022 Alzheimer's Disease Facts and Figures

WHAT ARE THE RISK FACTORS FOR ALZHEIMER'S?

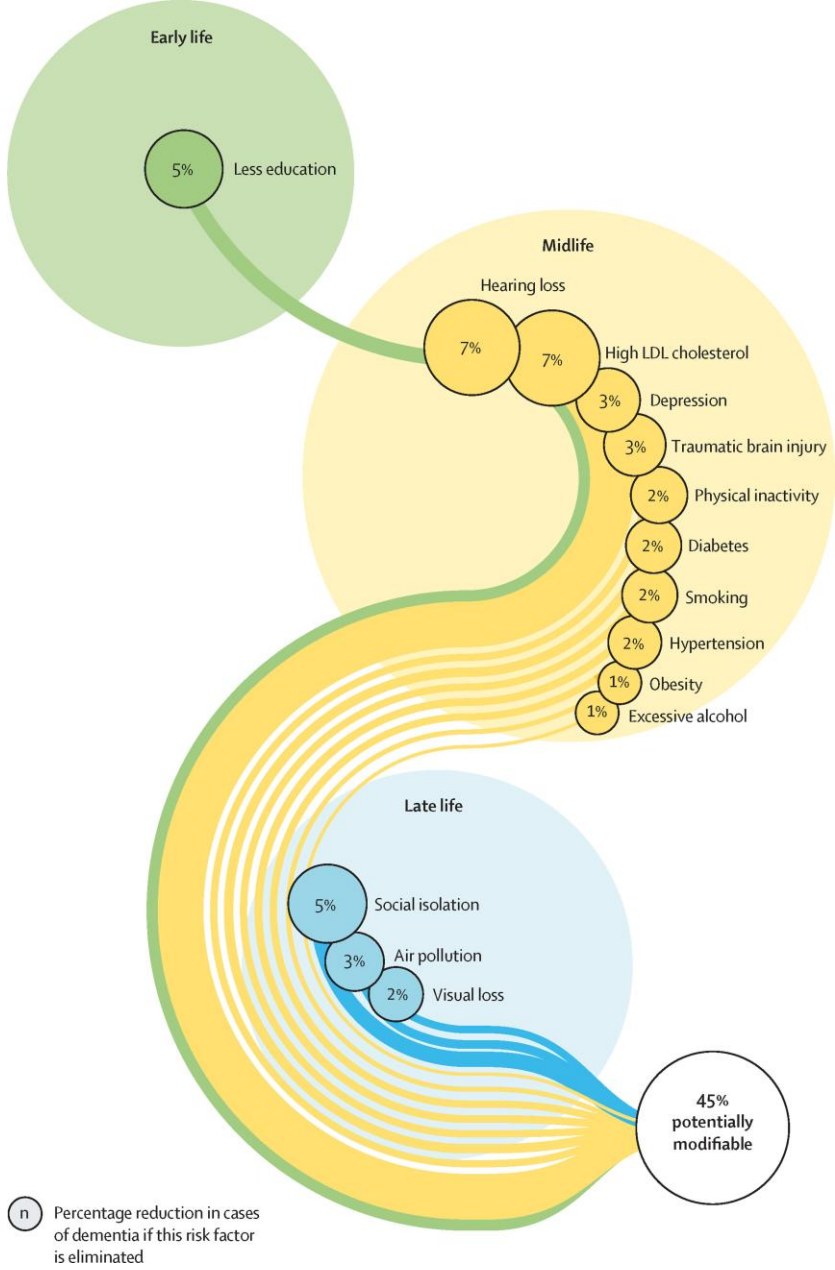
- Aging
- Family history
- Having a mutated gene that causes early onset AD (<2% of all AD cases)
- Carrying 1 or 2 ApoE 4 genes
- Down's syndrome
- Female gender
- Head injury
- Factors associated with atherosclerosis

DIFFERENCES BY RACE

- Data from the The Chicago Healthy Aging Project study indicates 19% of Black and 14% of Hispanic adults age 65 and older have Alzheimer's dementia compared with 10% of White older adults.
- In line with these observations, most other prevalence studies indicate that Black older adults are about twice as likely to have Alzheimer's or other dementias as White older adults
- Research suggests that differences in life experiences, health conditions most likely explain the difference in risk including cardiovascular disease and diabetes

https://dss.niagads.org/cohorts/chicago-health-and-aging-project-chap/

MODIFIABLE RISK FACTORS FOR DEMENTIA



The Lancet 2024 396413-446DOI: (10.1016/S0140-6736(20)30367-6)

14 RISK FACTORS AND THEIR IMPACT

Preventable Dementia Cases

Nearly 45% of dementia cases worldwide could be prevented by tackling 14 modifiable risk factors across life stages.

Life-Course Risk Factors

Risk factors include education, hearing loss, and social isolation, varying across early, mid, and late life stages.

Proactive Prevention

Taking action at any age through lifestyle changes and public health policies can significantly reduce dementia risk.

Lancet 2025

LIFE COURSE RISK FACTOR

Early life (childhood–young adulthood)

- Lower education (limited schooling reduces cognitive reserve)

Midlife (~40–65 years)

- Hearing loss (treat with hearing aids; reduce noise exposure).
- High LDL (“bad”) cholesterol (begin from ~age 40).
- Hypertension.
- Obesity.
- Excess alcohol use.
- Traumatic brain injury (use helmets / head protection).
- Smoking (midlife smoking is particularly harmful)

Later life (65+ years)

- Untreated vision loss
- Physical inactivity.
- Diabetes.
- Social isolation (increase social contact/supportive environments).
- Air pollution (reduce exposure)

EDUCATION LEVELS

EDUCATION LEVELS

Shanghai Study

2,210 elderly residents studied: For women 75-84, dementia prevalence 4% if >6 years of educatin but 18% if <6 years

Zhang et al: Ann Neurol 27:428, 1990

Nun Study

The essays of nuns at age were divided into those with high density of ideas and those without. At autopsy, those with high density of ideas had few tangles, but those with low density of ideas had many tangles

Snowdon et al: JAMA 275:528, 1996

VASCULAR RISK FACTORS

JAMA | Original Investigation

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia

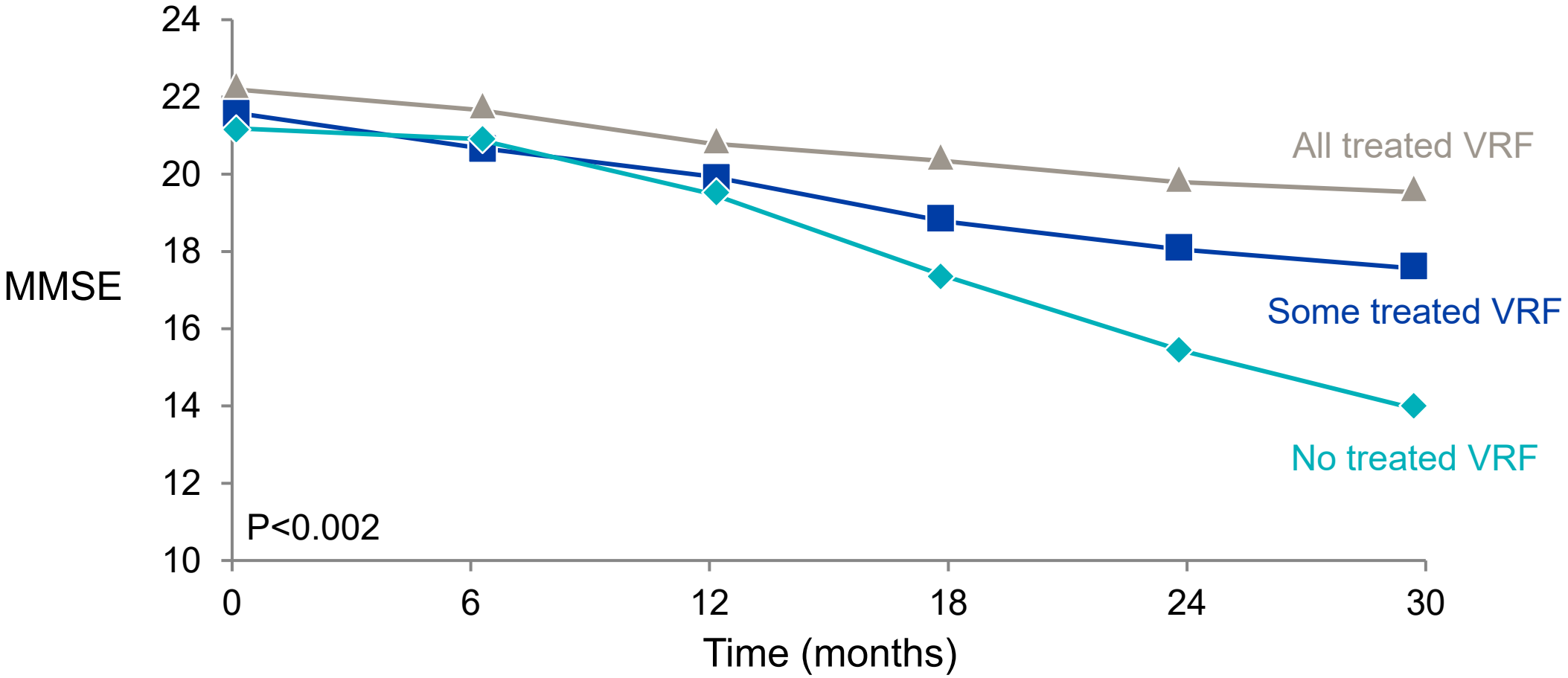
A Randomized Clinical Trial

The SPRINT MIND Investigators for the SPRINT Research Group

- Participants were randomized to a systolic blood pressure goal of either less than 120 mm Hg (intensive treatment group) or less than 140 mm Hg
- Intensive BP control significantly reduced mild cognitive impairment 14.6 vs 18.3 cases per 100 person years; HR 0.81 (95%CI, 0.69-0.96)

JAMA. 2019;321(6):553-561.

Memory and thinking skills change over time in people with Alzheimer's Disease



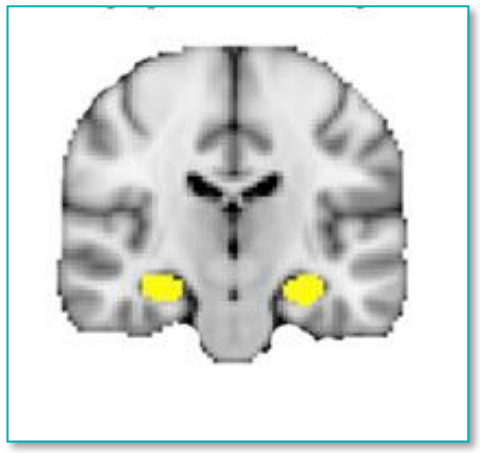
Deschaintre et al: Neurology 73:674, 2009

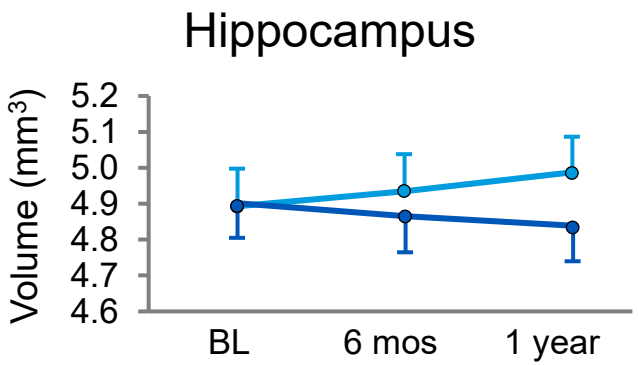
Bottom line: Those who treat their vascular risk factors (like high blood pressure) will do better!

EXERCISE

EXERCISE TRAINING INCREASES SIZE OF HIPPOCAMPUS AND IMPROVES MEMORY

- Prospective randomized single-blind study 120 older adults, half doing aerobic exercise and half toning and stretching for 1 year
- Anterior hippocampus increases 2% with exercise and decreases 1.4% in controls
- Improved visual memory is associated with increased hippocampal volume





Erickson PNAS epub: Jan 2011

From: **Associations of Physical Activity and β-Amyloid With Longitudinal Cognition and Neurodegeneration in Clinically Normal Older Adults**

JAMA Neurol. 2019;76(10):1203-1210. doi:10.1001/jamaneurol.2019.1879

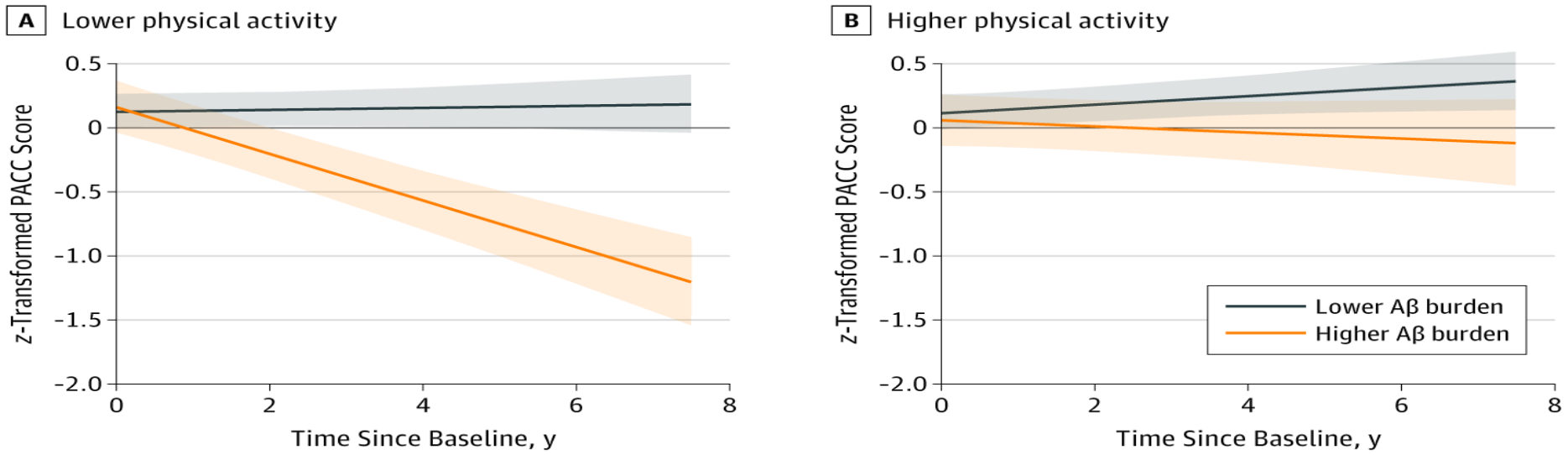


Figure Legend:

Interactive Associations of Physical Activity and β-Amyloid (Aβ) Burden on Cognitive Decline For visualization purposes, modeled longitudinal change in a cognitive composite (Preclinical Alzheimer Cognitive Composite [PACC]) is depicted in individuals with lower (A) and higher (B) levels of physical activity. To create the 2 groups, we used the values that correspond to 1 SD below and above the group mean (2900 steps per day and 8300 steps per day, respectively). Lower and higher Aβ burden groups were created using the median Aβ levels in Aβ-negative and Aβ-positive groups, which correspond to a distribution volume ratio value of 1.1 and 1.9, respectively. The plots demonstrate that greater physical activity protects against Aβ-related cognitive decline (physical activity × Aβ × time; $P < .001$). Shaded regions represent the 95% CIs.

BOTTOM LINE: EXERCISE IMPROVES BRAIN HEALTH AND MAY DELAY COGNITIVE DECLINE

DIETARY HABITS

Alcohol consumption, even at moderate levels, is associated with adverse brain outcomes including hippocampal atrophy.

Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study

Anya Topiwala *clinical lecturer in old age psychiatry*[1], Charlotte L Allan *academic clinical lecturer in old age psychiatry*[1], Vyara Valkanova *specialist registrar in old age psychiatry*[1], Enikő Zsoldos *postdoctoral scientist*[1], Nicola Filippini *postdoctoral scientist*[1], Claire Sexton *postdoctoral scientist*[2], Abda Mahmood *research assistant*[1], Peggy Fooks *medical student*[3], Archana Singh-Manoux *professor of epidemiology and public health*[4], Clare E Mackay *associate professor*[1], Mika Kivimäki *professor*[4], Klaus P Ebmeier *professor of old age psychiatry*[1]

Topiwala et al: BMJ 2017;357:j2353 doi: 10.1136/bmj.j2353

Mediterranean diet and Alzheimer disease mortality

Nikolaos Scarmeas, MD
Jose A. Luchsinger, MD
Richard Mayeux, MD
Yaakov Stern, PhD

MeDi may affect not only risk of AD but also subsequent disease course. It is also associated with lower mortality.

Scarmeas et al: Neurology® 2007;69:1084-1093

COMPONENTS OF THE MEDITERRANEAN DIET

- **Fruits and Vegetables**: A variety of fresh, seasonal produce.
- **Whole Grains**: Foods like whole wheat, oats, and brown rice.
- **Healthy Fats**: Primarily from olive oil, nuts, and seeds.
- **Legumes**: Beans, lentils, and chickpeas.
- **Fish and Seafood**: Especially fatty fish like salmon and sardines.
- **Poultry and Eggs**: In moderation.
- **Dairy**: Mainly cheese and yogurt.
- **Herbs and Spices**: For flavoring instead of salt.
- **Red Wine**: In moderation, typically with meals.
- **Limited Red Meat and Sweets**: Consumed occasionally.

GENES AND ENVIRONMENT (NATURE MEDICINE 2025)

- **Genes Shape Your Blood Chemistry:**
  - People with the APOE4 gene have **distinct patterns of blood metabolites** (tiny molecules that reflect how your body processes food and fats).
  - Some of these metabolites are linked to **higher dementia risk**, while others may be **protective**.
- **Mediterranean Diet Changes These Metabolites:**
  - Eating a Mediterranean diet **altered the blood metabolite profile** in a way that **reduced dementia risk**.
  - This effect was **strongest in APOE4 homozygotes**, suggesting that diet can **balance harmful metabolic changes** caused by genetics.
- **Metabolites May Explain How Diet Protects the Brain:**
  - The study found that **about 40% of the diet's protective effect** in APOE4 carriers was **mediated by changes in blood metabolites**.
  - In other words, the diet seems to **trigger beneficial chemical changes** in the blood that help protect the brain.

FINGER Study – Can We Prevent Dementia?

- Large study **1,200 older adults at risk for dementia**
- Tested a **combination of healthy lifestyle changes**
- Participants were split into two groups:
  - One group received general health advice
  - One group received: Brain-healthy diet, Exercise program, Brain training activities, Treatment for blood pressure, cholesterol, etc.)

Key Findings:

✓ Those in the healthy lifestyle group had **better memory, thinking, and daily functioning**

✓ Showed that dementia risk can be reduced

Bottom Line:

- A healthy lifestyle can help keep your brain sharp

Research

JAMA | Original Investigation

Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function

The US POINTER Randomized Clinical Trial

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

IMPORTANCE Identifying new interventions to slow and prevent cognitive decline associated with dementia is critical. Nonpharmacological interventions targeting modifiable risk factors are promising, relatively low-cost, accessible, and safe approaches.

OBJECTIVE To compare the effects of two 2-year lifestyle interventions on cognitive trajectory in older adults at risk of cognitive decline and dementia.

DESIGN, SETTING, AND PARTICIPANTS Single-blind, multicenter randomized clinical trial enrolling 2111 participants from May 2019 to March 2023 (final follow-up, May 14, 2025) at 5 clinical sites in the US. Participant inclusion criteria enriched risk of cognitive decline and included age 60 to 79 years, sedentary lifestyle, and suboptimal diet plus at least 2 additional criteria related to family history of memory impairment, cardiometabolic risk, race and ethnicity, older age, and sex.

INTERVENTIONS Participants were randomly assigned with equal probability to structured (n = 1056) or self-guided (n = 1055) interventions. Both interventions encouraged increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring, but differed in structure, intensity, and accountability.

MAIN OUTCOMES AND MEASURES The primary comparison was difference between intervention groups in annual rate of change in global cognitive function, assessed by a composite measure of executive function, episodic memory, and processing speed, over 2 years.

RESULTS Among the 2111 individuals enrolled (mean age, 68.2 [SD, 5.2] years; 1455 [68.9%] female), 89% completed the year 2 assessment. The mean global cognitive composite *z* score increased from baseline over time in both groups, with a mean rate of increase per year of 0.243 SD (95% CI, 0.227-0.258) for the structured intervention and 0.213 SD (95% CI, 0.198-0.229) for the self -guided intervention. The mean rate of increase per year was statistically significantly greater for the structured group than the self-guided group by 0.029 SD (95% CI, 0.008-0.050; *P* = .008). Based on prespecified secondary subgroup comparisons, the structured intervention benefit was consistent for *APOE* ε4 carriers and noncarriers (*P* = .95 for interaction) but appeared greater for adults with lower vs higher baseline cognition (*P* = .02 for interaction). Fewer ascertained adverse events were reported in the structured group (serious: 151; nonserious: 1091) vs the self-guided group (serious: 190; nonserious: 1225), with a positive COVID-19 test result being the most common adverse event

Visual Abstract

Editorial page 674

Supplemental content

Results from the U.S. POINTER clinical trial found that two lifestyle interventions targeting a combination of physical activity, improving nutrition, cognitive and social challenge, and health monitoring improved cognition in older adults at risk of cognitive decline.

MEDICATION USE

Original Investigation

Cumulative Use of Strong Anticholinergics and Incident Dementia

A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD; Rod Walker, MS; Onchee Yu, MS; Paul K. Crane, MD, MPH; Eric B. Larson, MD, MPH

CONCLUSIONS AND RELEVANCE Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time

Over-the-counter sleep aids
- Tylenol PM
- Nyquil PM
- Sominex
- Benadryl

Overactive Bladder
- Ditropan
- Detrol

Antidepressant
- Amitriptyline
- Imipramine

Nausea/dizziness
- Reglan
- Meclizine

Antispasmodic for stomach
- Bentyl (dicyclomine)
- Hyoscyamine

Gray et al: JAMA Intern Med. 2015;175(3):401-407

HEARING LOSS AND DEMENTIA – WHAT'S THE CONNECTION?

- Hearing loss is **very common** as we age
- Studies show hearing loss is linked to a **higher risk of memory and thinking problems**
- Possible reasons:
  - Straining to hear takes effort away from thinking
  - Social isolation from hearing loss may affect brain health
  - Hearing loss may directly affect brain structure
- **The Good News:**
  ✓ Using hearing aids may help lower the risk of cognitive decline
  ✓ Protecting your hearing is an important part of brain health

RECOMMENDATIONS FOR POSSIBLE PREVENTION

- Treat cardiovascular risk factors
- Keep mind active
- Exercise
- Eat fish
- Treat hearing loss
- Mediterranean/MIND diet
- Quality sleep (RX sleep apnea)

WHAT ABOUT MEDICATIONS TO SLOW ALZHEIMER'S?

CLARITY AD RESULTS

Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline

Primary Endpoint

Reduced clinical decline on CDR-SB, compared with placebo at 18 months from baseline

27% (P=0.00005)

Key Secondary Endpoints

All key secondary endpoints also met, demonstrating highly statistically significant results (P<0.01)

Safety

ARIA-E: 12.5% (symptomatic: 2.8%)
ARIA-H: 17.0% (symptomatic: 0.7%)

TRAILBLAZER RESULTS

Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline

Primary Endpoint

Reduced clinical decline on iADRS (Alzheimer's Disease Rating Scale), compared with placebo at 76 weeks from baseline

35% reduced decline

Key Secondary Endpoints

All key secondary endpoints also met, demonstrating highly statistically significant results (P<0.01)

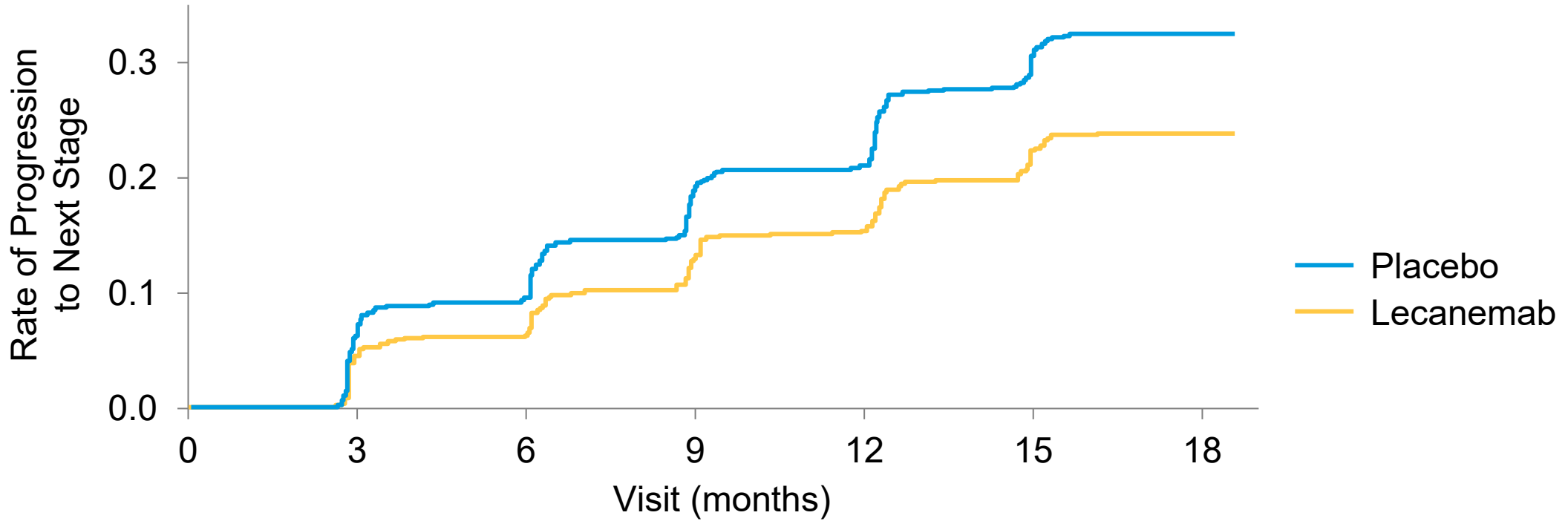
Safety

ARIA-E: 15.7%
ARIA-H: 26.8%

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

ALZHEIMER'S DISEASE PROGRESSED MORE SLOWLY IN PEOPLE ON LECANEMAB, DELAYING ARRIVAL OF THE NEXT DISEASE STAGE

Time to Worsening of Global CDR Scores



(N) Placebo	875	792	757	649	603	524	265*
(N) Lecanemab	859	801	765	677	642	554	299*

Lecanemab treatment showed 31% lower risk of converting to next stage of disease by Global CDR assessment (Hazard Ratio: 0.69).

NEW BLOOD TEST FOR ALZHEIMER'S DISEASE

- FDA-approved blood test detecting Alzheimer's-related brain changes through specific protein measurement.
- Less Invasive and Affordable
- This test offers a less invasive and more cost-effective alternative to PET scans and lumbar punctures.
- Quick and Convenient Results (2 days)
- 90% accurate but cannot diagnose Alzheimer's alone

IMPORTANCE OF EARLY DIAGNOSIS AND COGNITIVE EVALUATION IN ALZHEIMER'S DISEASE

- Alzheimer's begins 20+ years before symptoms appear.
- Early diagnosis allows:
  - Access to disease-modifying treatments
  - Planning for care, legal, and financial decisions.
  - Improved quality of life and safety.
  - Improved clarity, education and understanding that follow.
  - Empowering individuals through knowledge to promote a sense of self-control and agency over decisions.
  - Promoting healthy behaviors, such as exercise and a nutritious diet.
  - Prompting safety measures, such as managing driving, medications Participation in clinical trials.

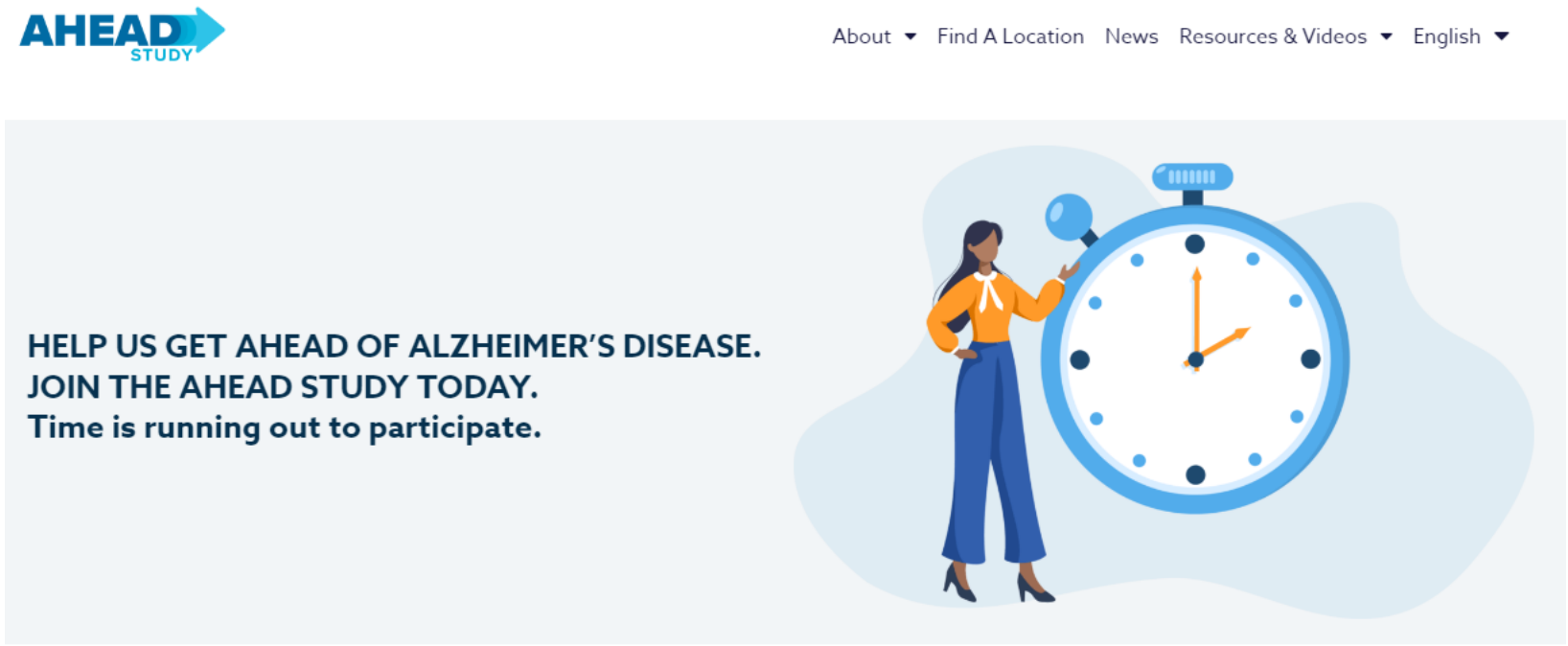
BIOMARKERS AND COGNITIVE EVALUATION

- Biomarkers (e.g., beta-amyloid, tau) detectable decades before symptoms.
- Emerging blood-based biomarker tests offer promise for accessible early detection.
- Cognitive evaluation tools:
  - MMSE, MoCA, AD8, and computerized assessments.
  - Functional assessments of ADLs/IADLs.

BARRIERS TO EARLY DIAGNOSIS

- Limited access to specialists.
- PCPs report low confidence in diagnosing dementia.
- Need for education, training, and clinical guidelines.
- Expand use of cognitive assessments in primary care.
- Integrate biomarker testing into routine evaluations.
- Promote public awareness and reduce stigma.

ONGOING RESEARCH STUDIES

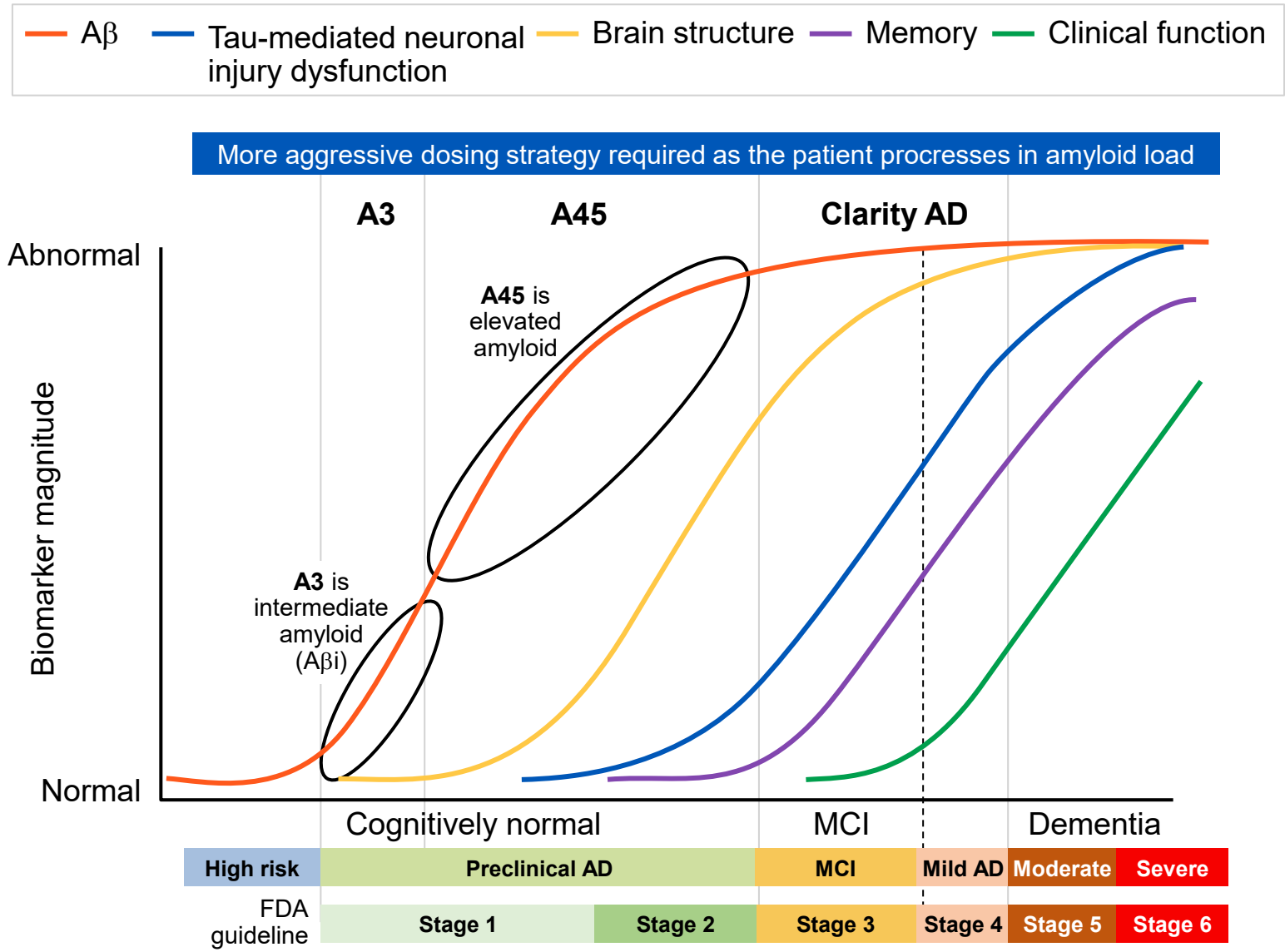


https://www.aheadstudy.org/

. 2023

AHEAD STUDY

Model of progression of biomarkers over the course of AD



Rafii M et al. Alzheimers Dement. 2023

CONCLUSIONS:

- Early diagnosis is not just a clinical milestone—it’s a gateway to better care, empowered patients, and reduced burden.
- Let’s make early detection the standard, not the exception.