Alzheimer’s Disease: Research Overview

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Together We’re Stronger

53,000 Mainers w/AD by 2020

20-45% prevalence rates in these rapidly growing age cohorts

Source: U.S. Census Bureau
Research

• Understanding the disease is the only hope
  – Prevention
  – Diagnosis
  – Treatment
  – Quality of life
  – Caregiver/family support
Major Sources of Funding

• Federal: NIH/NIA; HRSA; CMS
• Foundations: Alzheimer’s Association and multiple others
• Industry: Large pharma; small biotech
NIA Strategic Directions 2016

Goals for improving health, well-being and independence of adults as they age:

D-1 Understand the mechanisms involved in normal brain aging; the role of cognition and sleep in everyday functioning, and protective factors for sensory, motor, emotional, and cognitive function.

D-2 Identify and understand the molecular and cellular mechanisms underlying the pathogenesis of Alzheimer’s disease (AD) and other neurodegenerative disorders of aging.

D-3 Expand research to improve assessment and diagnostic tools for distinguishing people with normal brain aging from those who will develop mild cognitive impairment (MCI), Alzheimer’s disease (AD), and related conditions.

D-4 Translate discoveries about the cellular and molecular mechanisms of cognitive, emotional, sensory, motor, and sleep function with age and the mechanisms of early and late stage AD pathogenesis into diagnostic, treatment, and/or prevention strategies.

D-5 Conduct research to better understand and develop interventions to address the special caregiving needs of patients with AD and other dementias, as well as the needs of their caregivers.
Natural History of Cognitive Change

- Normal Aging
- Noticeable symptoms
- Dementia
- Diagnosis
## Spectrum of Progression

<table>
<thead>
<tr>
<th>Normal</th>
<th>Preclinical (Presymptomatic)</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal overall cognition and ADLs</td>
<td>• Thinking effectively but more slowly</td>
<td>• Subjective problem in memory or another domain</td>
<td>• Clear deficits in 2 or more core cognitive domains</td>
</tr>
<tr>
<td>• APOE-e4 risk gene</td>
<td>• APOE-e4 risk gene</td>
<td>• Normal overall cognition and ADLs</td>
<td>• ADLs affected</td>
</tr>
<tr>
<td>• Tau or amyloid in CSF or blood</td>
<td>• Tau or amyloid in CSF or blood</td>
<td>• MRI, PET</td>
<td>• MRI, PET</td>
</tr>
<tr>
<td>• Occasionally misplacing things</td>
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</tbody>
</table>
Primary Prevention
Sperling RA et al. Alzheimer’s Dementia 2011

- 13.5 million with AD by 2050
- Intervention that delays dementia from AD by 5 yrs.: ↓incidence by 57%; ↓Medicare costs from $627B to $344B
- Employment of targeted 1° prevention will require capability in reliable biomarkers
  – Genotyping, FDG-PET, amyloid/tau PET
Risk Factors

– Stress
– Stroke
– Depression
– Head injuries
– Sleep disorders
– Lack of exercise
– High animal fat diet
– Genes/family history
– Diabetes and insulin resistance
**Primary Prevention**
Patterson C et al. CMAJ 2008

### Table 1: Risk factors for Alzheimer disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Systolic hypertension &gt; 160 mm/Hg</td>
<td>RR: 1.5 (1.0-2.3)⁴ OR: 2.3 (1.0-5.5)⁵</td>
</tr>
<tr>
<td>Serum cholesterol &gt; 6.5 mmol/L</td>
<td>RR: 2.1 (1.0-4.4)⁵</td>
</tr>
<tr>
<td>Moderate wine consumption (250-500 mL/d) compared with more or less than this amount</td>
<td>RR: 3.1 (1.2-8.5)⁶</td>
</tr>
<tr>
<td>High level of physical activity* compared with little or no regular exercise</td>
<td>RR: 0.53 (0.3-0.95)⁷</td>
</tr>
<tr>
<td>Smoking, current</td>
<td>RR: 0.5 (0.28-0.90)⁸</td>
</tr>
<tr>
<td>Head injury, with loss of consciousness</td>
<td>RR: 0.55 (0.34-0.88)⁹</td>
</tr>
<tr>
<td></td>
<td>RR: 0.69 (0.5-0.96)¹⁰</td>
</tr>
<tr>
<td>Smoking, current</td>
<td>RR: 1.74 (1.21-2.50)¹¹</td>
</tr>
<tr>
<td>Head injury, with loss of consciousness</td>
<td>RR: 1.99 (1.33-2.98)¹²</td>
</tr>
<tr>
<td>Moderate</td>
<td>HR: 2.32 (1.04-5.1)¹³</td>
</tr>
<tr>
<td>Severe</td>
<td>HR: 4.51 (1.77-11.47)¹³</td>
</tr>
<tr>
<td>Education &gt; 15 yr (v. &lt; 12 yr)</td>
<td>RR: 0.48 (0.27-0.84)¹⁴</td>
</tr>
<tr>
<td>Statin drugs</td>
<td>RR: 0.82 (0.46-1.46)¹⁵</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>RR: 1.19 (0.35-2.96)¹⁶</td>
</tr>
<tr>
<td></td>
<td>RR: 0.42 (0.26-0.66)¹⁷</td>
</tr>
<tr>
<td></td>
<td>RR: 0.51 (0.37-0.70)¹⁸</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, RR = relative risk, OR = odds ratio, HR = hazard ratio.

*See section on lifestyle factors for details about physical activity.
MIND diet associated with reduced incidence of Alzheimer’s disease

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Abstract

\textbf{Introduction:} In a previous study, higher concordance to the MIND diet, a hybrid Mediterranean-Dietary Approaches to Stop Hypertension diet, was associated with slower cognitive decline. In this study we related these three dietary patterns to incident Alzheimer’s disease (AD).

\textbf{Methods:} We investigated the diet-AD relations in a prospective study of 923 participants, ages 58 to 98 years, followed on average 4.5 years. Diet was assessed by a semiquantitative food frequency questionnaire.

\textbf{Results:} In adjusted proportional hazards models, the second (hazards ratio or HR = 0.65, 95% confidence interval or CI 0.44, 0.98) and highest tertiles (HR = 0.47, 95% CI 0.26, 0.76) of MIND diet scores had lower rates of AD versus tertile 1, whereas only the third tertiles of the DASH (HR = 0.61, 95% CI 0.38, 0.97) and Mediterranean (HR = 0.46, 95% CI 0.26, 0.79) diets were associated with lower AD rates.

\textbf{Discussion:} High adherence to all three diets may reduce AD risk. Moderate adherence to the MIND diet may also decrease AD risk.

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Keywords: Cognition; Alzheimer’s disease; Nutrition; diet; Epidemiological study; Aging
“One of the theories of Alzheimer’s disease is that there are proteins (beta amyloid and tau peptide) which clump up and cause harm to the brain. So we found that a particular extract from maple syrup prevented this clumping”

Dr. Donald Weaver
University of Toronto

Mr. Serge Beaulieu, President of the Federation of Quebec Maple Syrup Producers, revealing a new interest in neuroscience, said that “Brain health is the latest topic…..we look forward to learning more about”
Brain Healthy Foods

- Leafy greens
- Blueberries
- Nuts and seeds
- Fatty fish
- Wine

- Olive oil
- Lentils
- Legumes
- Whole grains
- Coffee/tea
Brain Healthy Lifestyles

- Exercise
- Cognitive activities
- Sleep
- Meditation
- Periodic fasting
- Helpful or not? Issues in Methodology:
  - Cohort vs. Randomized controlled trial
  - Specific/symptomatic vs. Neuroprotective
Prevention Requires Early Identification:

• Biomarkers
  – Imaging
    • CT, MRI, SPECT, FDG-PET, molecular PET
  – CSF: β-amyloid, tau
  – Genetic
Hypothetical Progression of Biomarkers
Jack CR et al. Lancet Neurology 2010

Figure 2. Dynamic biomarkers of the Alzheimer’s pathological cascade
Aβ is identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
Alzheimer’s Disease Neuroimaging Initiative (ADNI)

- Longitudinal study
- AD, MCI, AAMI, older adults w/o memory complaint
- Consortium of US research centers to validate biomarker diagnostic and outcome measures
Together We’re Stronger

PIB beta-amyloid PET

- **RED** = maximum uptake
- **VIOLET** = minimum uptake
IDEAS

• CMS/American College of Radiology and Alzheimer’s Association
• Medicare pays for amyloid PET
• Study to determine if results affect clinical decision making
• Sites in Maine: MMC Neurology, EMHS Neurology and Acadia Hospital Mood and Memory Clinic
From: Cerebrospinal Fluid β-Amyloid(1-42) in Alzheimer Disease: Differences Between Early- and Late-Onset Alzheimer Disease and Stability During the Course of Disease

Treatment

• Symptomatic
  – Current treatments compensate for damage
  – Improves symptoms
    • cognitive, behavioral, functional

• Disease modification
  – Future treatments will slow the pathologic process
  – Could potentially prevent AD
  – May improve symptoms
Comparing Strategies

Hypothetical Data:

![Graph comparing strategies]

- Symptomatic
- Disease Modification
What Dr. Alzheimer saw:

- Tangles
- Plaques
Drug target: Beta-amyloid, the main plaque component

2nd step in beta-amyloid production:

- APP remnant from beta-secretase
- gamma-secretase
- inside neuron (nerve cell)
- outside cell
- beta-amyloid

All the steps in beta-amyloid production are potential targets

• Blocking the enzymes beta-secretase (BACE study) and gamma-secretase

• Administering a “vaccine” to help the body clear beta-amyloid from the brain

• Preventing beta-amyloid pieces from sticking together and forming plaques
Tau is the “tangle protein”—another potential drug target

- Microtubules = cell “scaffold” transporting food and supplies
- Tau “spacer” protein keeps microtubules orderly
- AD chemically changes tau, twisting it into tangles
- Scaffold collapses, cell dies
More Targets for Drug Intervention

- Beta-amyloid
- Tau protein (AADvac1)
- Inflammation
- Free-radical oxidation
- Insulin resistance

- Copper and zinc binders
- Neurotrophic enhancers
- Nicotine receptor activators
Amyloid Immunotherapy

• Initial active vaccination trials proved too risky
• Current efforts use “monoclonal” antibodies to provide “passive immunotherapy”......giving antibodies that target parts of beta-amyloid
• Examples:
  – Bapineuzumab, solanezumab, crenezumab, gantenerumab
Immunotherapy cont’d

• Evidence that they do reduce amyloid in brain……but provide minimal effect on dementia symptoms or progression (too late?)
• Studies now underway crenezumab in pre-dementia phase
• Anti-tau antibodies being tested in animal models
Clinical Trials

- Research studies conducted in people to determine whether treatments are safe and effective.
- Treatment trials usually involve a placebo
- Clinical trials of new drugs usually involve many sites and hundreds or thousands of patients:
  - Phase 1: Initial safety and dosing studies
  - Phase 2: Initial comparison studies against placebo or known treatment
  - Phase 3: Large studies to establish superior efficacy against a placebo and/or active drug comparison

- Why participate?
- How? Go to Alzheimer’s Association TrialMatch or clinical trials.gov to find studies (we’re on there!)
Clinical Screening

• Research to address questions such as these:
  – Should all older adults be screened for cognitive impairment?
  – If so, at what age should screening start?
  – What tools or assessment scales be used for screening?
  – What tools or assessment scales be used for diagnosis of AD?
  – What tests should be ordered in everyone to rule out other causes of dementia?
  – Who should be evaluated by a dementia specialist?
Clinical Practice

• Research devoted to early detection of AD in the clinic:
  – Efforts to get health care providers to do simple cognitive and functional assessment for early detection, accurate diagnosis and early referral
  – Distinguish normal aging, mild cognitive impairment and dementia
Can (and Should) Health Care Providers Identify MCI?
Maine DHS Dementia Capable Grant

• “Single door” gateway for service
• Enhanced primary care screening, diagnosis and referral
• Maine General Hospital (Renfrew)
• Eastern Maine Medical Center (Singer)
RAND ACOVE Quality Indicators
Chow TW and MacLean CH; Ann Internal Medicine 2001; 135:8:668-76

• Cognitive & functional screen
• Medication review
• Labs/Imaging
• Discussion of meds to treat dementia
• Caregiver support
• Patient safety
• Stroke prophylaxis
• Depression
• Driving
• Restraints
Quality of Life

• Environment and architecture
• Neuropsychiatric symptoms
• Ethics and decision making
• Cognitive habilitation
• Caregiver wellbeing
• Quality of life
• Cost of care
• End of life
University of Maine at Orono: New Initiatives in Aging

• Technology to assist aging in place
• Sleep and dementia (Marie Hayes)
• New faculty recruited:
  – Gait slowing with multi-tasking as a marker for cognitive decline
  – Vascular disease and cognitive decline
Slowing of Gait with Cognitive Interference

Percent Change Relative to Standard TUG

- Months FWD (Easy Task)
- Months BKWD (Difficult Task)

Acadia Hospital
Empowering People to Improve Their Lives
Together We’re Stronger
The Other Dementias

Table 2: Types of dementia seen in patients referred to dementia clinics in Canada

<table>
<thead>
<tr>
<th>Type of dementia</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>47.2</td>
</tr>
<tr>
<td>Mixed Alzheimer disease</td>
<td>27.5</td>
</tr>
<tr>
<td>Mixed others</td>
<td>6.3</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>8.7</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>5.4</td>
</tr>
<tr>
<td>Dementia associated with Parkinson disease or with Lewy bodies</td>
<td>2.5</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>1.8</td>
</tr>
<tr>
<td>Other</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Source: Feldman et al. 34
Current Clinical Trials in Maine

• Memory disorder clinics:
  – MMC Neurology (Dr. Dinnerstein)
    • MCI and Mild dementia (3 studies)
  – Acadia Hospital (Dr. Singer)
    • MCI and Mild dementia (4 studies)

• Clinical trial centers
  – Freeport
  – Augusta
Summary

• Research is our hope
• More than just drugs
• There are many benefits to participation
• Alzheimer’s disease is the most important, but not the only dementia
• Progress is being made but we need to pick up the pace
We’ll have a cure for AD when dogs can fly…and it looks like we’re getting close!