

# *Is prevention of Alzheimer's disease possible?*



Brain Awareness Lecture Series  
*April 8, 2023*

Aimee Pierce, MD  
Associate Professor, Neurology  
Layton Aging and Alzheimer's Disease Center  
Oregon Health & Science University



## Disclosures/Conflict of Interest

- I am site-principal investigator for Alzheimer's disease clinical trials funded or sponsored by Eli Lilly, Eisai, Alector, and the National Institute on Aging.

## Outline

1. Alzheimer's disease background
2. Biomarkers
3. Prevention strategies
4. Current research

### **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*

**P**ercentage of Adults Aged 65 and Older with Alzheimer's Disease by Race and Ethnicity



296249A



[www.cdc.gov/aging](http://www.cdc.gov/aging)

Centers for Medicare and Medicaid Services, 2014

**A**lzheimer's Disease Projected to Nearly Triple by 2060



Census Population Projections Program, 2014 to 2060

### 2023 ALZHEIMER'S DISEASE FACTS AND FIGURES

**More than 6 million Americans** are living with Alzheimer's

**Over 11 million Americans** provide unpaid care for people with Alzheimer's or other dementias. These caregivers provided more than 18 billion hours valued at nearly **\$340 billion**.

It kills more than **breast cancer + prostate cancer** combined. The lifetime risk for Alzheimer's at age 45 is **1 in 5** for women and **1 in 10** for men.

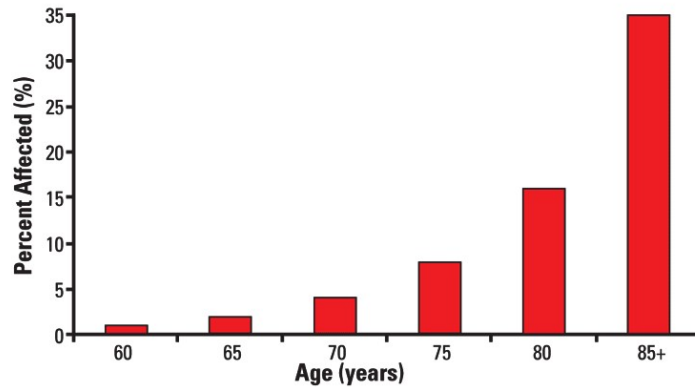
Between 2000 and 2019, deaths from heart disease has **decreased 7.3%**, while deaths from Alzheimer's disease have **increased 145%**.

In 2023, Alzheimer's and other dementias will cost the nation **\$345 billion**. By 2050, these costs could rise to nearly **\$1 trillion**.

While only 4 in 10 Americans talk to their doctor right away when experiencing early memory or cognitive loss, 7 in 10 would want to know early if they have Alzheimer's disease if it could allow for earlier treatment.

ALZHEIMER'S ASSOCIATION

**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.

Please email questions to [spoden@ohsu.edu](mailto:spoden@ohsu.edu)

## 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

## Dementia

- Not a normal part of aging
- Characterized by problems with:
  - Language
  - Memory
  - Judgment
  - Reasoning
- Problems with thinking impact day-to-day life
- Many causes of dementia



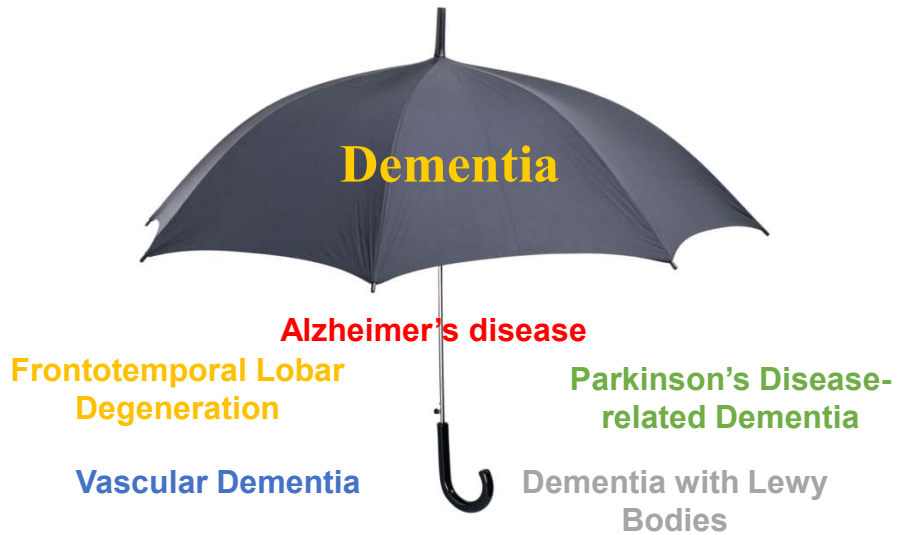
### **Complex activities:**

Employment  
 Finances and other paperwork  
 Medication management  
 Managing appointments  
 Driving  
 Shopping  
 Cooking

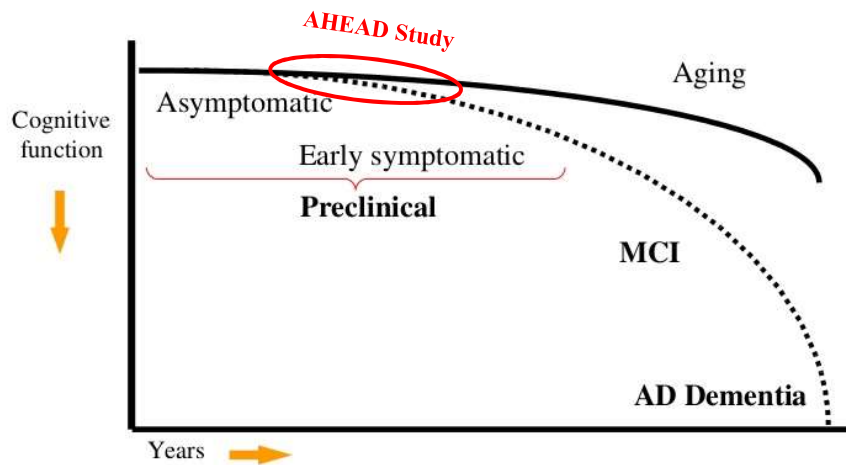
### **Basic activities**

Eating  
 Dressing  
 Bathing  
 Toileting

# What is Dementia?



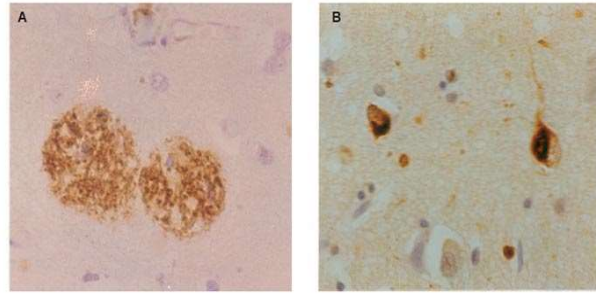
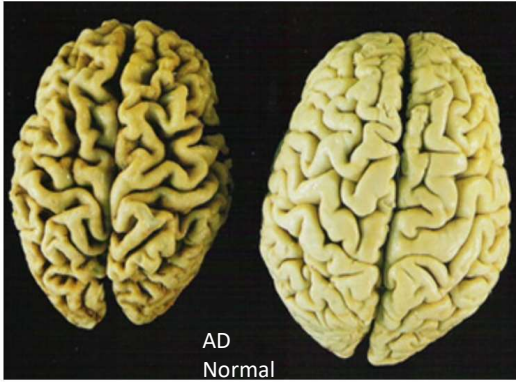
# The continuum of Alzheimer's disease



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

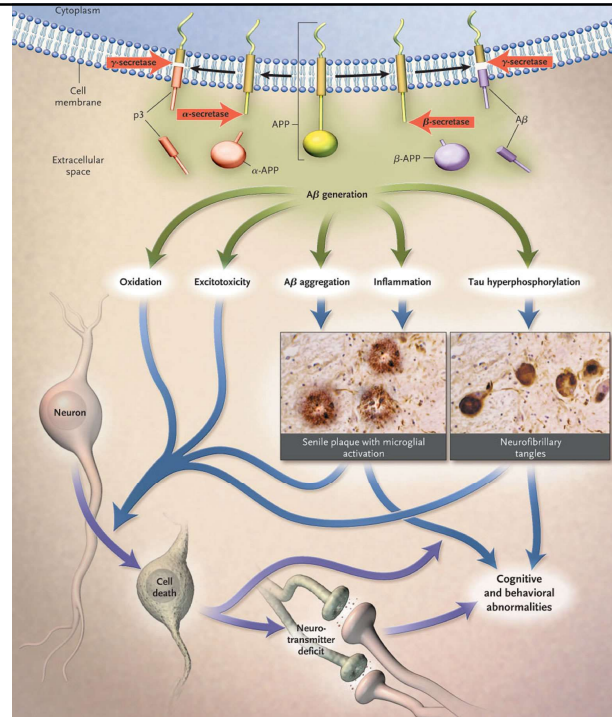
# Alzheimer's Disease

- Pathology: cerebral atrophy, amyloid plaques, and neurofibrillary tangles



**FIGURE 1**  
Neuropathology of Alzheimer's disease: **A**,  $\beta$ -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 ( $\beta$ -amyloid immunohistochemistry). **B**, neurofibrillary tangles (NFT) in the cerebral cortex appearing as inclusion bodies within neurons (tau immunohistochemistry).

## Amyloid Cascade Hypothesis



## Biomarkers of Alzheimer's disease

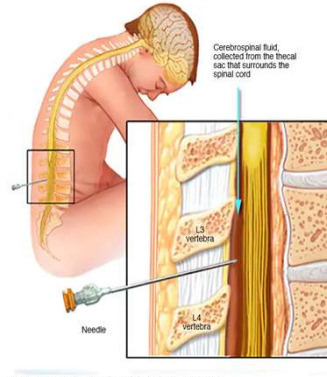
### Brain imaging

- PET scans
- Amyloid
- Tau



### Cerebrospinal fluid (CSF)

- Amyloid
- Tau

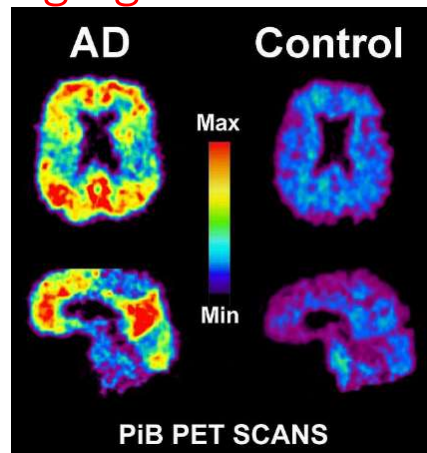


### Blood

- Amyloid
- Tau

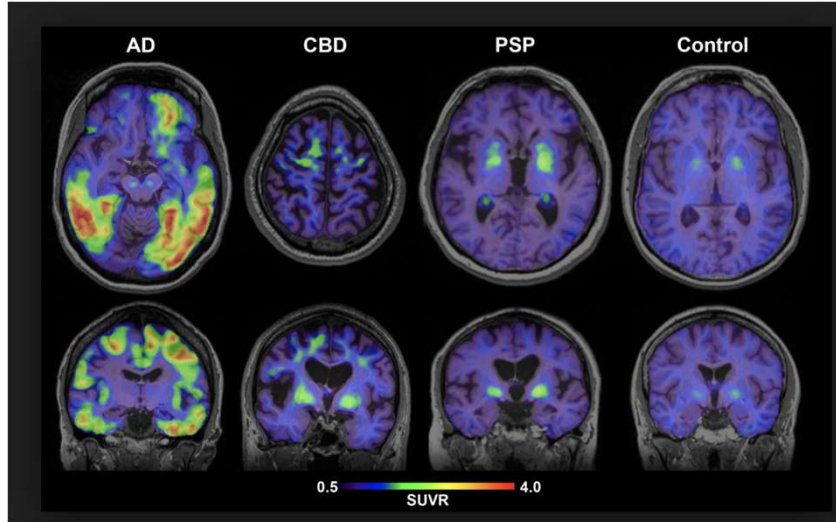


## Dementia workup: Biomarkers - Amyloid PET Imaging



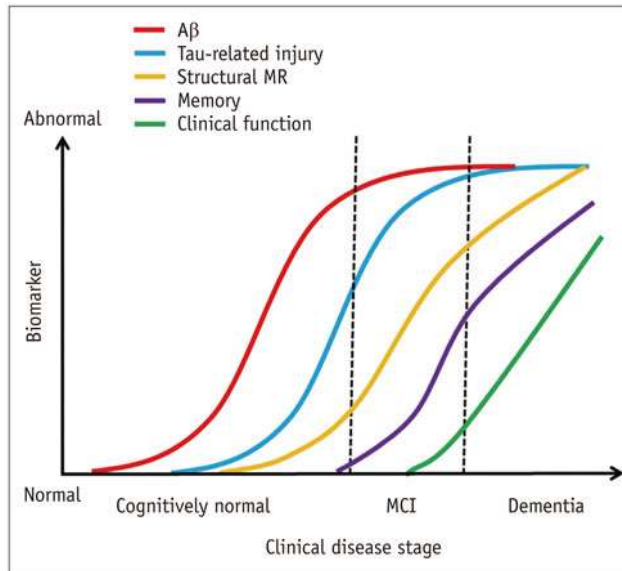
Sperling, Johnson, *NeuroMolecular Med*, 2010

# Tau PET Imaging



Ossenkoppele R, et al. *JAMA* 2018.

# Biomarker Progression



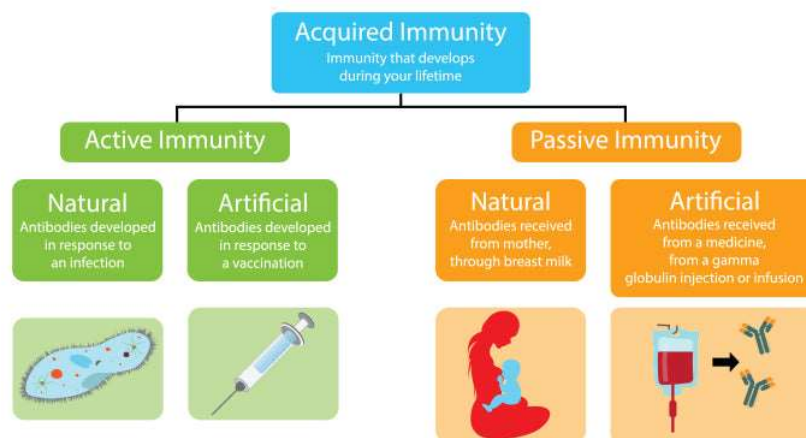
Jack CR, et al. *Lancet Neurol*, 2013.



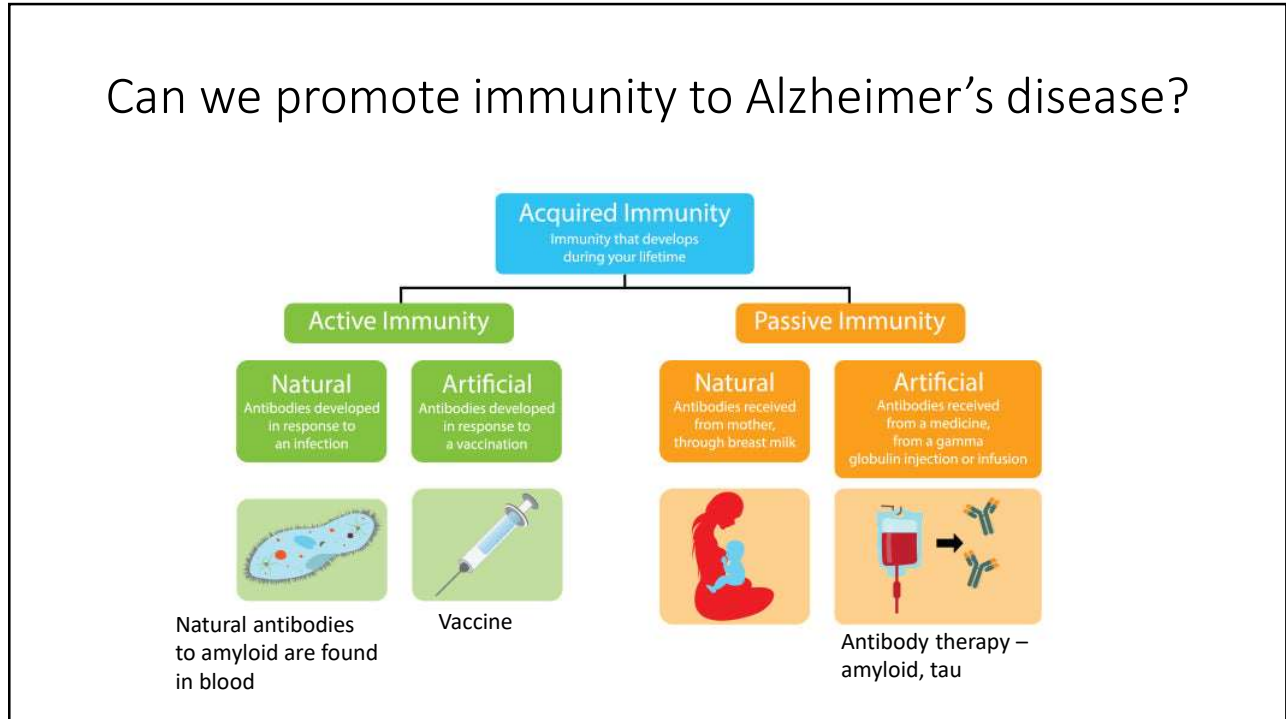
## Major targets for Alzheimer's prevention

1. Anti-amyloid:
  - Reduce production
  - Reduce toxicity
  - Increase clearance
2. Anti-tau
3. Metabolism/Inflammation
4. Neuroprotection
5. Genes
6. Multi-domain lifestyle

## Understanding the concept of immunity



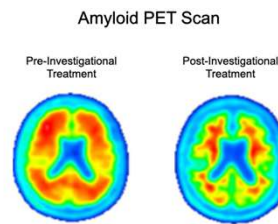
# Can we promote immunity to Alzheimer’s disease?



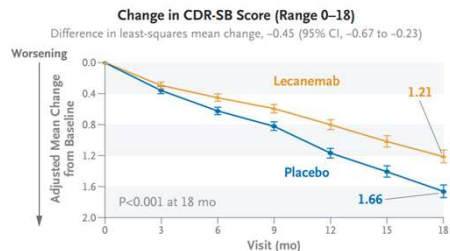
## 1. Anti-amyloid

- Many clinical trials targeting amyloid were negative, until...
- Accelerated FDA approval for two anti-amyloid antibodies - Aducanumab (2021) and Lecanemab (2023)

- Every antibody is different – those which can remove plaque have shown benefit on memory
- Current trials selected participants more stringently and treat earlier and longer



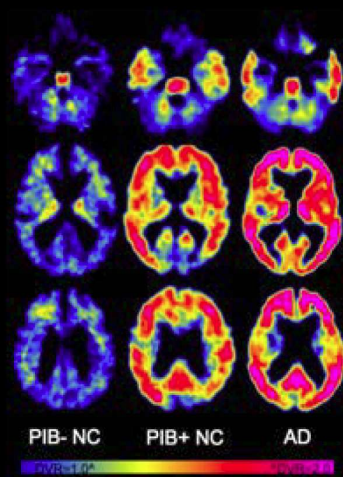
Amyloid PET imaging scans from a representative participant in the Phase 2 trial of BAN2401 (lecanemab)—the investigational treatment being tested in the AHEAD Study. Amyloid PET scans measure the levels of amyloid plaque in the brain. The image on the left is taken before the participant has started 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)



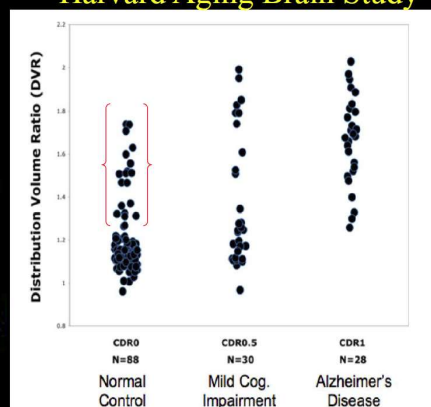
## Need for earlier intervention in Alzheimer's disease

- Intervention prior to dementia (widespread irreversible brain cell loss) may likely have better chance of changing the course of disease
- Think about what happens in cancer, atherosclerosis, osteoporosis... if we wait to treat until after symptoms appear?

## PET Amyloid Imaging



### Harvard Aging Brain Study



Sperling, Johnson *NeuroMolecular Med* 2010

# AHEAD Study: Anti-Amyloid Treatment in Preclinical Alzheimer’s Disease with Elevated or Intermediate Amyloid

Share Tweet LinkedIn Share Email Print

OHSU part of clinical trial aiming to prevent Alzheimer’s before symptoms start

Participant says she’s committed to preventing Alzheimer’s in her daughters’ generation

By Erik Robinson January 26, 2023 Portland, Oregon



Amyloid accumulates in the brain a decade or more before memory loss symptoms

This study aims to enroll 1400 healthy older adults with normal memory and intermediate or elevated amyloid, and treat them with an anti-amyloid antibody – lecanemab

Initial screening based on blood test for amyloid

Participants will receive an amyloid PET brain

Intravenous infusions every 2-4 weeks for 4 years

Funding by National Institute on Aging

[www.aheadstudy.org](http://www.aheadstudy.org)



APRIL 6, 2023

contribute now



In The News

Semiconductor bill passes

Portland students protest guns

Orchard robotics

Glass artist Dylan Martinez

Oregon bonds

## Alzheimer's Disease

### Latest Stories

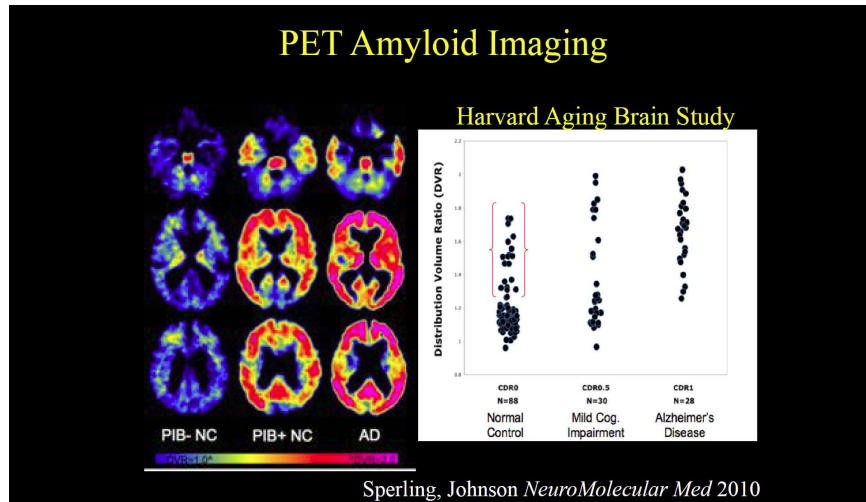


At OHSU, researchers test a promising Alzheimer’s drug — and search for a cause

0:00 / 8:01

Drugs to treat Alzheimer's disease have been in development for decades, but almost every clinical trial has ended in disappointment. One theory is that we're treating people too late and not long enough.

## A4 Study: Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease



Amyloid accumulates in the brain a decade or more before memory loss symptoms

A4: The First Anti-Amyloid Prevention Study in Alzheimer's Disease

This study enrolled 1000 healthy older adults with normal memory but amyloid already in the brain, and treated them with an anti-amyloid antibody (solanezumab) for 4.5 years

Results March 8, 2023: Solanezumab did not slow memory decline, did not reduce the risk of developing AD

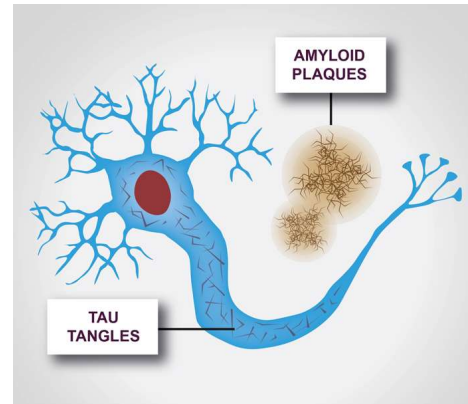
Solanezumab did not clear amyloid from the brain

## 1. Anti-amyloid

- **Reduce production** – several medications have been tested, studies halted due to toxicity
- **Reduce toxicity** – upcoming trials VIVA-MIND, START (in early stage of Alzheimer's)
- **Increase clearance** – antibodies, vaccines
- Active vaccine for Alzheimer's disease was tested in the early 2000s – 372 patients – AN1792 – 6% of patients developed brain inflammation – studies and development halted
- Renewed interest in developing active vaccines that do not induce such a strong T cell response and are tested earlier (before symptoms)

## 2. Anti-tau

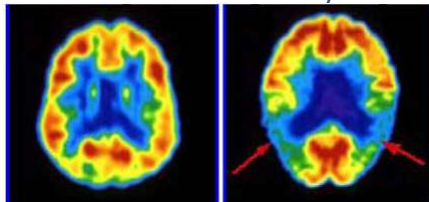
- Antibodies and vaccines under development
- Approaches – reduce hyperphosphorylation, reduce aggregation, reduce propagation, increase clearance



## 3. Metabolism/Inflammation

There is evidence of insulin resistance and altered glucose metabolism in AD.

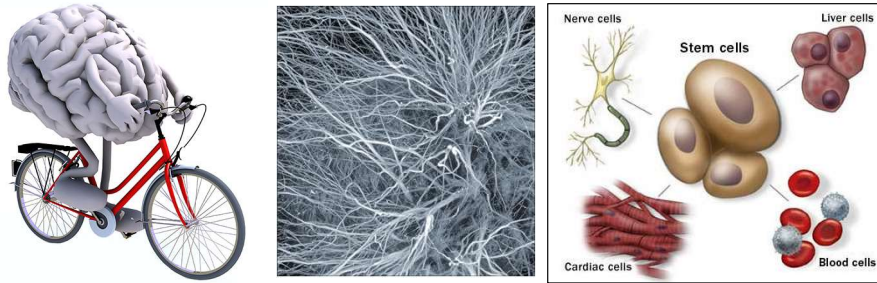
- Diabetes treatments are under study, including semaglutide (Ozempic)!
- Microbiome is under study.



Reduced glucose metabolism evident in brain of patient with AD (right).

## 4. Neuroprotection/neurogenesis

- Physical exercise
- Growth factors, Stem cells



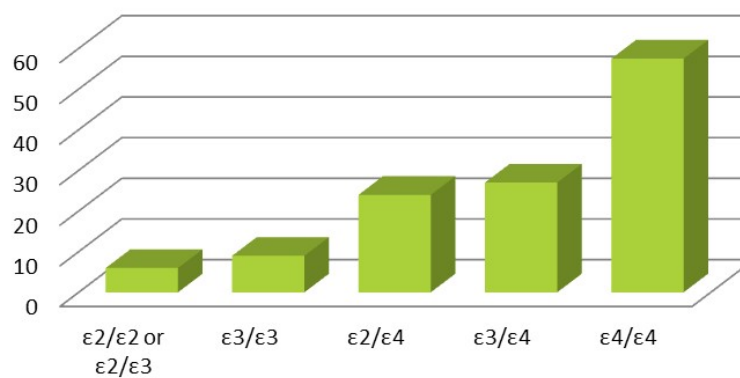
## 5. Targeting Genes

- 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\***





## 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*

## 5. Gene therapy – focus on APOE carriers

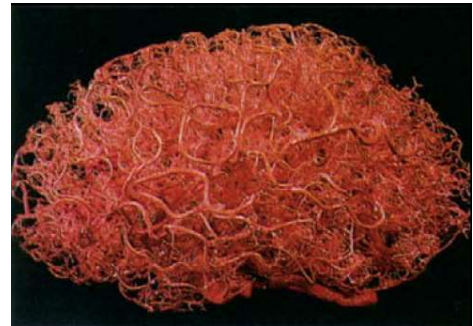
- Generation studies tested a BACE inhibitor in APOE carriers – halted early due to adverse drug effects
- APOE gene therapy
  - Viral vectors
  - CRISPR – Nobel Prize in 2020

*Emmanuelle Charpentier and  
Jennifer Doudna*



## 6. Lifestyle and Environment: 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



Zlokovic and Apuzzo,  
Neurosurgery, 1998.

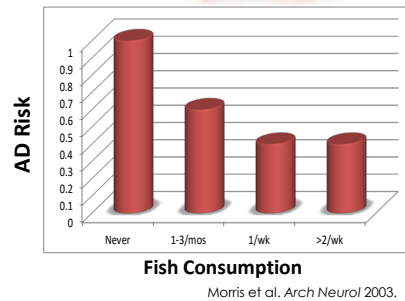
## Dieting Away from Dementia

- 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

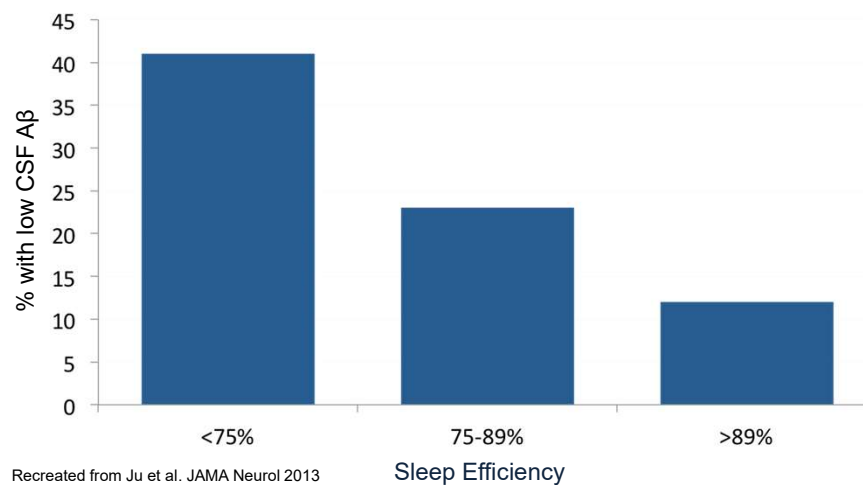
Barberger-Gateau, et al. Neurology 2007.

## 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)



## Sleep and Amyloid $\beta$



## 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 $\beta$  production
  - Recovery may increase A $\beta$  production

Heyman A, et al. Ann Neurol 15:335-341, 1984. Mayeux et al., 1991. Neurology. Brody et al., Science 2008.

## Wear a Helmet!

---

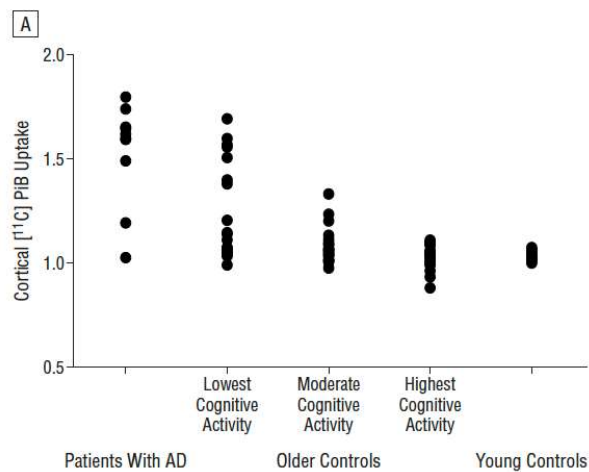
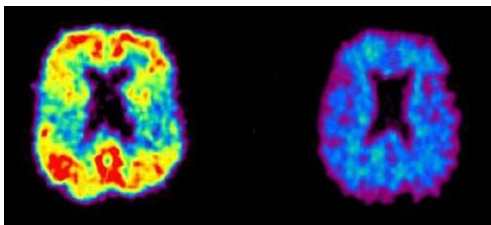


## Cognitive Activity in Older Persons


- 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

Bennett D, et al., *Lancet Neurol.* 2006. Wilson RS, et al., *Neurology.* 2007;69:epub.

## Lifetime Cognitive Activity is Associated with Reduced Levels of A $\beta$




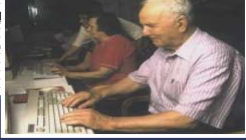
Landau et al. *Arch Neurol.* 2012.



**CROSSWORD PUZZLE**

## Exercise - mental





Diagnosis	Design	Number	Outcome	Intervention/Measure	Results	
Scarmas et al. [36]	Healthy subjects	Prospective cohort	1772	Dementia	Leisure activities	Decreased risk for dementia
Wang et al. [37]	Healthy subjects	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	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
Helmmer 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

Polidori, et al. International J of AD 2010

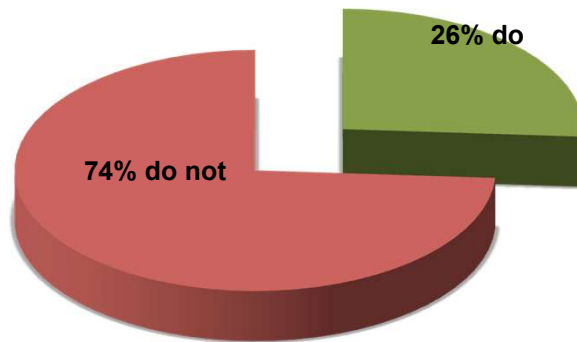
Aimee Pierce
AD Other Dementias 9/27/22
43

## 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



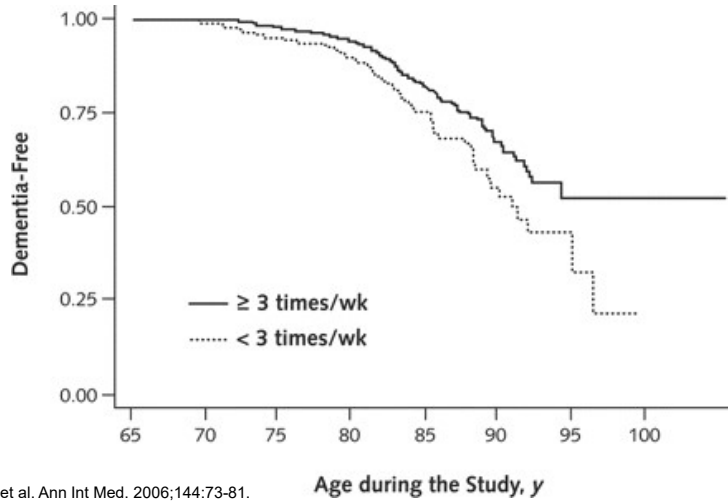
Hillman CH, et al., Nat Neurosci. 2008;9:58-65. Colcombe S, Kramer AF. Psychol Sci. 2003;14:125-130.

## Cerebral Effects of Exercise

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

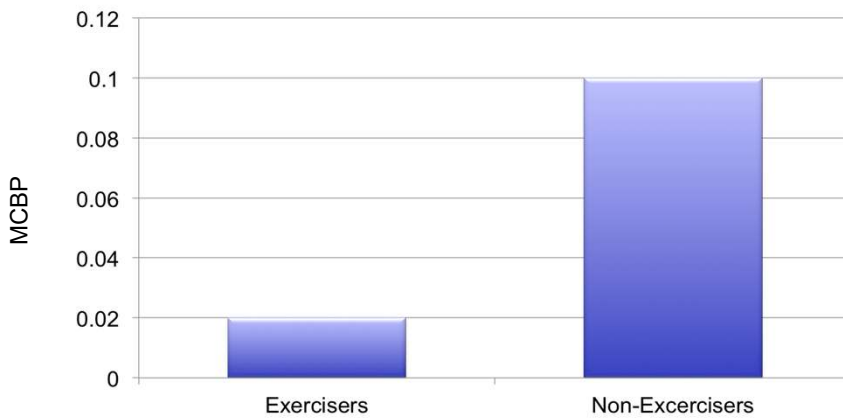
Kleim JA, et al. Brain Res. 2002;934:1-6. Van Praag H, et al. Nat Neurosci. 1999;2:266-270.

## Exercise Decreases Risk for Dementia



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

## Brain Amyloid Levels and Exercise



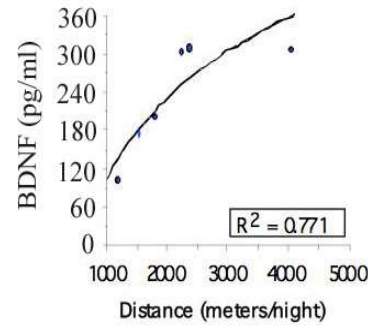
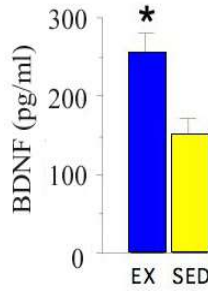
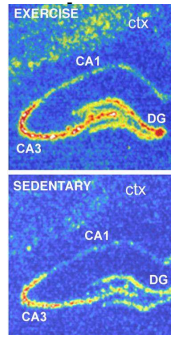
Do or do not follow the recommendation of the American Heart Association (AHA) for older adults: 30 minutes of moderate exercise 5 days/wk

Liang et al. Ann Neurol, 2010



## Exercise increases BDNF levels in the hippocampus

### HIPPOCAMPUS



Rats: 1, 4 weeks wheel-running

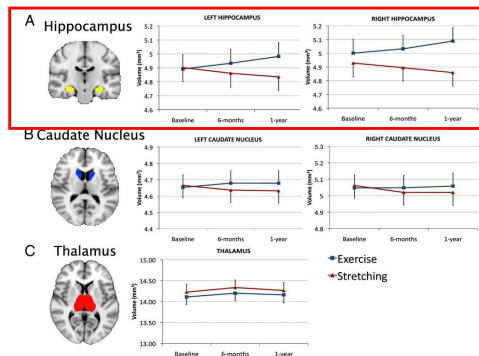
Neeper, 1995; Berchtold et al., 2002; Adlard et al., 2005

## 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

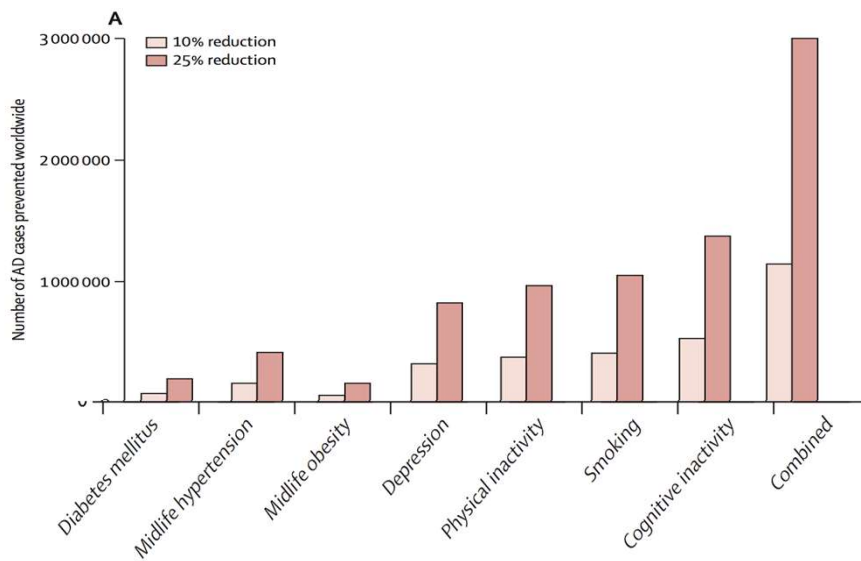
# Exercise - physical



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	766	Cognition	Physical activity and walking	Better cognitive function/less cognitive decline with physical activity and walking
Stevens and Kilken [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	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 lev of resistance train-

Polidori, et al. International J of AD 2010

## 6. Lifestyle and Environment



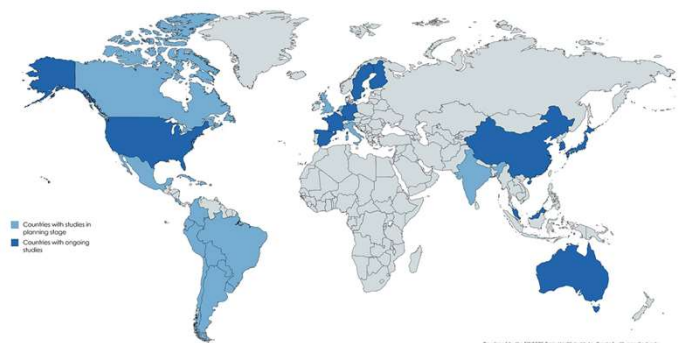
Barnes and Yaffe, *Lancet Neurol*, 2011.

## 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

[Call Home With Us](#)

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

As people age, they may experience changes in their cognitive abilities. These changes can affect their ability to perform daily activities, such as driving, shopping, and managing their finances. The SHARP study is a research program that aims to help African American seniors maintain their cognitive health and improve their quality of life. SHARP participants will receive a walking route, a guide, and a digital camera.

Our aim is to maintain or improve cognitive health among African Americans through physical activity and social engagement in culturally relevant ways that respect the rich history of their community, 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

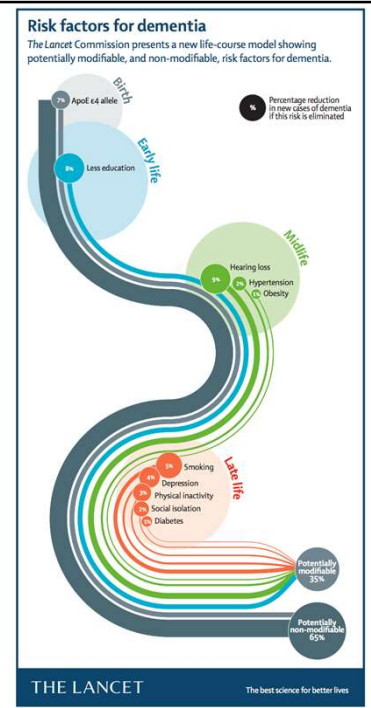
[www.sharpwalkingstudy.org](http://www.sharpwalkingstudy.org)

## Challenges of randomized clinical trials of lifestyle interventions

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

## Is prevention of Alzheimer's disease possible?

- Major risk factors for Alzheimer's disease include aging, genetics, environment, and lifestyle.
- Up to 40% of risk may be reduced –in fact genetic risk may be modifiable in the future
- 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



## Research volunteers hold the key to discovery!

- All research is voluntary
- Many types of studies
  - Healthy adults, people with memory concerns, and people with Alzheimer's disease
  - Observational studies
  - Studies of digital in-home technology
  - Clinical trials of complementary medicine
  - Clinical trials of investigational treatments
- Clinical trials are moving towards prevention
- Clinical trial entry is being honed by imaging and biomarkers
- Combination therapy may be beneficial



Contact us  
Phone: 503-494-7647

Email:  
adoutreach@ohsu.edu

Registry:  
alzactnow.org

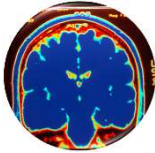
## The NIA-Layton Alzheimer's Disease Research Center (ADRC) at OHSU



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



Administrative  
Core



Clinical Core



Education  
Core



Neuropath  
Core



Data Core



Biomarker  
Core



Neuroimaging  
Core

Thank you!

Any questions?

