What can I do to prevent Alzheimer's disease?

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How to preserve brain health with aging

- Exercise and physical activity
- Maintain ideal body weight
- Mediterranean diet (fruits, vegetables, nuts, beans, olive oil, fish…)
- Limit alcohol consumption (1-2 drinks/day)
- Mental and social activities
- Avoid traumatic brain injury (seat belts, helmets, fall prevention…)
- Adequate sleep
- No smoking
- Minimize stress
- Use visual and hearing aids – if needed
- Treat hypertension, diabetes, high cholesterol, sleep apnea, and depression with your doctor
- If memory problems develop, rule out thyroid disorder, vitamin B12 deficiency, and HIV with your doctor
Case 1

• A 64 year old judge was referred by her PCP for evaluation of memory loss. Her husband confirms her memory loss and “repeating questions” for about 18 months. Her colleagues and law clerks have expressed concerns due to several small mistakes. She reports that she has “fallen a little behind at work”, and is planning to retire in 1 month because she has lost the “trust and confidence” of her colleagues…
Case 1

- She has a history of well-controlled hypertension and takes only an anti-hypertensive medication. She has no other medical or psychiatric history. There is no history of stroke, TIA, alcohol abuse, gait disorder, falls, or head trauma. Her parents died in their 60s of “old age”. She works as a judge and lives with her husband. She states that at one time her IQ was “140”.
Risk factors for AD

- Age
- **Family history/genetics**
  - ApoE polymorphism
  - Minority (African-American, Hispanic)
  - Downs syndrome
- Diabetes, midlife obesity, metabolic syndrome
- Traumatic brain injury with loss of consciousness
- Smoking
- Stroke
- Low education, occupational level
10 Signs of Alzheimer’s

- Memory loss that disrupts daily life (amnesia)
- Challenges in planning or solving problems (executive dysfunction)
- Difficulty completing familiar tasks at home, at work, or at leisure (executive dysfunction)
- Confusion with time or place (disorientation)
- Trouble understanding visual images and spatial relationships (visual agnosias)
10 Signs of Alzheimer’s

- New problems with words in speaking or writing (dysnomia, anomia)
- Misplacing things and losing the ability to retrace steps (amnesia)
- Decreased or poor judgment (executive dysfunction)
- Withdrawal from work or social activities (apathy)
- Changes in mood and personality (depression, anxiety)
**Mini-Mental State Examination (MMSE)**

<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Score</th>
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<tbody>
<tr>
<td>5</td>
<td></td>
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<tr>
<td>5</td>
<td></td>
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<tr>
<td>3</td>
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<td>1</td>
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</tr>
</tbody>
</table>

**Orientation**
- What is the (year) (season) (date) (day) (month)?
- Where are we: (state) (county) (town or city) (hospital) (floor)?

**Registration**
- Name 3 common objects (eg, “apple, table, penny”):
- Take 1 second to say each. Then ask the patient to repeat all 3 after you have said them. Give 1 point for each correct answer.
- Then repeat them until he/she learns all 3. Count trials and record.
- Trials:

**Attention and Calculation**
- Serial 7’s backwards. Give 1 point for each correct answer. Stop after 5 answers. Alternatively, spell “WORLD” backwards. One point for each correct letter.

**Recall**
- Ask for the 3 objects repeated above. Give 1 point for each correct answer (Note: Recall cannot be tested if all 3 objects were not remembered during registration.)

**Language**
- Name a “pencil,” and a “watch.”
- Repeat the following: “No ifs, ands, or buts.”
- Follow a 3-stage command:
  - “Take a paper in your right hand, fold it in half, and put it on the floor.”
- Read and obey the following:
  - Close your eyes.
- Write a sentence.
- Copy the following design:

**Total Score** __________
ADLs

• Complex
  – Working, living independently, driving, keeping appointments, handling finances, daily medications…

• Basic
  – Dressing, bathing, grooming, toileting, walking, transfers, eating…
Loss of ADLs and MMSE Scores

Case 1

• Pleasant, cooperative, and well-appearing elderly woman. Vital signs normal, as is the general medical examination. Mental status examination reveals good attention with deficits in memory, orientation, language, and visuospatial skills. The MMSE score is 25/30, with points off for orientation and memory, consistent with a mild dementia.
Case 1

- The remainder of the neurological examination reveals normal eye movements, strength, tone, sensation and coordination. There are no signs of parkinsonism. Reflexes are 2+ and symmetric – no signs of stroke. Gait is normal.
Case 1

• Blood tests, including thyroid function tests, and B$_{12}$ were all normal. A test for syphilis was negative. HIV test was negative.

• A head MRI revealed cortical atrophy and periventricular white matter changes. No tumor, hemorrhage, subdural hematoma, or large cerebral infarct.

• Neuropsychologic evaluation confirmed mild dementia, with deficits in memory, language, visuospatial skills, and frontal/executive function, and a lower than expected IQ.
Case 1

• …has multiple cognitive deficits which impair her functional abilities and represent a cognitive decline.
• There is no evidence for delirium or depression by history, examination, or laboratory evaluation.
• Diagnosed with mild dementia due to probable Alzheimer’s disease.
Case 1

• prescribed a cholinesterase inhibitor; effects and side-effects of the drug were discussed.
• advised to continue treatment for hypertension with her primary care physician.
• discussed prognosis, advance directives, and limitations concerning complex ADLs, including driving, handling finances, taking medications...
• recommended *ad libitum* physical activity, social activity, and mental activity.
• qualified and interested - enrolled in a 12 month clinical trial of drug x (add-on to current drug therapy).
Diagnostic criteria

A. Dementia

- Interferes with ability to function at work or at usual activities
- A decline from a previous level of functioning
- Not delirium or psychiatric disorder
- Diagnosed by history, examination
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment
Diagnostic criteria

A. Probable AD
   • Dementia
   • Insidious onset
   • Worsening of cognition over time
   • Amnestic vs. non-amnestic presentation
   • Not due to another dementia diagnosis

B. Probable AD with evidence of AD pathophysiology
   • Aβ (CSF or amyloid PET)
   • Neuronal injury (CSF tau, FDG-PET, structural MRI)
Federal Gov’t Expenditures

People in US with Alzheimer’s

<table>
<thead>
<tr>
<th>Year</th>
<th>AD Cost to Medicare and Medicaid (bn)</th>
<th>AD Research Funding (current trends)</th>
<th>Number of Americans with AD (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$0.43bn</td>
<td>$0.45bn</td>
<td>5.1mn</td>
</tr>
<tr>
<td>2015</td>
<td>$0.45bn</td>
<td>$0.48bn</td>
<td>5.3mn</td>
</tr>
<tr>
<td>2020</td>
<td>$0.5bn</td>
<td>$0.53bn</td>
<td>5.7mn</td>
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<tr>
<td>2025</td>
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<td>$0.55bn</td>
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<tr>
<td>2030</td>
<td>$0.55bn</td>
<td>$0.58bn</td>
<td>7.8mn</td>
</tr>
<tr>
<td>2035</td>
<td>$0.58bn</td>
<td>$0.6bn</td>
<td>9.5mn</td>
</tr>
<tr>
<td>2040</td>
<td>$0.6bn</td>
<td>$0.63bn</td>
<td>$1,167bn</td>
</tr>
<tr>
<td>2045</td>
<td>$0.63bn</td>
<td>$1,167bn</td>
<td>12.6mn</td>
</tr>
<tr>
<td>2050</td>
<td>$0.63bn</td>
<td>$1,167bn</td>
<td>13.4mn</td>
</tr>
</tbody>
</table>

Sources: Alzheimer’s Study Group, A National Alzheimer’s Strategic Plan: The Report of the Alzheimer’s Study Group (March 2009); Alzheimer’s Association. 2009 Alzheimer’s Disease Facts and Figures (March 2009); National Institutes of Health Office of the Budget
HIGHEST NATIONAL LIFE EXPECTANCY AT BIRTH: 1840–2000

Life expectancy in years

World population is graying rapidly

The centurions
Number of Japanese people aged over 100

Source: Ministry of Health, Labour and Welfare

Economist.com
AD Facts and Figures (Alz. Assoc.)

Percentage by Age Group:
- **65 to 74**
  - White: 2.9%
  - African-American: 9.1%
  - Hispanic: 7.5%
- **75 to 84**
  - White: 10.9%
  - African-American: 19.9%
  - Hispanic: 27.9%
- **85+**
  - White: 30.2%
  - African-American: 58.6%
  - Hispanic: 82.9%
Genetics of sporadic AD

Apolipoprotein E (ApoE)

Strittmatter et al, Science 1993
Neuropathology of AD

Cruz et al, PNAS 1997
Reagan Pathologic Criteria for AD

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuritic plaques and neurofibrillary tangles</td>
<td>A more limited distribution or severity</td>
<td>Limbic regions</td>
<td>Neocortex</td>
</tr>
<tr>
<td>CERAD plaque score</td>
<td>infrequent</td>
<td>moderate</td>
<td>frequent</td>
</tr>
<tr>
<td>Braak and Braak staging</td>
<td>I/II</td>
<td>III/IV</td>
<td>V/VI</td>
</tr>
</tbody>
</table>

Neurobiology of Aging 18, S1-S2, 1997
Amyloid Precursor Protein (APP) catabolism

NH$_2$ -- Aβ -- COOH

α-secretase

γ-secretase (presenilin)

β-secretase (BACE-1)

γ-secretase

p3

Aβ
Causes
- Aging
- ApoE4 > 3 > 2
- Downs syndrome
- Familial AD mutations

Drug treatments
- donepezil
- rivastigmine
- galantamine
- memantine

APP turnover
- Aβ accumulation
- Aβ oligomers, fibrils
- amyloid plaques
- neurotoxicity
- neurofibrillary tangles

Biomarkers
- low Aβ, high tau in cerebrospinal fluid
- positive amyloid-PET
- focal hypometabolism on FDG-PET
- atrophy, white matter changes on MRI

mild cognitive impairment (MCI)
- microgliosis and astrocytosis
- inflammation
- focal encephalopathy
- neuronal morbidity
- synaptic and neurotransmitter loss

neuronal mortality
- brain atrophy
- white matter rarefaction
- Dementia (AD)
- death

Turner, in Alzheimer’s Disease, 2012
FDA-approved drugs for dementia due to AD

Mild-Moderate-Severe AD
• Donepezil (Aricept)
• Rivastagmine (Exelon)
• Galantamine (Razadyne, Razadyne ER)

Moderate-Severe AD
• Memantine (Namenda)
Donepezil (Aricept)

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

Rogers et al, Neurology 1998
The continuum of Alzheimer’s disease

Cognitive function

Preclinical

Aging

MCI

Dementia

Years

Years
Appearance of Plaques vs. Dementia

- **Amyloid Plaques at Autopsy**
- **Prevalence of AD Dementia**

Percent positive (%) vs Age (years):
- 46-50: 10%
- 51-55: 20%
- 56-60: 30%
- 61-65: 40%
- 66-70: 50%
- 71-75: 60%
- 76-80: 70%
- 81-85: 80%
- 86-90: 90%
PET Amyloid and Tau Imaging

Amyloid-\(\text{\(\beta\)}\) (PiB)

Tau (T807)

Clinically Normal

Clinically Normal

Alzheimer’s Dementia
Mean cortical SUVRs

Age and ApoE4 Genotype Increase Amyloid PET

ALL healthy controls

ApoE4-

ApoE4+

Fleisher et al. Neurobiol Aging. 2013
CSF Biomarkers
Autopsy-confirmed data

Shaw et al, Annals Neurology 2009

Aβ42

Tau

AD

Normal

CSF biomarkers
FDG-PET: AD

MCI

Langbaum et al, Neuroimage 2009
AD brains reveal atrophy -- particularly in regions mediating higher cognitive functions.
MRI atrophy in MCI & AD

McDonald et al, Neurology 2009
Summary

- We are witnessing a growing epidemic of dementia - most of which is AD
- The amyloid hypothesis is alive and well, and *does not exclude* other important and essential pathologic processes
- The genetics of familial AD provides the strongest evidence for the amyloid hypothesis
- Despite recent high-profile failures, many active trials target Aβ/amyloid generation or clearance
- Other AD trials target other essential pathologic processes, with the probable result of a therapeutic cocktail (as now...)
Summary

- Current (FDA-approved) therapies for AD provide consistent yet modest, temporary, and palliative benefits.
- We are searching for disease-modifying treatments to halt dementia progression, or prevent dementia onset.
- We are in need of validated biomarkers for: screening, diagnosis, prognosis, evidence of efficacy, reduction of clinical trial costs.
- Treatments are increasingly target individuals with MCI and healthy high-risk individuals - prevention.
- Future treatments will be tailored to ApoE genotype (pharmacogenomics, personalized medicine, precision medicine).
Georgetown University
Memory Disorders Program:
Multi-center studies ongoing

- MCI and AD treatment trials
  - Lilly (Solanezumab) and (BACE1-I)
  - Merck (BACE1-I)
  - Biogen (Aducanumab)
  - Astra-Zeneca (Fyn kinase inhibitor)
  - Toyama (Neuroprotective sigma2 agonist)
- Prevention trials
  - Lilly (Solanezumab) in amyloid-positive subjects
  - Novartis vaccine vs BACE1-I in ApoE4/4 subjects
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