Is prevention of Alzheimer’s disease possible?

Brain Awareness Lecture Series
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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

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

- 14% African American
- 12% Hispanics
- 10% Non-Hispanic whites

Alzheimer’s Disease Projected to Nearly Triple by 2060

- 5 million in 2014
- 14 million in 2060

www.cdc.gov/aging
Centers for Medicare and Medicaid Services, 2014
Census Population Projections Program, 2014 to 2060
2023 ALZHEIMER'S DISEASE FACTS AND FIGURES

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

- 1 in 3 seniors dies with Alzheimer's or another dementia.
- It kills more than breast cancer + prostate cancer combined.
- Between 2000 and 2019, deaths from breast cancer has decreased 73%.
- White deaths from Alzheimer's disease have increased 145%.
- In 2023, Alzheimer's and related dementias will cost the nation $345 billion.
- By 2050, these costs could rise to nearly $1 trillion.

ALZHEIMER'S ASSOCIATION

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FIGURE 1
ALZHEIMER'S DISEASE DOUBLES IN FREQUENCY EVERY 5 YEARS AFTER 60 YEARS OF AGE


Please email questions to spoden@ohsu.edu
Cognitive changes with normal aging

<table>
<thead>
<tr>
<th>Decline</th>
<th>Maintain or improve</th>
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<tbody>
<tr>
<td>Attention</td>
<td>Language</td>
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<tr>
<td>Word-finding</td>
<td>Visuospatial function</td>
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<tr>
<td>Short-term memory</td>
<td>Executive function</td>
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<td>Long-term memory</td>
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• 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?

- Alzheimer’s disease
- Frontotemporal Lobar Degeneration
- Parkinson’s Disease-related Dementia
- Vascular Dementia
- Dementia with Lewy Bodies

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

Amyloid Cascade Hypothesis
### Biomarkers of Alzheimer’s disease

<table>
<thead>
<tr>
<th><strong>Brain imaging</strong></th>
<th><strong>Cerebrospinal fluid (CSF)</strong></th>
<th><strong>Blood</strong></th>
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<tbody>
<tr>
<td>• PET scans</td>
<td>- Amyloid</td>
<td>- Amyloid</td>
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<tr>
<td>- Amyloid</td>
<td>- Tau</td>
<td>- Tau</td>
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Dementia workup: **Biomarkers - Amyloid PET Imaging**

![PET Scan](image1.png)

![CSF](image2.png)

![Blood](image3.png)

Sperling, Johnson, NeuroMolecular Med, 2010
Tau PET Imaging


Biomarker Progression

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
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
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
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


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

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 β

Recreated from Ju et al. JAMA Neurol 2013
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 Aβ production
  • Recovery may increase Aβ production


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


Lifetime Cognitive Activity is Associated with Reduced Levels of Aβ

Landau et al., Arch Neurol. 2012.
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

74% do not
26% do


Cerebral Effects of Exercise

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

Exercise Decreases Risk for Dementia


Brain Amyloid Levels and Exercise

Liang et al. Ann Neurol, 2010

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

**HIPPOCAMPUS**

Rats: 1, 4 weeks wheel-running

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

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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

Exercise - physical

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

- 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
- 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

Thank you!

Any questions?