

Etiology of Alzheimer's Disease and What Puts Patients at Risk

*OHSU 56th Annual Primary Care Review
February 12, 2025*

Breakout Session I

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Disclosures/Conflict of Interest

- I am site-principal investigator for Alzheimer's disease and related disorders studies sponsored by the Alzheimer's Association, Alector, Cognition Therapeutics, Eisai, and the National Institute on Aging.

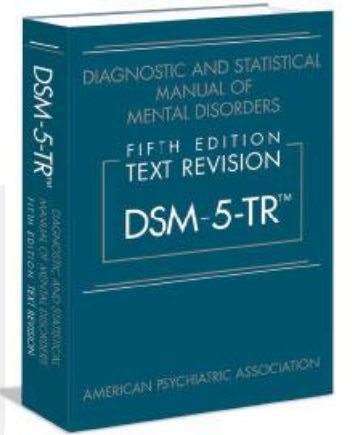
Session Objectives

1. Review the definitions of dementia, mild cognitive impairment, and Alzheimer's disease
2. Identify the common genetic and environmental risk factors for Alzheimer's disease
3. Develop a patient-centered prevention strategy

Outline

1. Importance and definition of Alzheimer's disease
2. Why is it difficult to determine the cause
3. What do we know
4. Moving towards prevention trials
5. What to tell patients

Groundwork for terminology



- Dementia = major neurocognitive disorder (DSM-5)
- Mild cognitive impairment = mild neurocognitive disorder (DSM-5)
- AD / ADRD = Alzheimer's Disease and Alzheimer's Disease Related Disorders (NIH)
 - ADRD = The most common forms of neurodegenerative and vascular dementias (FTD, DLB, vascular dementia, multiple-etiology dementia)
- Primary care, internal medicine, geriatrics, neurology, psychiatry, patients, and families may use or prefer different terminology



New Estimates of Americans with Alzheimer's Disease and Related Dementias Show Racial and Ethnic Disparities

Number of Americans with Alzheimer's Disease Expected to Increase

Percentage of Adults Aged 65 and Older with Alzheimer's Disease by Race and Ethnicity



296249A



www.cdc.gov/aging

Centers for Medicare and Medicaid Services, 2014

Alzheimer's Disease Projected to Nearly Triple by 2060

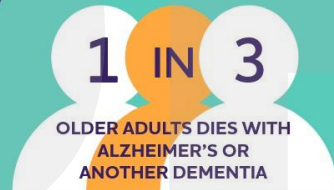


Census Population Projections Program, 2014 to 2060

2024 ALZHEIMER'S DISEASE FACTS AND FIGURES



NEARLY
7 MILLION
AMERICANS ARE LIVING
WITH ALZHEIMER'S



IT KILLS MORE THAN
**BREAST CANCER AND
PROSTATE CANCER**
+
COMBINED

OVER **11 MILLION**
AMERICANS PROVIDE
UNPAID CARE
FOR PEOPLE WITH ALZHEIMER'S
OR OTHER DEMENTIAS

BETWEEN 2000 AND 2021, DEATHS
FROM HEART DISEASE HAVE
DECREASED 2.1%



WHILE DEATHS FROM
ALZHEIMER'S DISEASE HAVE
INCREASED 141%

IN 2024, ALZHEIMER'S
AND OTHER DEMENTIAS WILL
COST THE NATION
\$360 BILLION
————— \$\$\$\$\$ —————

BY 2050, THESE COSTS
COULD RISE TO NEARLY
\$1 TRILLION

THESE CAREGIVERS
PROVIDED MORE THAN
18 BILLION HOURS
VALUED AT NEARLY
\$347 BILLION

THE LIFETIME RISK FOR
ALZHEIMER'S AT AGE 45 IS



70% OF DEMENTIA
CAREGIVERS
FEEL STRESSED WHEN
COORDINATING CARE

AND MORE
THAN HALF
OF CAREGIVERS
SAID NAVIGATING
HEALTH CARE IS
DIFFICULT



3 in 5 DEMENTIA
CAREGIVERS
SAY LESS STRESS AND MORE PEACE OF
MIND ARE POTENTIAL BENEFITS OF
HAVING A **CARE NAVIGATOR**

56% SAY IT COULD
HELP THEM BE
BETTER CAREGIVERS

For more information, visit alz.org/facts

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ALZHEIMER'S ASSOCIATION®

Does my patient have DEMENTIA?

- Patient has history (subjective) and testing (objective) consistent with decline in cognition, AND
- Decline in Day-to-Day abilities compared to previous level of functioning

- **Higher level activities (instrumental)**

- Finances and other paperwork
 - Medication management
 - Managing medical appointments
 - Driving
 - Shopping
 - Cooking

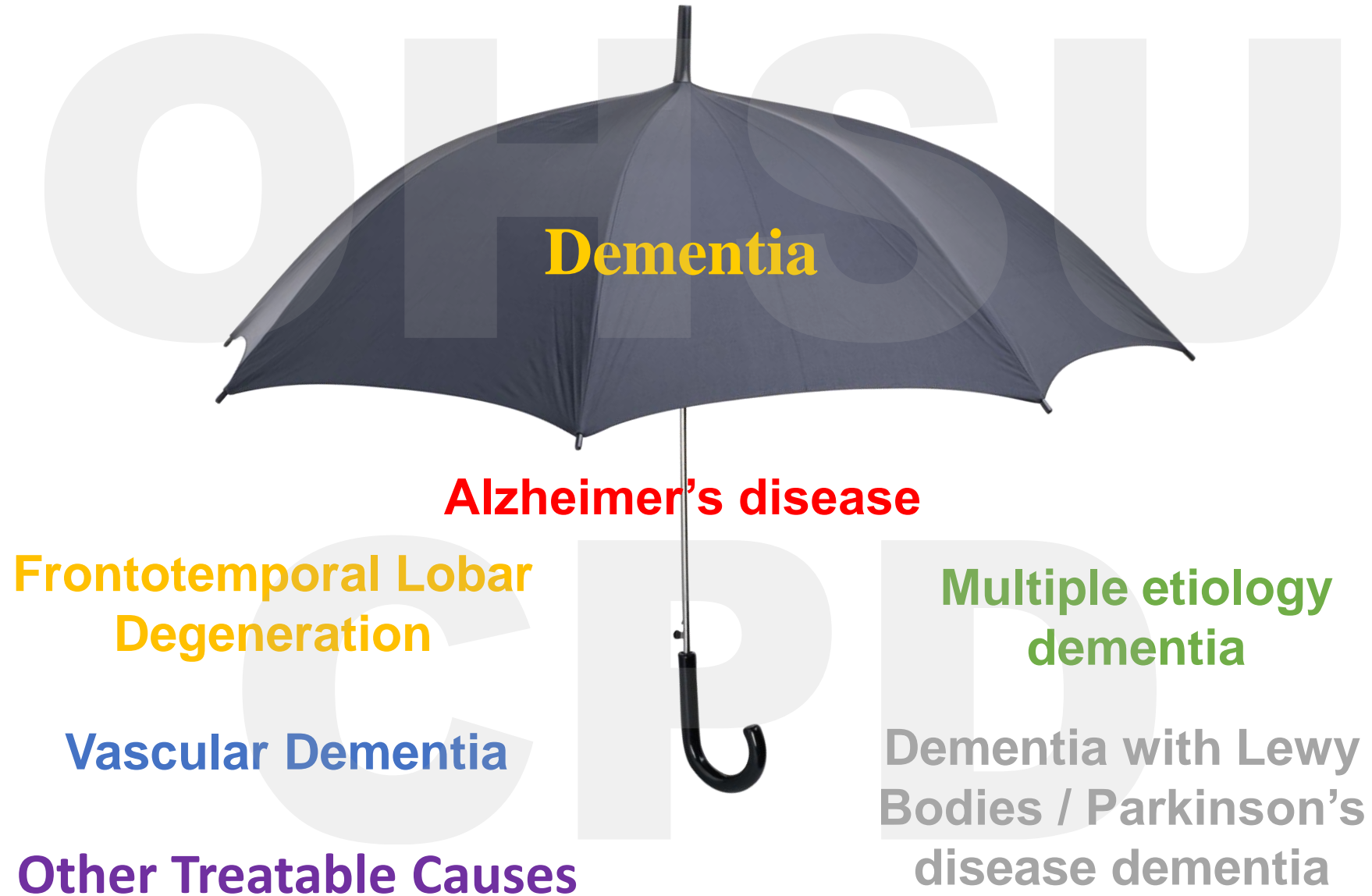
- **Lower level activities (basic)**

- Dressing
 - Bathing
 - Toileting

MILD COGNITIVE IMPAIRMENT

- Patient has history (subjective) and testing (objective) consistent with decline in cognition, AND
- NO DECLINE in day to day function
- Importance of MCI diagnosis?
 - Those with MCI are at higher risk of converting to dementia than others their same age without MCI
 - More careful follow up needed
 - Treatments and clinical trials may be appropriate

Dementia is a syndrome



Work up

- Goal is to eliminate potentially treatable non-degenerative etiologies:

Drug/medication toxicity

Emootional illness (e.g., severe depression)

Metabolic/endocrine disorders (e.g., thyroid)

Eye/ear/environment (e.g. sleep)

Nutritional (e.g., B₁₂ deficiency)

Tumors/structural (e.g., hydrocephalus, subdural hematoma)

Infection

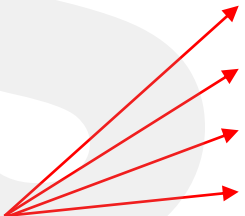
Alcoholism

- CT or MRI brain: Tumor, hydrocephalus, vascular, atrophy pattern
- Labs:
 - B12, TSH, RPR (if indicated), CBC, Chem 7, liver function, vitamin D
 - Other tests as needed – blood test for Alzheimer's ?

Key Elements for Diagnosis: ALZHEIMER'S DISEASE

- First Symptom(s)

- SHORT TERM MEMORY LOSS



- Forgets conversations
- Repeat questions
- Recent events forgotten
- Remembers distant past

- Other symptoms/findings

- Visual spatial skill problems
- Orientation difficulties
- Hippocampal atrophy on imaging

- Onset and progression

- Insidious onset, slow progression of symptoms

Hallmarks of Alzheimer's Disease Pathology

- With the naked eye: shrinkage of the brain (*cerebral atrophy*)
- Under the microscope: amyloid plaques and neurofibrillary tangles

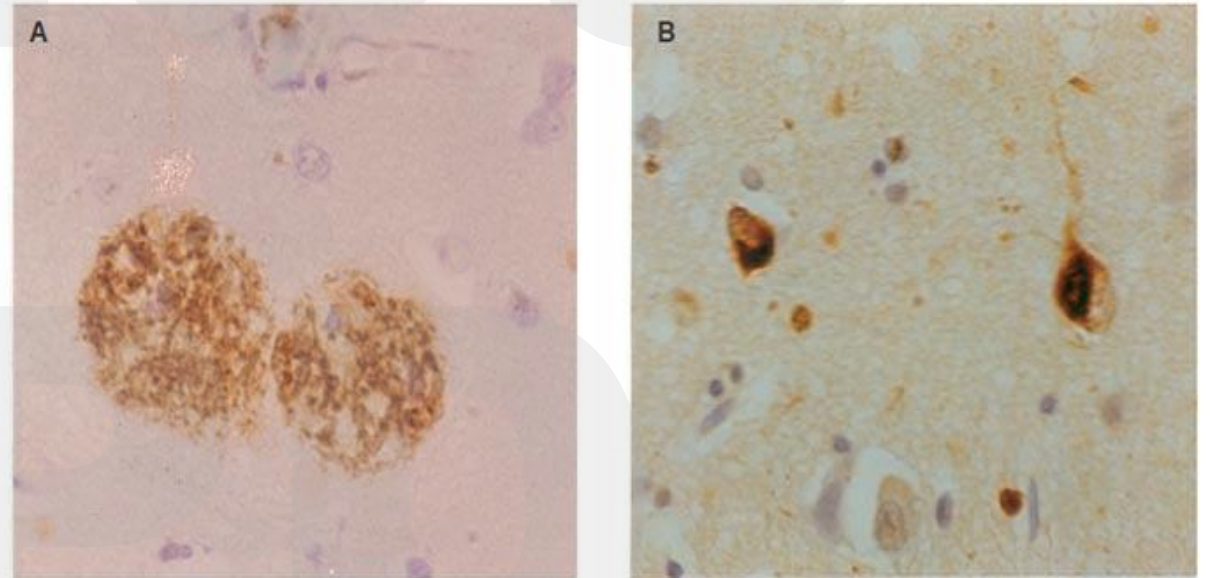
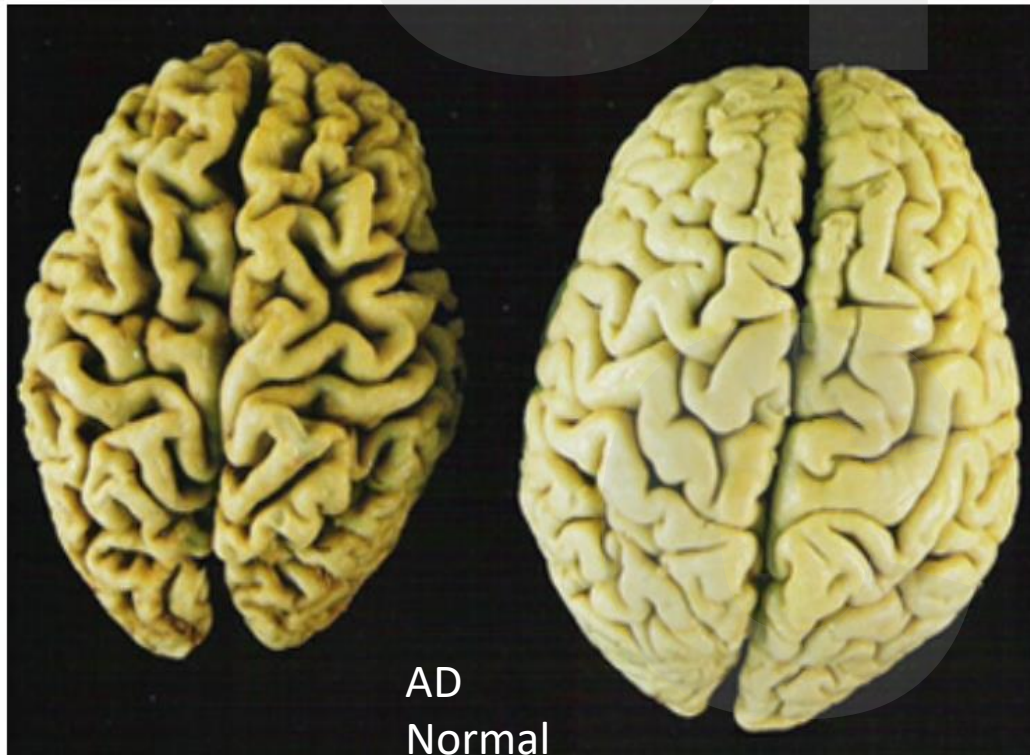


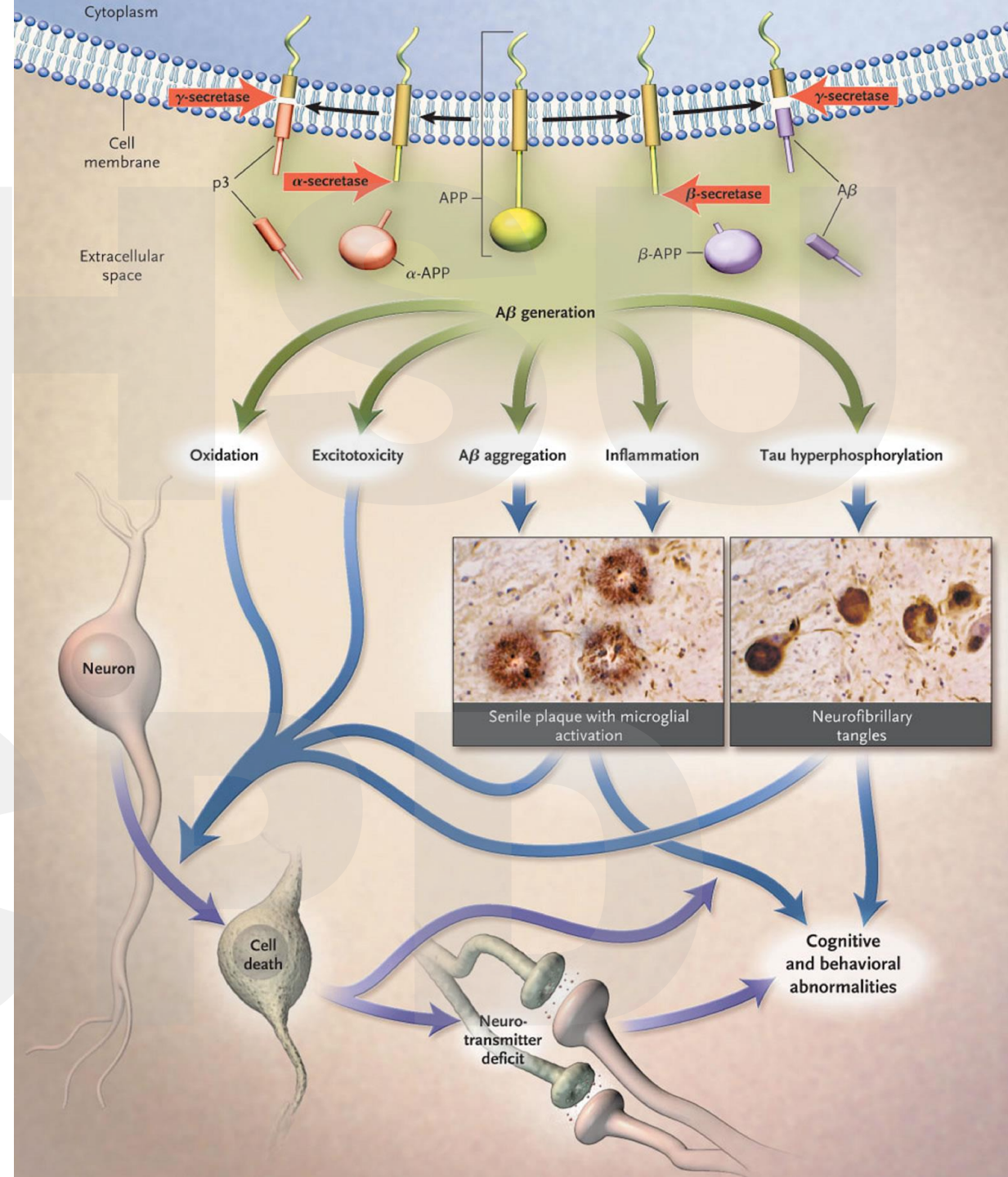
FIGURE 1

Neuropathology of Alzheimer's disease: **A.** β -amyloid ($A\beta$) deposits in the form of senile plaques (SP) in a section of the cerebral cortex. Deposits appear as brown patches and are widely distributed, especially in the cerebral cortex (β -amyloid immunohistochemistry), **B.** neurofibrillary tangles (NFT) in the cerebral cortex appearing as inclusion bodies within neurons (tau immunohistochemistry).

Amyloid Cascade Hypothesis:

Deposition of amyloid
in the brain is
- early
and
- critical

in the development of
Alzheimer's disease



Alzheimer's markers can now be seen in patients

Brain imaging – PET scans

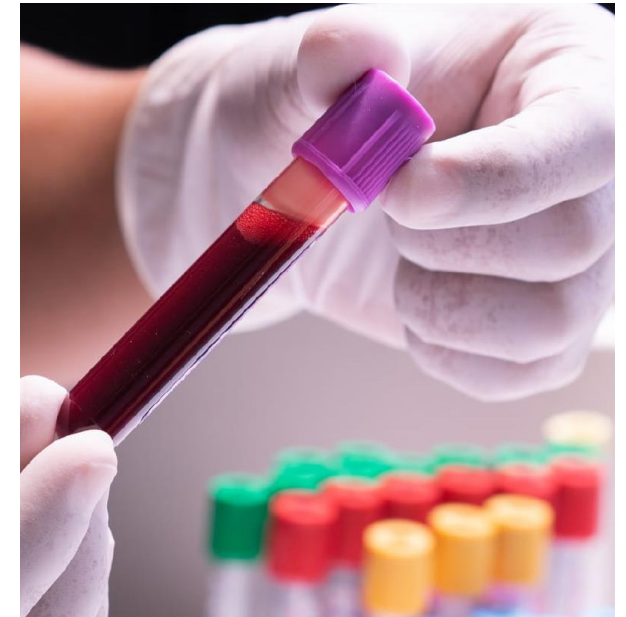
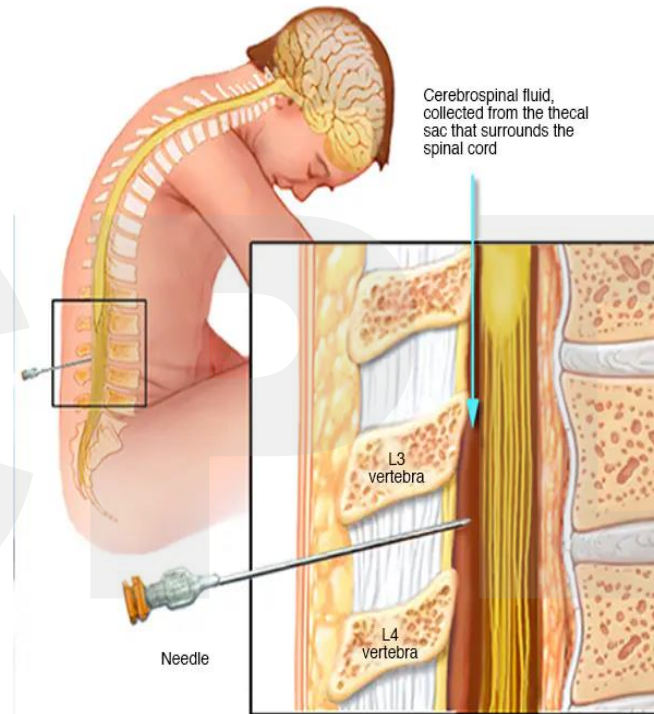
- Amyloid
- Tau

Cerebrospinal fluid (CSF)

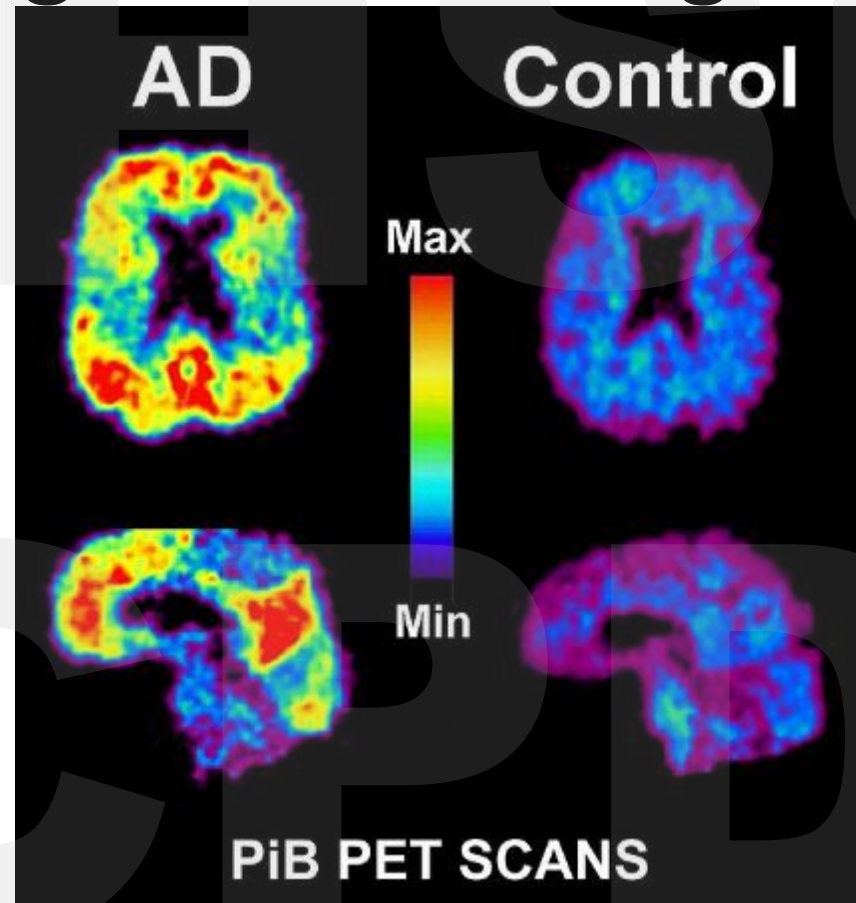
- Amyloid
- Tau

Blood

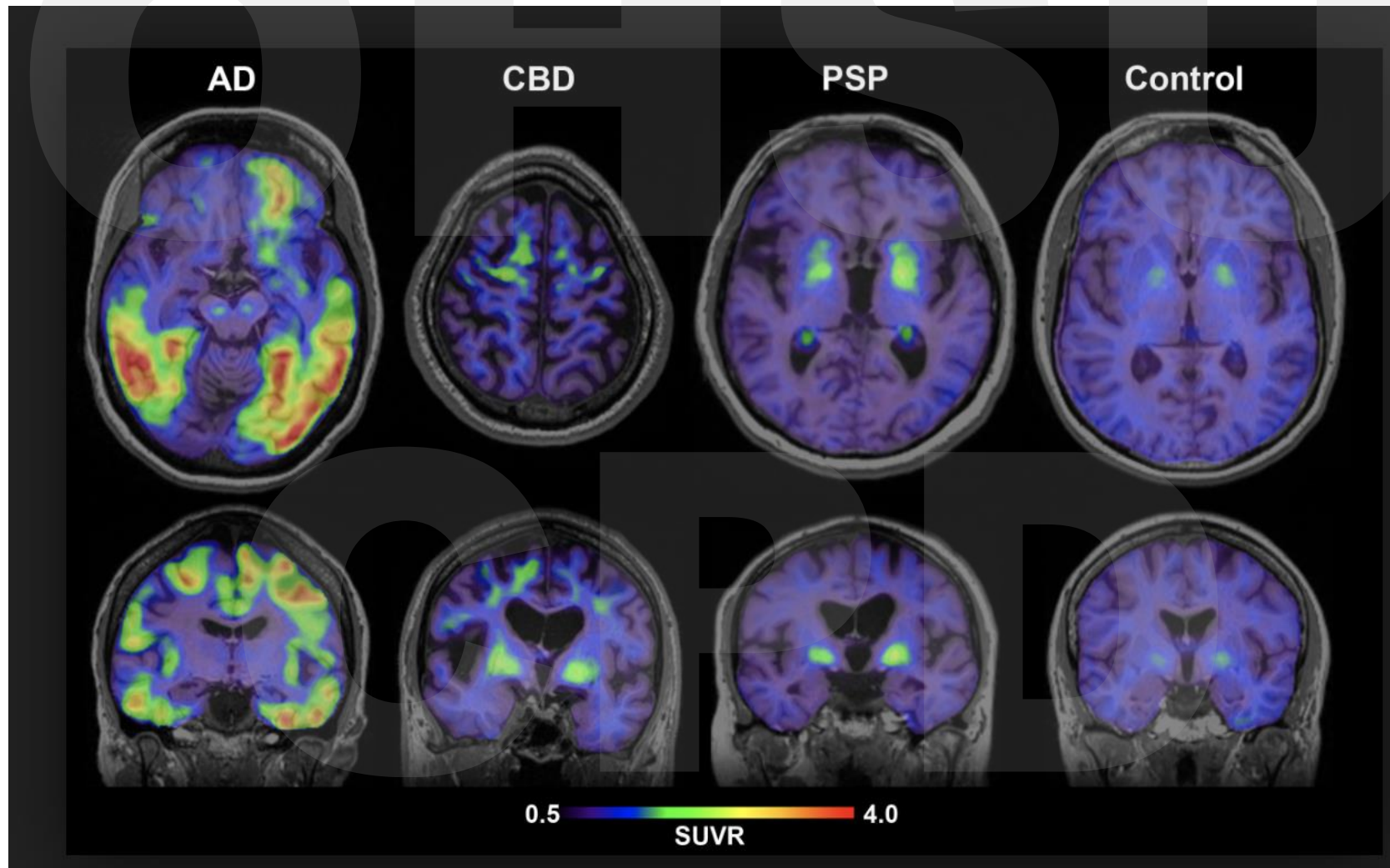
- Amyloid
- Tau



Amyloid PET scans - an advance for Alzheimer's diagnosis and targeted treatment



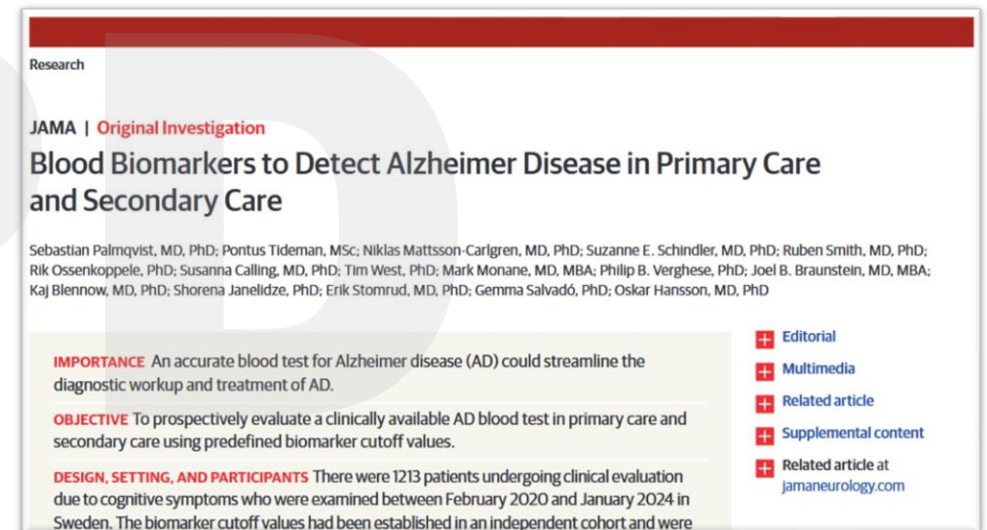
Tau PET Imaging



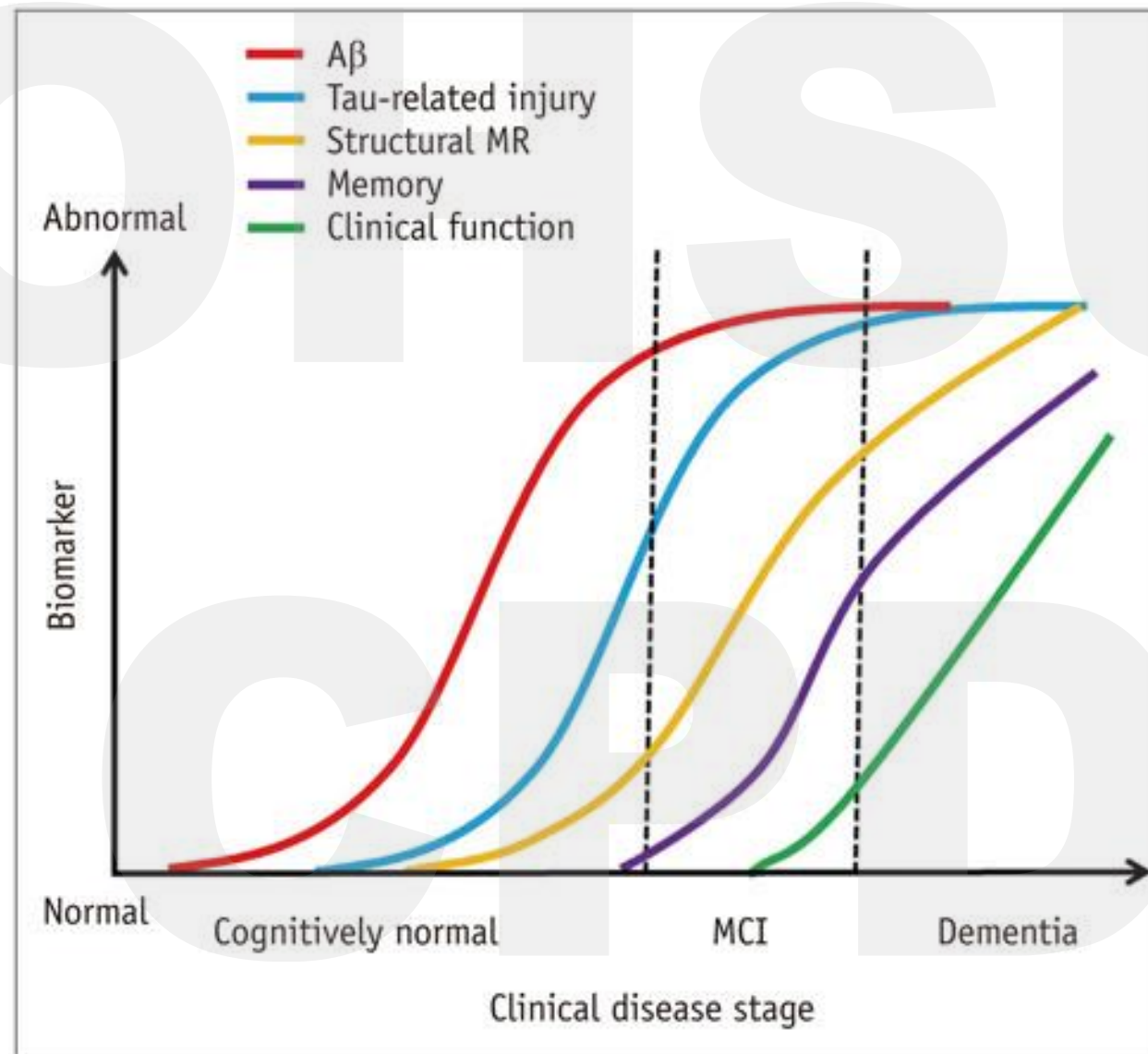
Ossenkoppele R, et al.
JAMA 2018.

2021-present: New blood tests for Alzheimer's disease

- Utilize mass spectrometry to measure amyloid beta 42 / 40 ratio in the blood, +/- APOE4 genotype, +/- immunoassays for phospho-tau 217 and other isoforms to predict amyloid in the brain
- Diagnostic accuracy ~ 90% (compared to cerebrospinal fluid)
- Approved for use in MCI and dementia – not for predictive use
- Currently out-of-pocket, not yet covered by insurance, cost \$500 - \$1200



Biomarker Progression

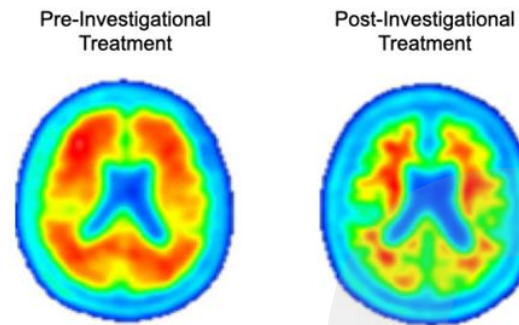


Jack CR, et al. *Lancet Neurol*, 2013.

Anti-amyloid treatment for mild Alzheimer's disease

- Lecanemab (2023) and donanemab (2024) are humanized monoclonal antibodies
- Reduce brain amyloid plaques and slow cognitive decline by ~ 30%
- Risks (brain edema and hemorrhage), burden, expense, access all limit use

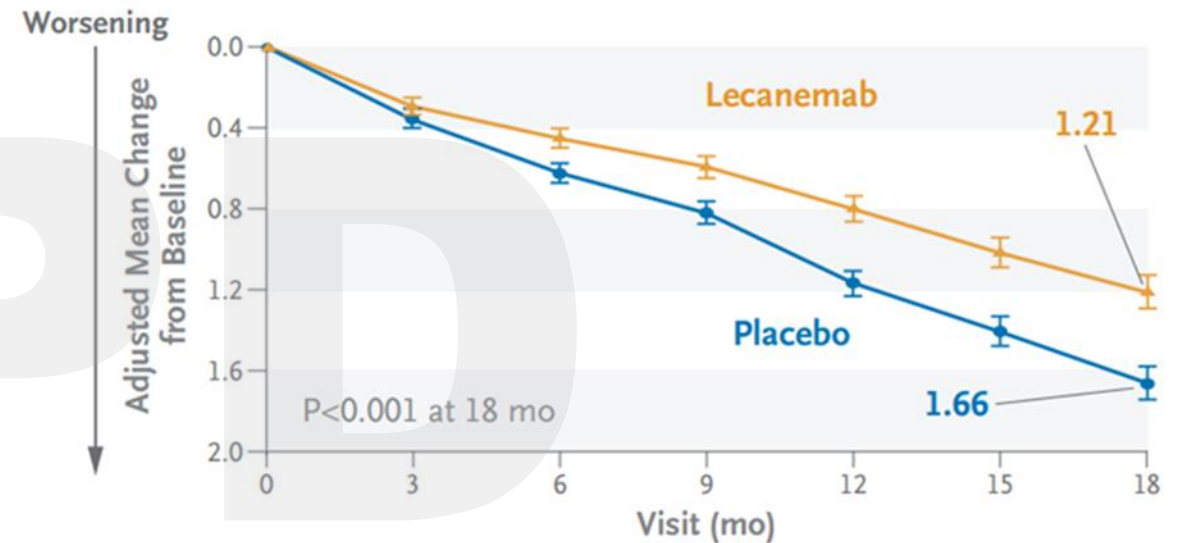
Amyloid PET Scan



Amyloid PET imaging scans from a representative participant in the Phase 2 trial of BAN2401 (lecanemab)—the investigational treatment being tested in the AHEAD Study. Amyloid PET scans measure the levels of amyloid plaque in the brain. The image on the left is taken before the participant has started on the investigational treatment. The image on the right is taken after 18 months of investigational treatment with BAN2401 (lecanemab), indicating a reduction of amyloid plaque burden in the brain. (Data presented at AAIC 2019)

Change in CDR-SB Score (Range 0–18)

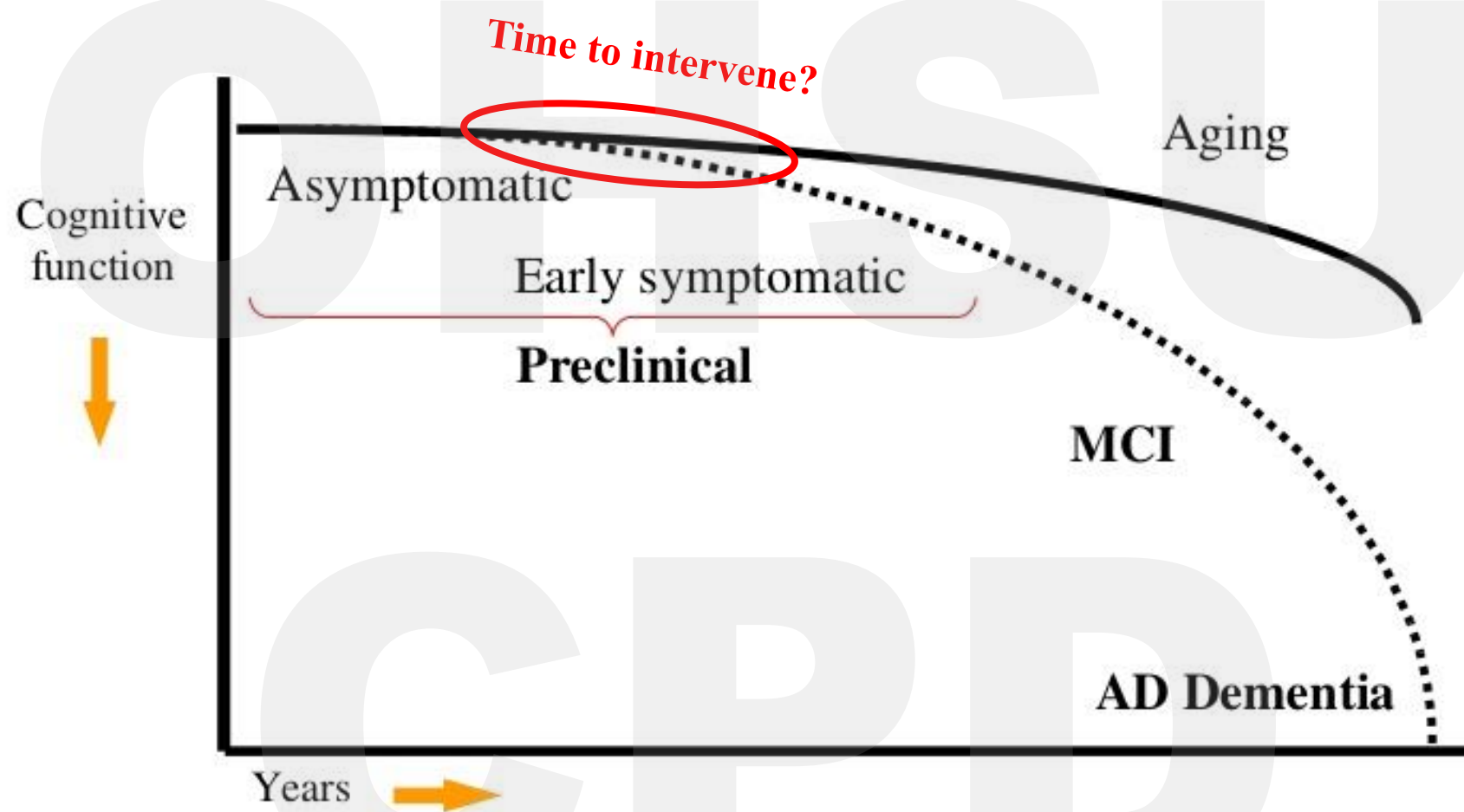
Difference in least-squares mean change, -0.45 (95% CI, -0.67 to -0.23)



Clinical versus pathologic diagnosis of AD

- For decades, clinical diagnosis of AD was based on typical presentation and ruling out of other causes = “Probable Alzheimer’s Disease”
- Pathologic diagnosis of AD was the gold standard = “Definite Alzheimer’s Disease”
- With advances in measuring AD markers in living patients, revised diagnostic criteria were proposed in 2024 that define AD *“to be a biological process that begins with the appearance of AD neuropathologic change while people are asymptomatic. Progression of the neuropathologic burden leads to the later appearance and progression of clinical symptoms.”*

The continuum of Alzheimer's disease



Sperling et al *Alzheimer & Dementia* 2011
NIA-AA Preclinical Workgroup

Challenges with epidemiologic studies of Alzheimer's disease

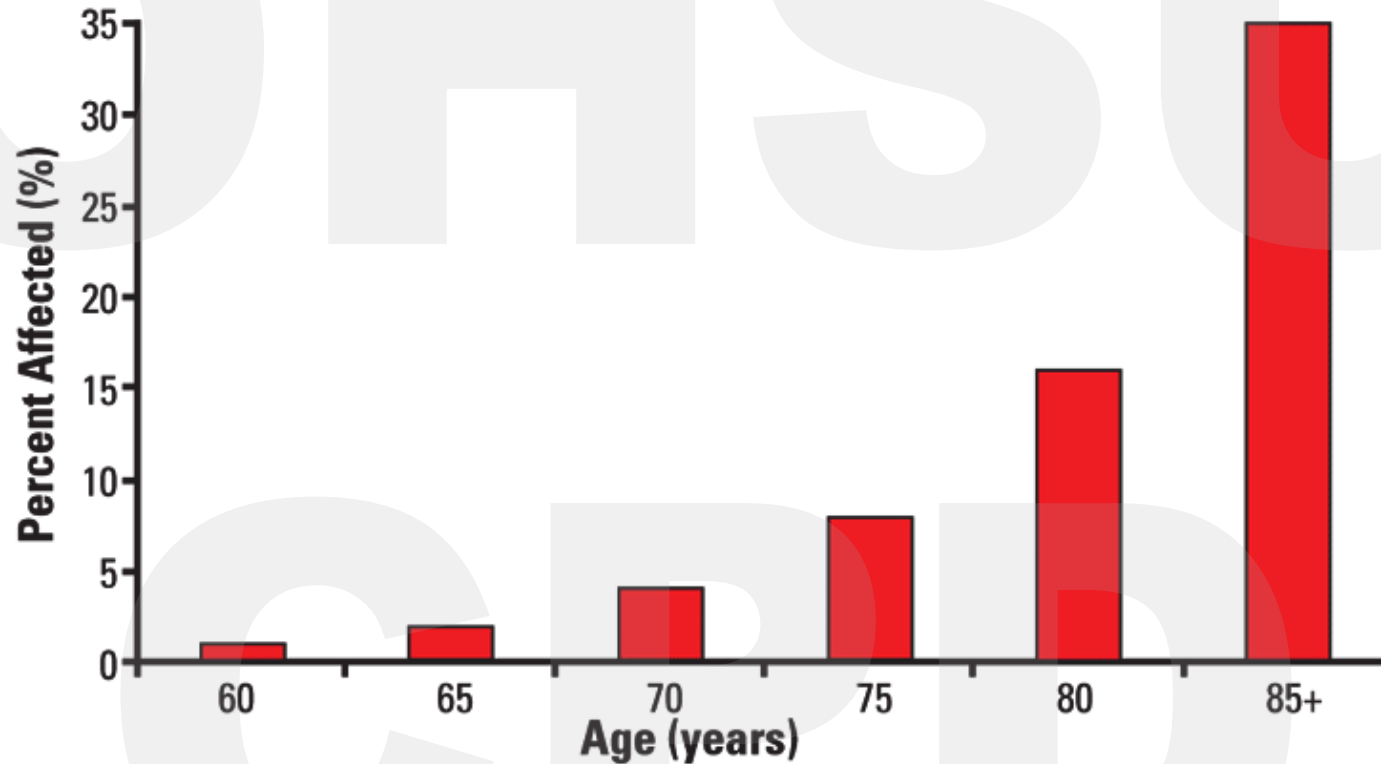
- Underdiagnosis
- Clinical versus pathologic diagnosis
- Novel, invasive, and not widely available biomarkers
- Early stages of AD may be indistinguishable from normal aging
- Lumping of all forms of MCI or dementia together

The major causes of Alzheimer's Disease

- Age
- Genetics
- Environment and Lifestyle

FIGURE 1

ALZHEIMER'S DISEASE DOUBLES IN FREQUENCY EVERY 5 YEARS AFTER 60 YEARS OF AGE



Cummings JL. *Primary Psychiatry*. Vol 15, No 2. 2008.

Cognitive changes with normal aging

Decline	Maintain or improve
Attention	Language
Word-finding	Visuospatial function
Short-term memory	Executive function
	Long-term memory

- Key is that activities of daily living remain unimpaired (people can compensate)
- Tip of the tongue phenomena, misplacing keys are common

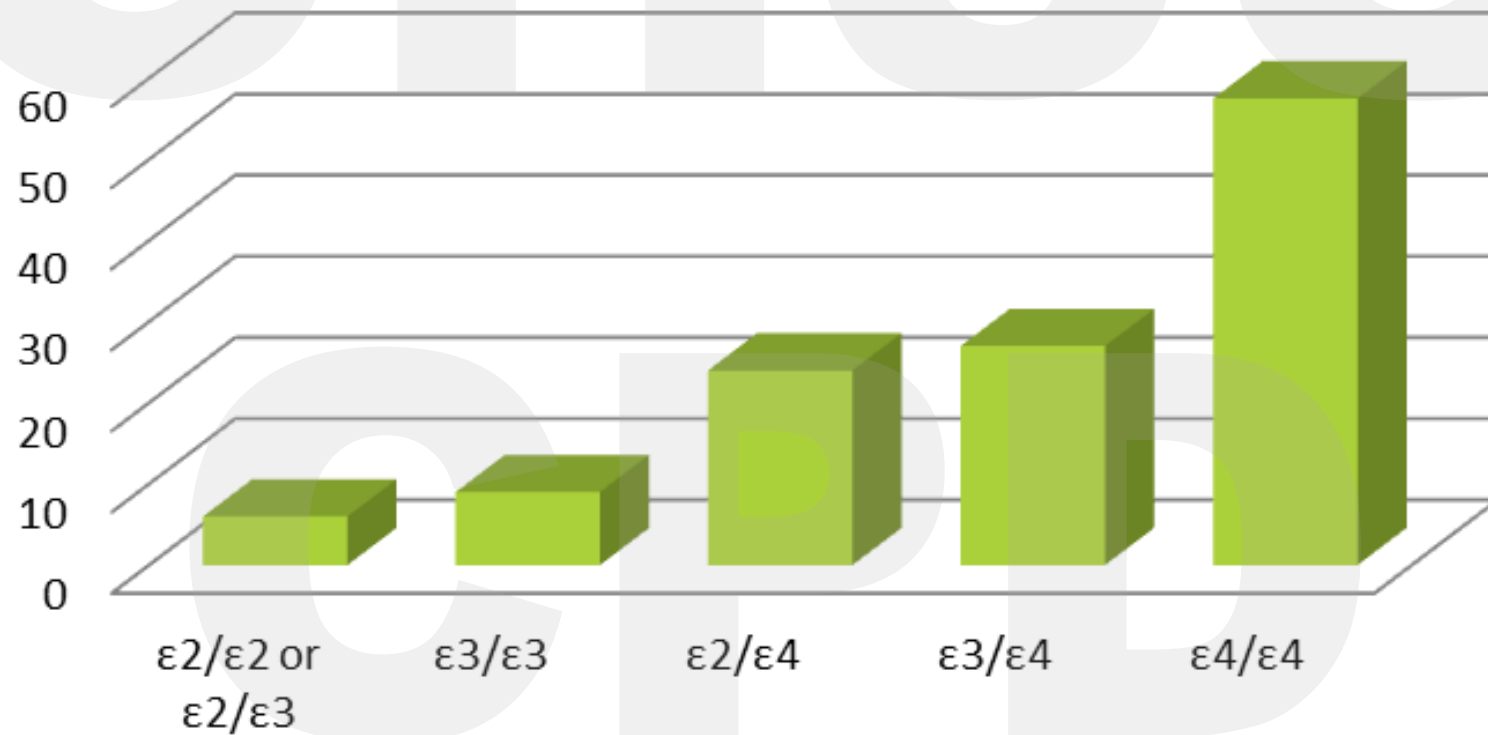
Genes

- An inherited (purely genetic) form of AD exists
 - ~1% of all cases
 - Caused by mutations to one of 3 genes – APP, PS1, PS2
 - Autosomal dominant
 - Very early-onset 30s, 40s, 50s
- For the other 99% of AD cases
 - Risk is increased approximately 3 fold for having a parent with AD
 - Stronger effect for maternal than paternal family history
 - Later onset 60s +
 - Multiple genes are involved -

Alzheimer's disease *risk factor* genes

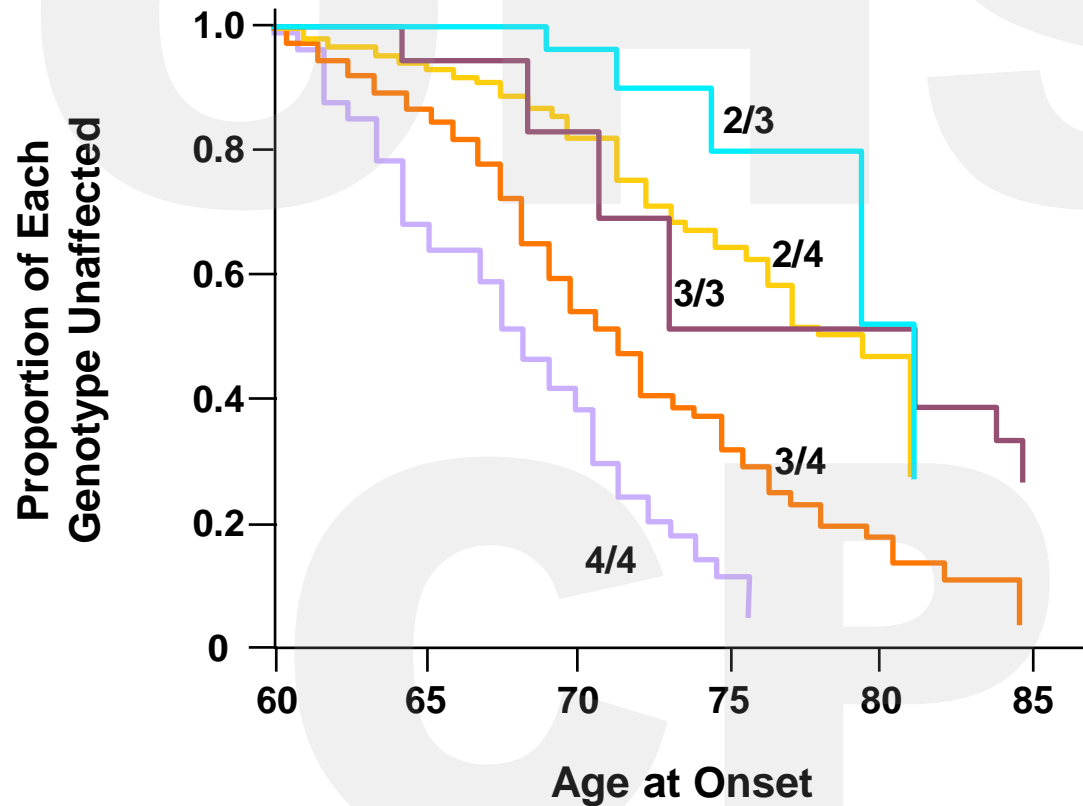
- Several have been identified, however the most common is APOE
- APOE is a lipid transport protein, why it affects AD risk is not fully known
- 3 versions of APOE: e2,e3,e4
- 1 copy from each parent
- APOE e4 is associated with risk of AD

Approximate Lifetime Risk (%) of Alzheimer's Disease Based on ApoE Genotype*



Corder EH, et al. *Science*. 1993;261:921-923.

ApoE4: A Susceptibility Gene Variant for Common Forms of Alzheimer's Disease

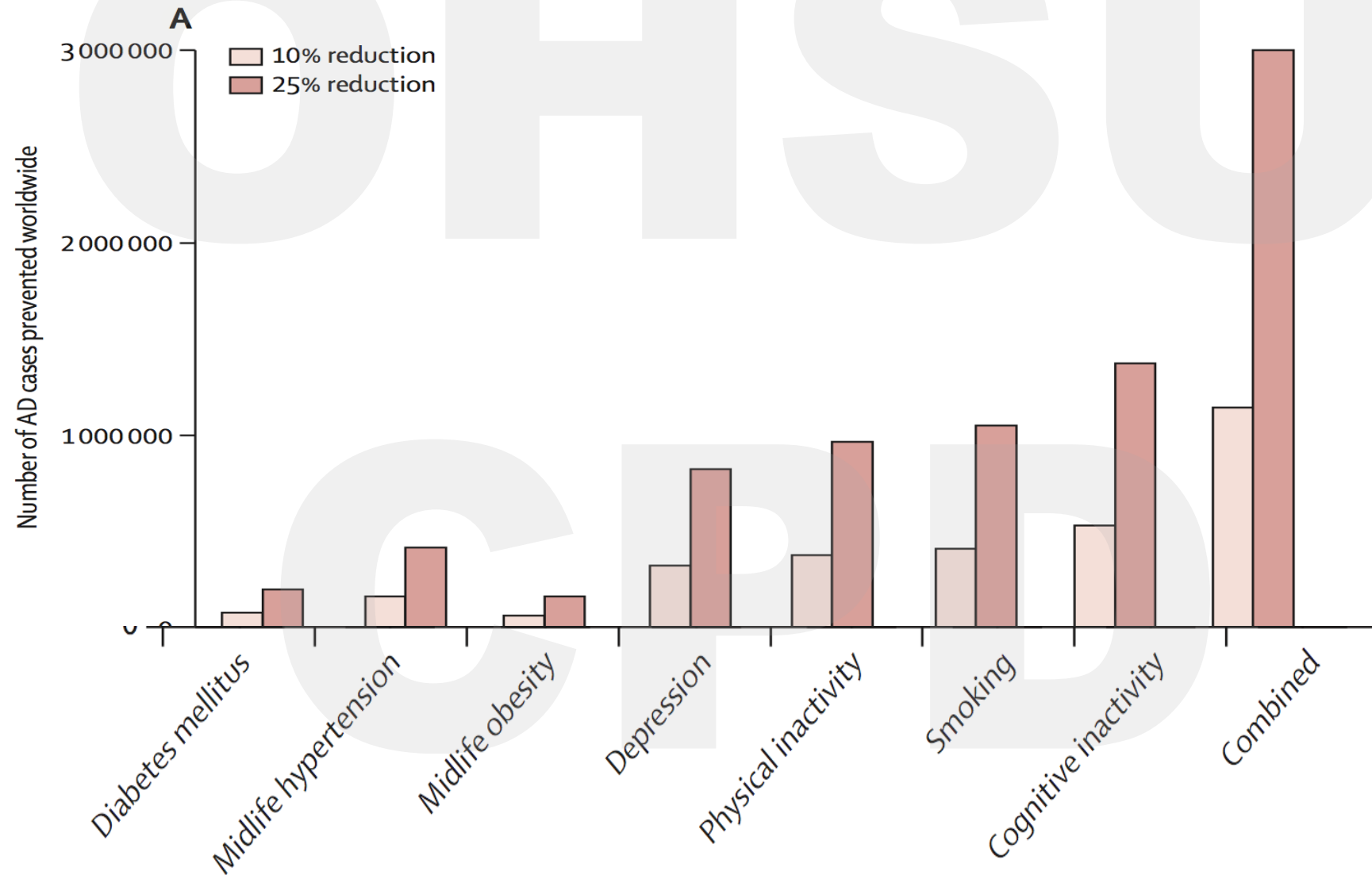


Mean age of onset of Alzheimer's disease as a function of the inheritance of the 5 common ApoE genotypes

APOE and risk of Alzheimer's disease

- You can have APOE e4/e4 or e3/e4 and never get Alzheimer's disease
- You can get Alzheimer's disease and not carry any copies of APOE e4
- General AD prevention measures apply whether you are an APOE e4 carrier or not
- I do not generally recommend this genetic test in healthy adults, *except for research*

Environment and Lifestyle



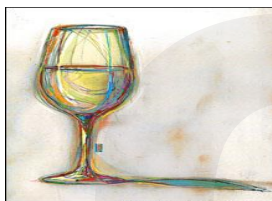
Barnes and Yaffe, *Lancet Neurol*, 2011.

Keep a Healthy Brain

- Eat a healthy (Mediterranean) diet
- Control diabetes
- Control hypertension
- Get a good night's sleep
- Protect your brain (wear a helmet)
- Keep your mind active
- Get regular exercise

Dieting Away from Dementia

- Many suggestions of dietary methods to avoid dementia
 - Barberger-Gateau et al
 - Daily consumption fruits and vegetables reduced risk for all-cause dementia
 - Weekly consumption of fish associated with reduced risk for AD
- Epidemiologic, not randomized controlled studies



Chronicle / Lance Jackson

Diet



	Diagnosis	Design	Number	Outcome	Intervention/Measure	Results
NUTRITION						
Barberger-Gateau et al. [43]	Healthy subjects	Prospective Cohort	8085	Dementia	Fruit and vegetable intake versus fish and omega-3 fat	Decreased risk for dementia with high fruit, vegetable, fish and omega-3 fat intake
Luchsinger et al. [44]	Healthy subjects	Prospective Cohort	980	AD	Daily intake of calories, carbohydrates, fats and proteins	Increased risk for AD with increased caloric and fat intake
Morris et al. [45]	Healthy subjects	Prospective Cohort	1718	Cognition	High versus low fruit and vegetable intake	Slower cognitive decline with high vegetable intake
Scarmeas et al. [46, 47]	Healthy subjects	Prospective Cohort	2258	AD	Adherence to Mediterranean diet versus no adherence	Decreased risk for AD with increased adherence to Mediterranean diet
Morris et al. [45]	Healthy subjects	Prospective Cohort	1041	AD	Nutritional folate, B12, B6 vitamins	No association

Polidori, et al. International J of AD 2010



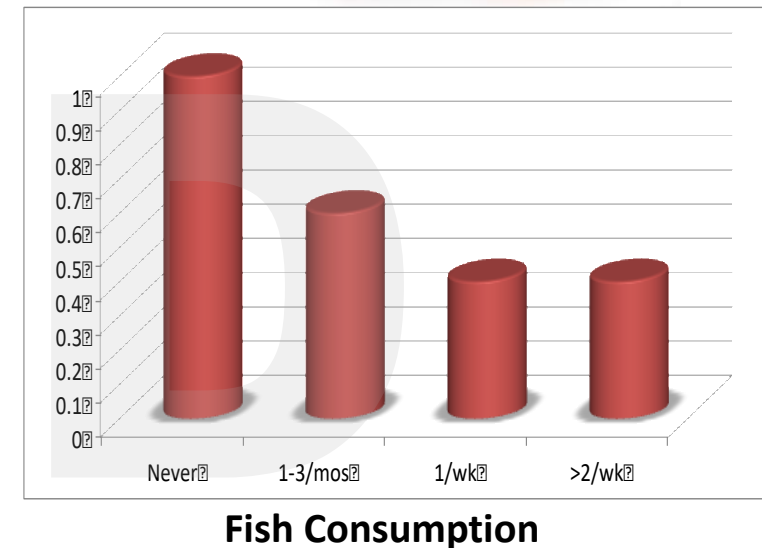
Barberger-Gateau, et al. BMJ 2002
 Luchsinger, et al. Archives of Neurology 2002
 Morris, et al. Neurology 2006
 Scarmeas, et al. Archives of Neurology 2006
 Scarmeas, et al. Annals of Neurology 2006

Dieting Away from Dementia

- Healthy diet (**Mediterranean**, **DASH**, or “**Mind**” Diets) may reduce risk
- **Fish** (omega-3 fatty acids; salmon, herring, other cold-water fish)
- **Fruits and vegetables** (antioxidants and anti-inflammatories: leafy greens [kale, spinach, brussel sprouts, collard greens], deeply hued produce [eggplant, bell peppers, tomatoes, and berries])
- **Olive oil** (monounsaturated fat: extra virgin)
- **Nuts** (monounsaturated fat: walnuts, pine nuts, pistachios, almonds)
- **Beans** (red kidney, pinto)
- **Red wine** (resveratrol, flavonoids: moderate consumption)



AD Risk



Morris et al. Arch Neurol 2003.

Maximize General Health: cerebrovascular health



- Treat hypertension
- Strict glucose control for diabetics
- Stop smoking

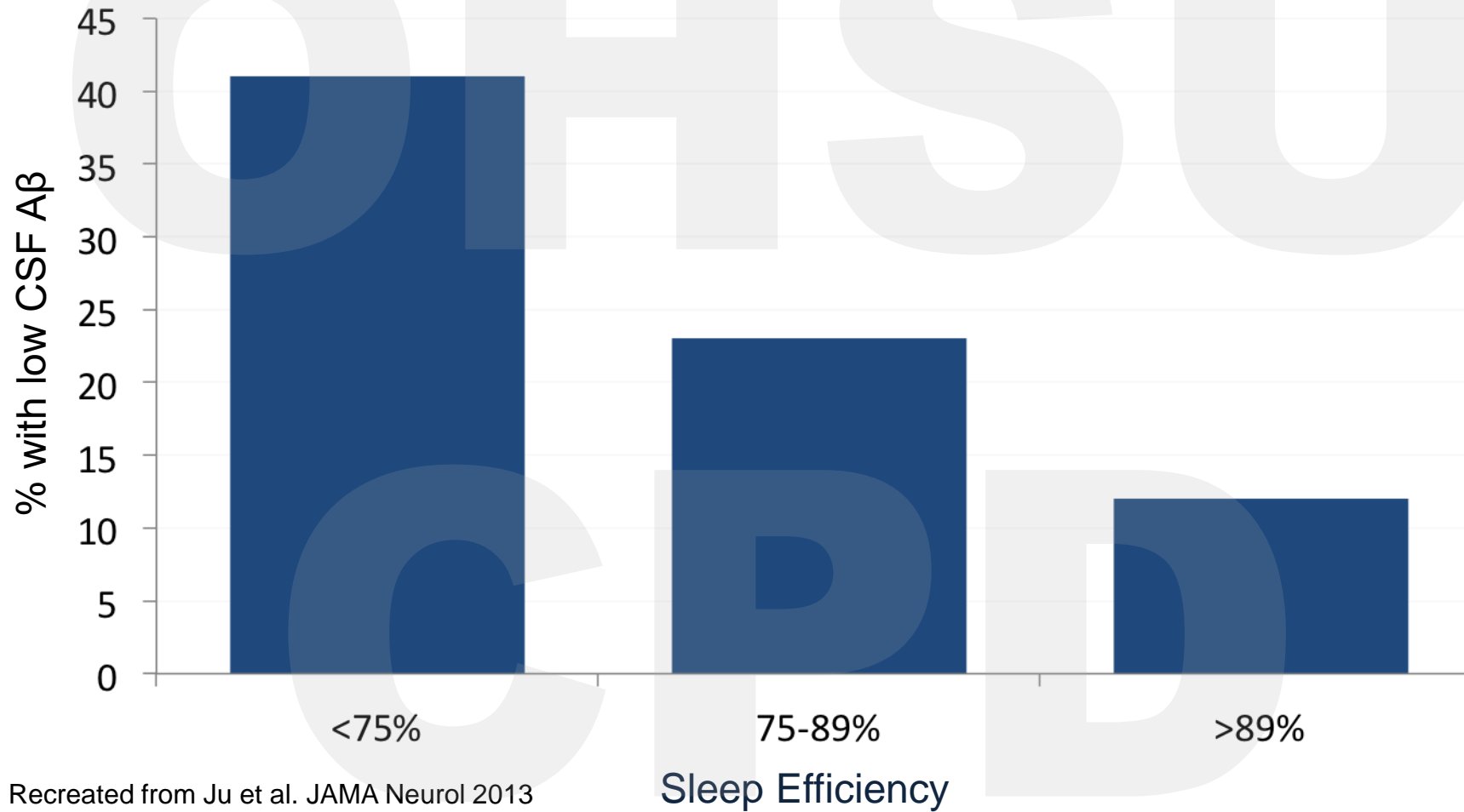
Hypertension

- The brain only weighs 2% of our body weight, but it uses 20% of our blood oxygen



Zlokovic and Apuzzo,
Neurosurgery, 1998.

Sleep and Amyloid β



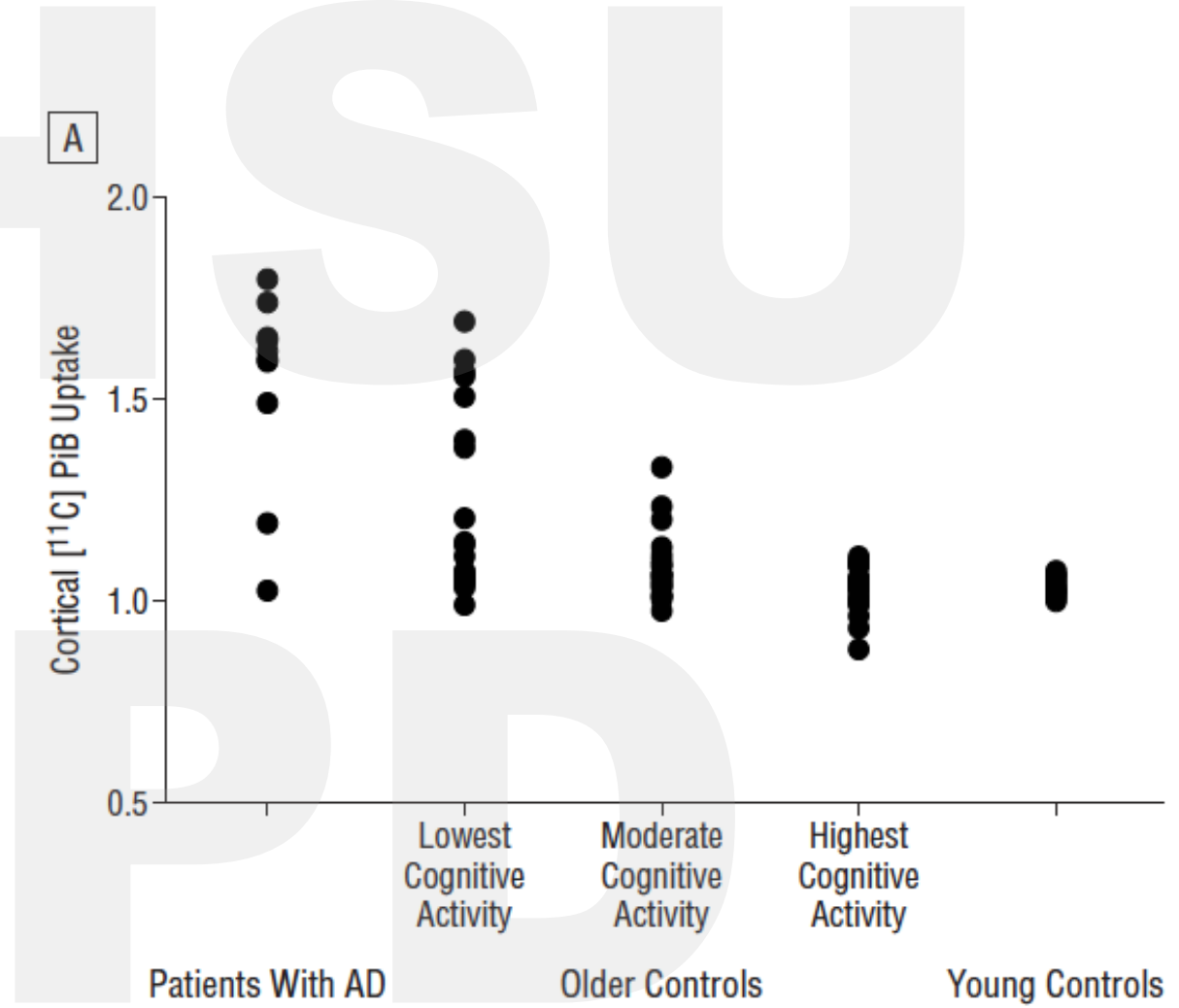
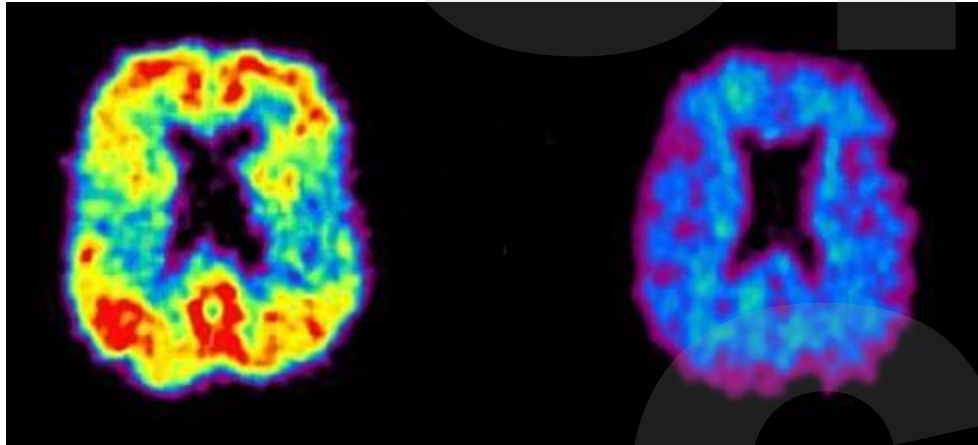
Head Trauma (Traumatic Brain Injury)

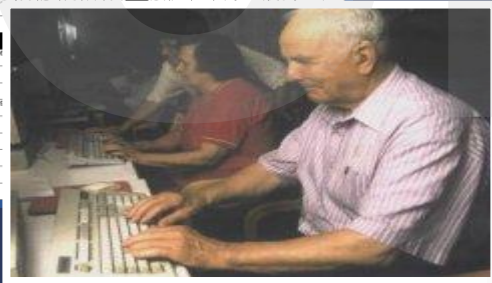
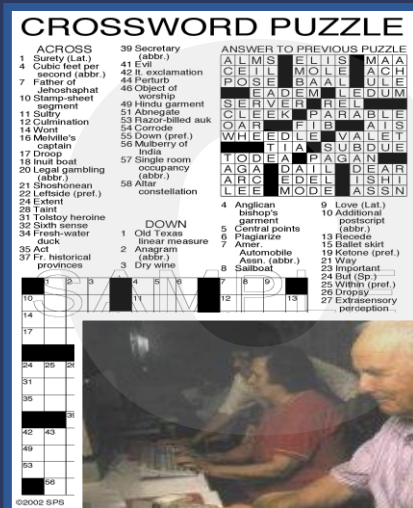
- Persons who experience head trauma are more likely to develop AD later in life
 - May interact with genotype
 - Injury may increase A β production
 - Recovery may increase A β production

Cognitive Activity in Older Persons

- Cognitively inactive persons over the age of 65 are 2.6 times more likely to develop AD
- Social network size modifies the association between disease pathology and cognitive function
 - Assuming equal pathology, a person with a greater social network will have better cognitive function

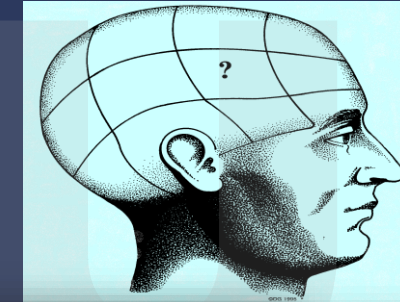
Lifetime Cognitive Activity is Associated with Reduced Levels of A β





Polidori, et al. International J of AD 2010

Exercise - mental



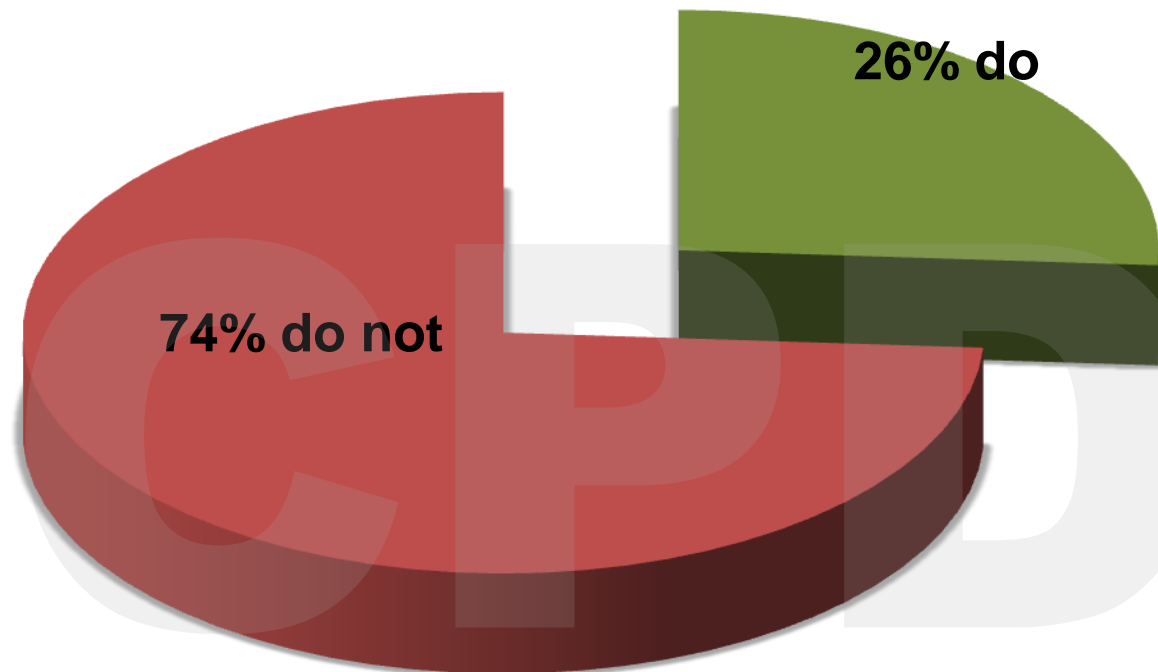
	Diagnosis	Design	Number	Outcome	Intervention/Measure	Results
Scarmeas et al. [36]	Healthy subjects	Prospective cohort	1772	Dementia	Leisure activities	Decreased risk for dementia
Wang et al. [37]	Healthy subjects Kungsholmen project	Prospective cohort	152	Dementia	Intellectual and social stimulation	Decreased risk for dementia
Verghese et al. [29]	Healthy subjects	Prospective cohort	469	Dementia	Leisure activities	Decreased risk for dementia
Karp et al. [38]	Healthy subjects Kungsholmen project	Prospective cohort	776	Dementia	Mental, physical or social activity versus two or more	Decreased risk for dementia with increasing number of activities
Verghese et al. [35]	Healthy subjects of the Bronx Aging Study	Prospective cohort	437	Amnesic MCI	Leisure activities	Decreased risk for MCI with increasing number of activities
Willis et al. [39]	Healthy subjects	RCT	2832	Cognition	Verbal episodic memory training versus Inductive reasoning training versus visual search and identification training versus no training	Improved cognition with any training type
Helzner et al. [40]	AD	Prospective cohort	287	Cognition	Leisure activities	No association
Wilson et al. [41]	Healthy subjects from Rush Memory and Aging Project	Prospective cohort	770	MCI	Cognitive activities	Decreased risk for MCI with increased cognitive activity

Mentally Stimulating/Leisure Activities

- Puzzles
 - Crossword
 - Sudoku
- Traveling
- Knitting
- Gardening
- Reading/Book clubs
- Movie clubs
- Board games
 - Chess
 - Checkers
- Musical instruments
- Visiting museums
- Attend plays

30 Minutes of Moderate Exercise is Recommended for Adults

% American adults who get the recommended 30 minutes of moderate exercise most days of the week



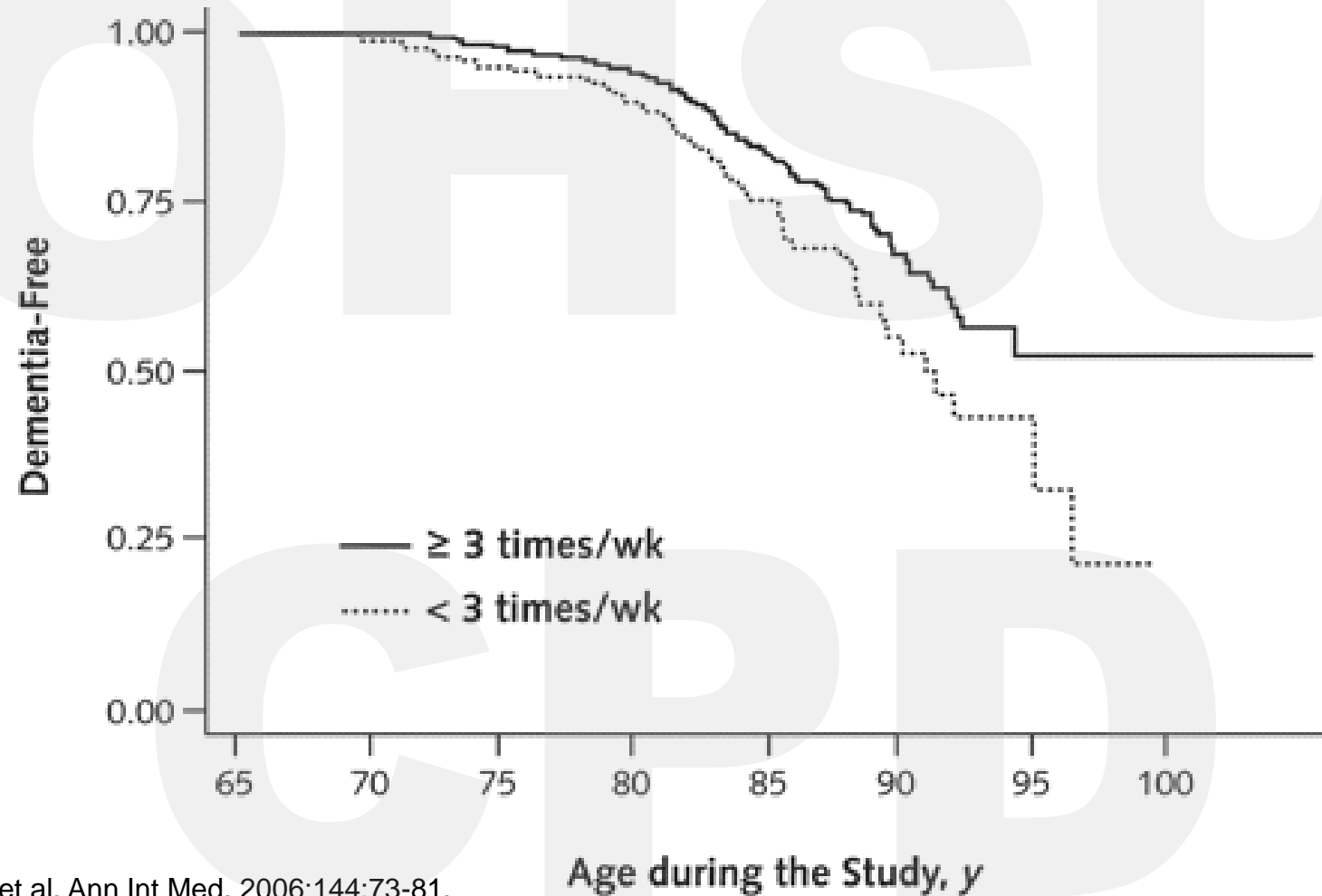
Frequent Cardiovascular Exercise Lowers Risk for:

- Diabetes
- Hypertension
- Obesity

Cerebral Effects of Exercise

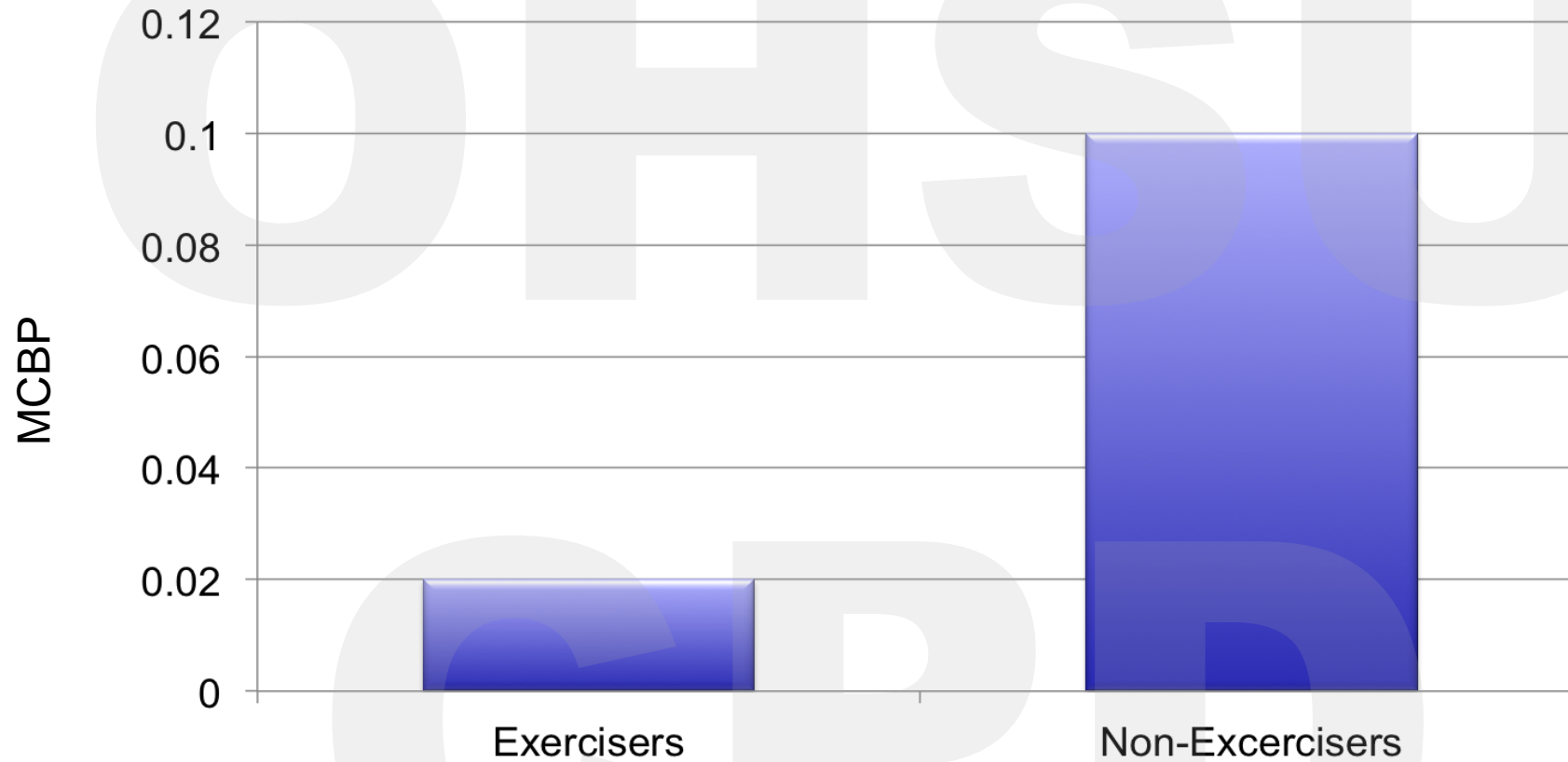
- Effects on neurogenesis
 - Proliferation
 - Neuronal fate
- Angiogenesis
- Blood flow
- Production of neurotrophic factors

Exercise Decreases Risk for Dementia



Larson EB, et al. Ann Int Med. 2006;144:73-81.

Brain Amyloid Levels and Exercise

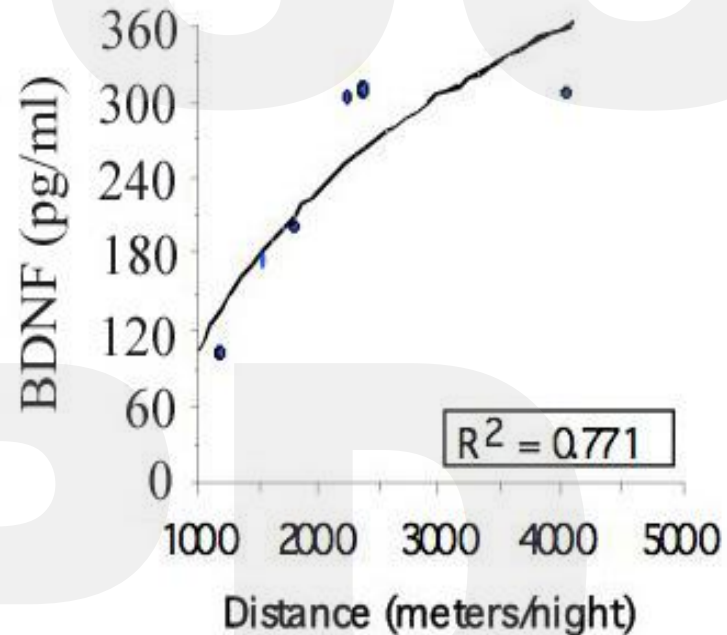
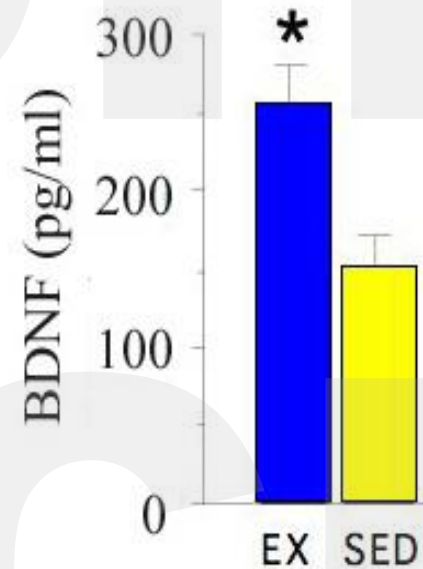
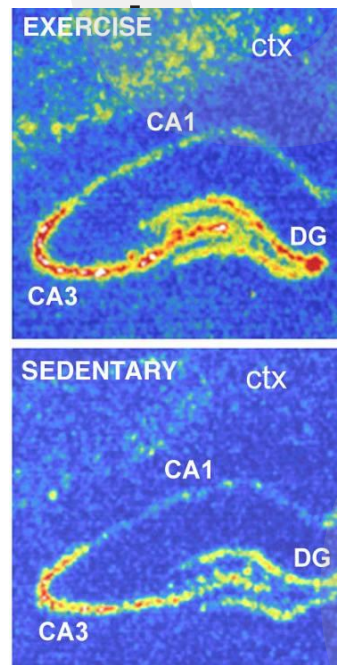


Do or do not follow the recommendation of the American Heart Association (AHA) for older adults: 30 minutes of moderate exercise 5 days/wk

Liang et al. Ann Neurol, 2010

Exercise increases BDNF levels in the hippocampus

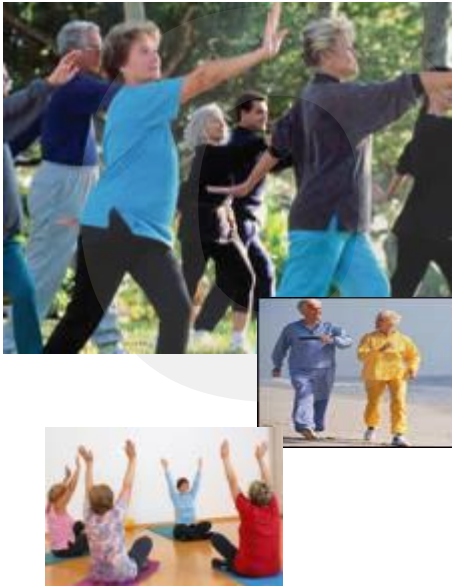
HIPPOCAMPUS



Rats: 1, 4 weeks wheel-running

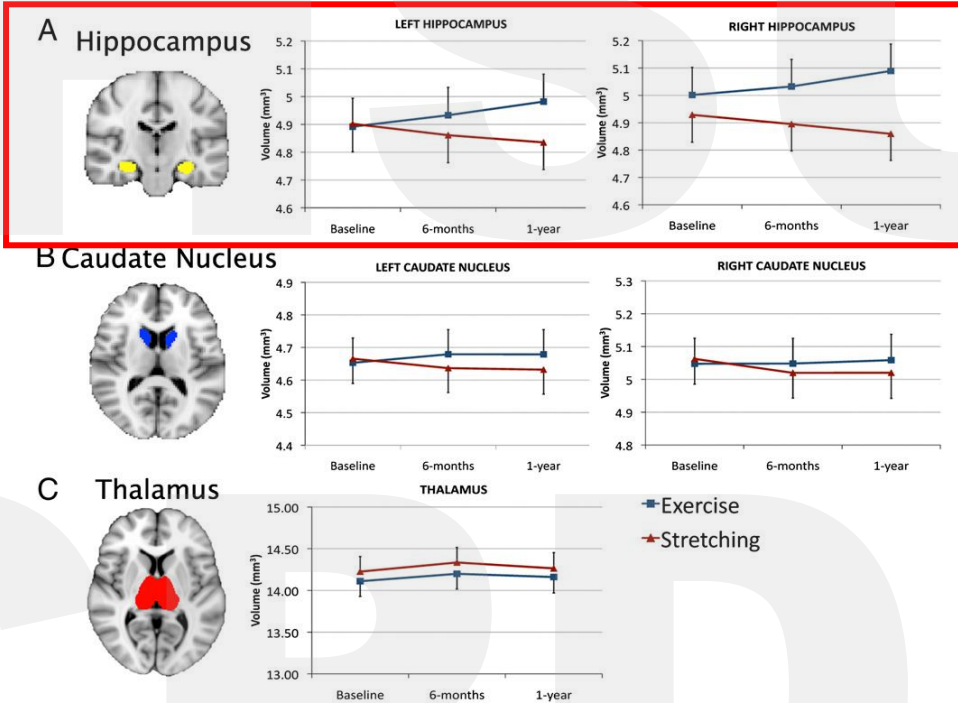
Neeper, 1995; Berchtold et al., 2002; Adlard et al., 2005

RTC: Exercise and hippocampal volume



- 120 older adults randomized to:
1. Aerobic exercise group
-moderate intensity 3 dys/wk
(walking x 40 minutes)
 2. Stretching control group

Mean age 67 yrs



Erikson, et al, Proc Natl Acad Sci USA vol 108, 3017-3022, 2012

Exercise - physical



	Diagnosis	Design	Number	Outcome	Intervention/Measure	Results
PHYSICAL ACTIVITY						
Baum et al. [24]	Mild Dementia (mean MMSE 21/30)	RCT	20	Cognition	Strength training or recreational therapy 6 months	Improved MMSE with physical activity
Van de Winkel et al. [25]	Severe Dementia (mean MMSE 13/30)	RCT	15	Cognition	Physical activity + music or conversation 3 months	Improved MMSE with physical activity
Weuve et al. [33]	Healthy women	Prospective cohort Nurses' Health Study	766	Cognition	Physical activity and walking	Better cognitive function/less cognitive decline with physical activity and walking
Stevens and Killeen [26]	Mild and Severe Dementia (MMSE 9-23/30)	RCT	75	Clock drawing test	Physical activity or social visit or none	Slower cognitive decline with physical activity
Lautenschlager et al. [27]	Subjective memory impairment	RCT	308	Dementia	Education and usual care versus physical activity for 6 mos	(Modest) Cognitive improvement at 18 mos
Brown et al. [28]	Healthy subjects	RCT	134	Cognition	Balance versus general training	Cognitive improvement at 6 months
Verghese et al. [29]	Healthy subjects	Prospective Cohort	469	Dementia	Physical activity versus Leisure/Cognitive Activity	Decreased risk for dementia
Abbott et al. [30]	Healthy subjects	Prospective cohort Honolulu Asia Aging	2257	Dementia	Physical activity, walking	Decreased risk for dementia
Larson et al. [31]	Healthy subjects	Prospective cohort	1740	Dementia	Physical exercise	Decreased risk for dementia
Cassilhas et al. [32]	Healthy subjects	RCT	62	Cognition	Moderate or High-level resistance training	Improvement of cognition with both levels of resistance training

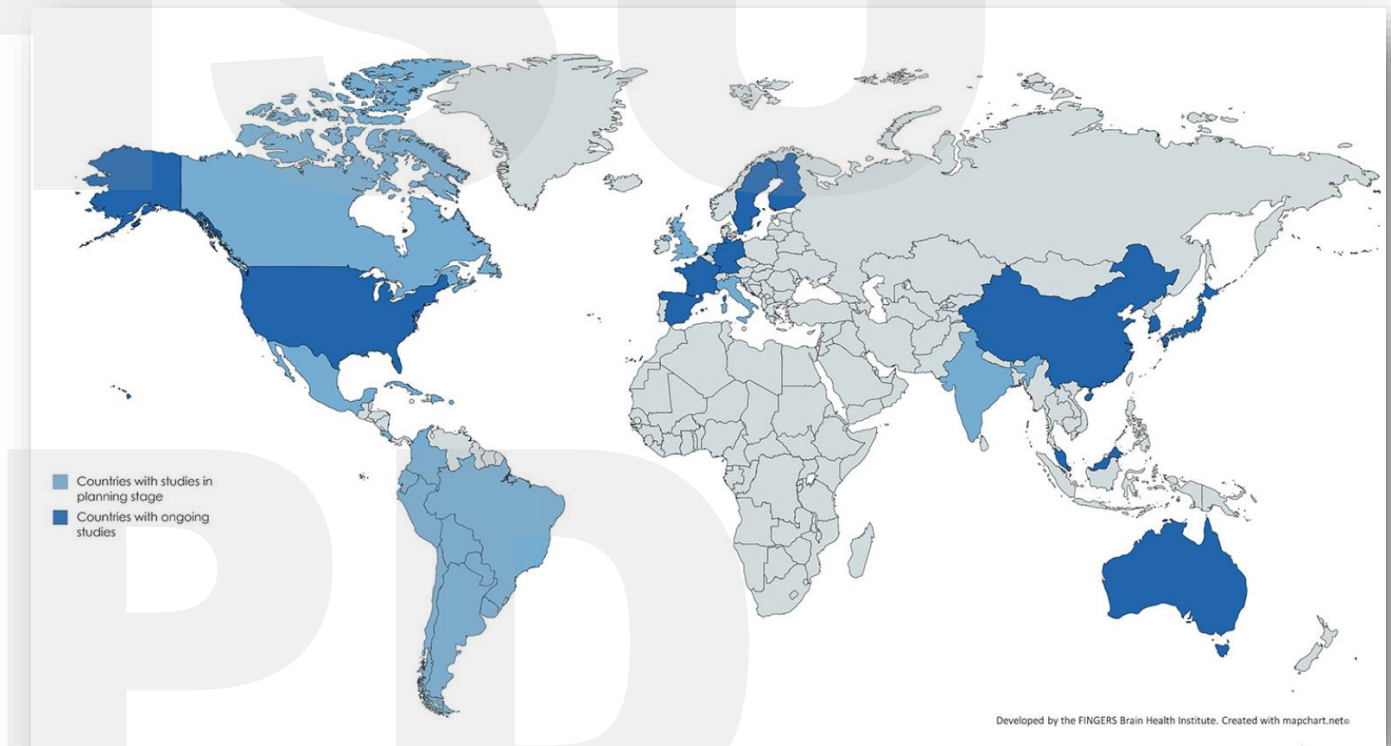
Polidori, et al. International J of AD 2010

Multidomain lifestyle interventions

- FINGER Study – Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- Enrolled 1260 seniors
- 2-year intervention:
 - Nutritional guidance
 - Physical exercise
 - Cognitive training
 - Social Activity
 - Intensive monitoring and management of metabolic and vascular risk factors
- Control group: general health advice
- Intervention group had beneficial effect on primary outcome – change in cognition on a neuropsychological test battery

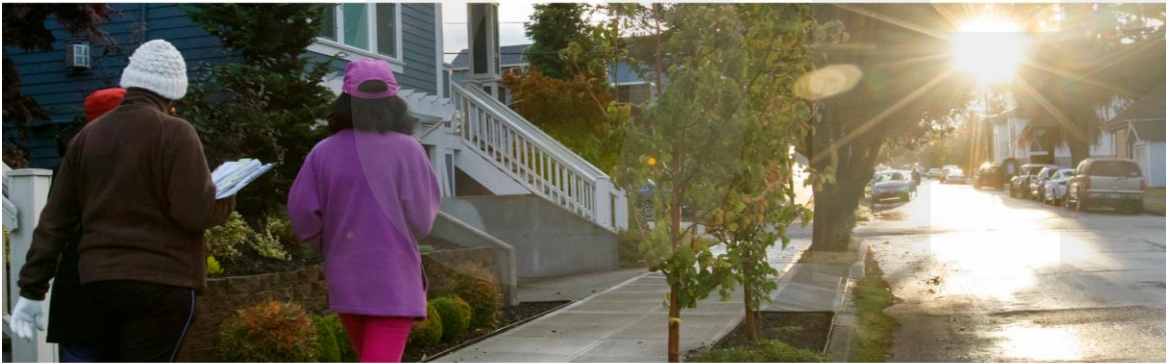
International collaborative projects

- Different groups of elderly may benefit from different interventions
- US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) – a 2 year trial testing multidomain intervention in 2500 adults age 60-79.
- World Wide FINGERS network – adapting and testing the FINGER model in diverse geographic and cultural settings



Testing lifestyle interventions: SHARP study

The SHARP Study



CELEBRATING HISTORY
AND ADVANCING
COMMUNITY HEALTH

ONE STEP AT A TIME

Collaborate With Us

The Sharing History through Active Reminiscence and Photo-Imagery (SHARP) study

Cognitive decline, including Alzheimer's disease, disproportionately affects Older African Americans; so does gentrification. SHARP strives to honor Black health and history. The SHARP study is a six month program in Portland, Oregon's historically Black neighborhoods that are undergoing rapid change. SHARP participants walk one-mile themed routes, equipped with a tablet and a digital recorder.

Our aims are to maintain or improve cognitive health among older African Americans through physical activity and social engagement in a culturally celebratory way that captures the oral history of Portland's historically Black neighborhoods.

The SHARP Study integrates these three brain-healthy behaviors



Physical Activity



Social Engagement



Reminiscence

NEIGHBORHOOD WALKING ROUTES

- Principal investigator Raina Croff, Ph.D. (OHSU)

Triad

- Physical activity
 - Social engagement
 - Reminiscence
-
- In African American seniors with normal cognition or MCI
 - Portland, Oregon's historically Black neighborhoods
 - Upcoming collaborations in other cities

www.sharpwalkingstudy.org

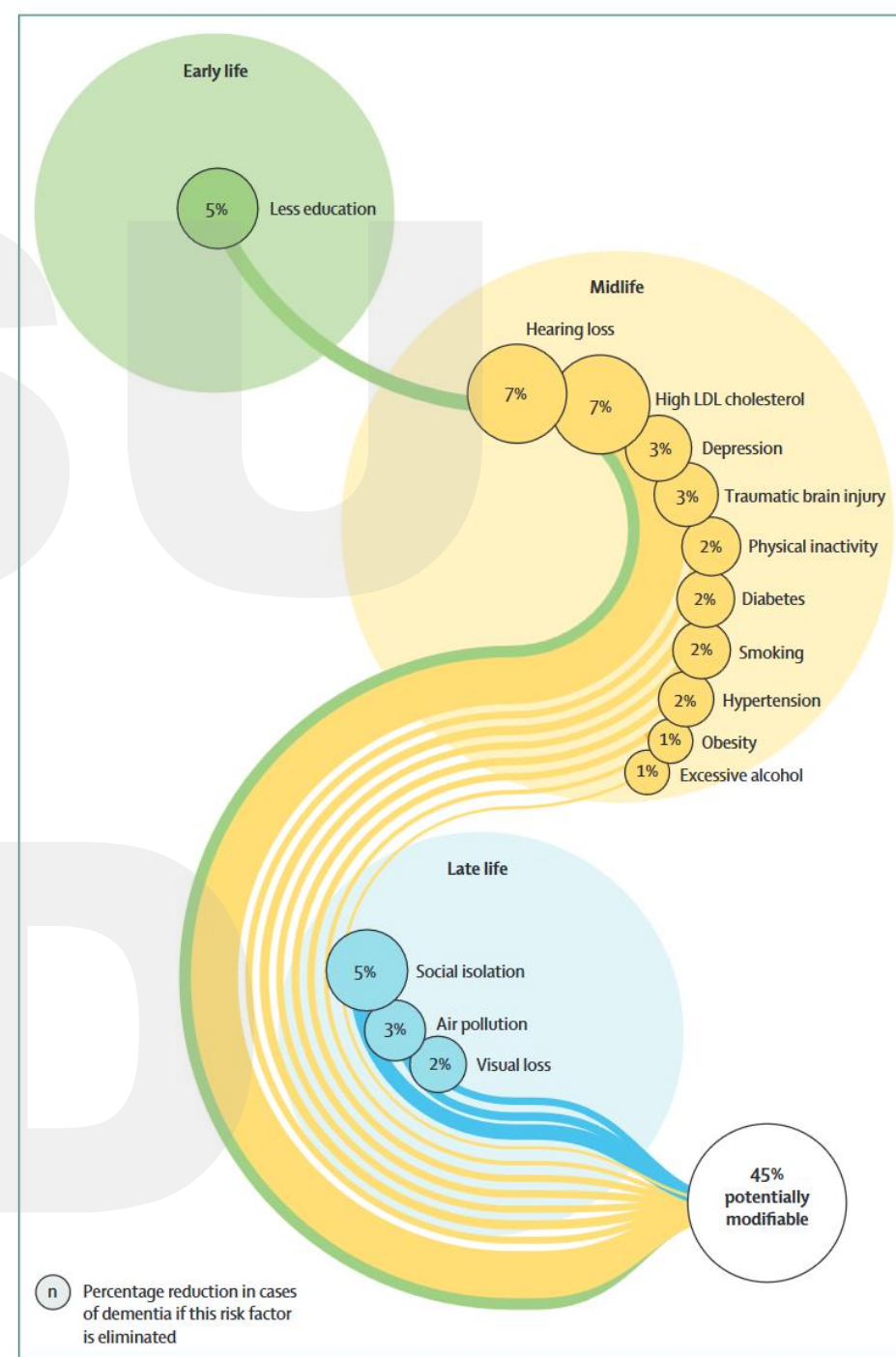
Challenges of randomized clinical trials of lifestyle interventions

- Double blinding is not possible, however outcome assessors should be blinded
- In cognitive training, intervention should not be too similar to outcome measures
- Timing – early initiation of intervention may lead to better results, but may lead to a very long term trial
- Choice of target populations
- Dose and adherence – focus on culturally relevant interventions

Is prevention of dementia possible?

- Up to 45% of risk of dementia may be reduced
- Recent breakthroughs in biomarker research, allowing detection of Alzheimer's disease in living people before symptoms start, have us poised to test Alzheimer's prevention strategies in the populations at highest risk
- Alzheimer's prevention research is challenging and exciting, and must be inclusive
- Sharing the potential of Alzheimer's prevention in an equitable manner requires commitment on the part of individuals, communities, nations, and the world

The Lancet Commission, 2024



Keep a Healthy Brain

- Eat a healthy (Mediterranean) diet
- Control diabetes
- Control hypertension
- Get a good night's sleep
- Protect your brain (wear a helmet)
- Keep your mind active
- Get regular exercise

Take home points

- Alzheimer's disease is the most common cause of dementia
- The major risk factors for Alzheimer's disease are "AGE"
 - Age
 - Genetics
 - Environment
- Risk may be reduced up to one-third
- Focus on brain health measures
 - Reduce cardiovascular risk
 - Cognitive, social, and physical exercise
 - Hearing and vision correction

Resources



The NIA-Layton Alzheimer's Disease Research Center (ADRC) at OHSU

We are the only
Federal designated
and funded
Alzheimer's disease
institute in Oregon



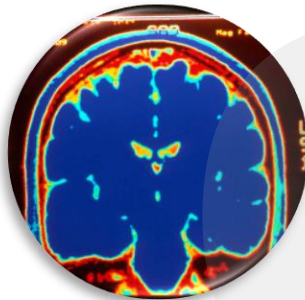
Contact us
Phone: 503-494-7647

Email:
adoutreach@ohsu.edu

Registry:
alzactnow.org



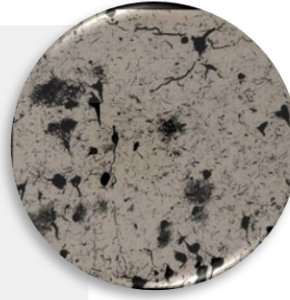
**Administrative
Core**



Clinical Core



**Education
Core**



**Neuropath
Core**



Data Core



**Biomarker
Core**



**Neuroimaging
Core**

Oregon ECHO Network: Community of Practice

Information and support for clinicians who care for those with dementia

Dementia Community of Practice

- Free, with free CME.
- **Audience:** Neurologists; primary care clinicians including MDs, DOs, NPs, and PAs; nurses; social workers; case managers; pharmacists; administrators; quality improvement specialists; and other interested team members
- **Schedule:** 9 sessions. Third Tuesday of each month, 12:00 - 1:00 p.m., PT, September 17, 2024 - June 17, 2025
- More info and registration at:
<https://www.oregonechonetwork.org/communities-of-practice>

Thank you!

Any questions?

