Preventing Alzheimer’s Disease
What We’ve Learned from the Oldest Old: The 90+ Study

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Disclosures

AVID Radiopharmaceuticals
  – A wholly owned subsidiary of Lilly Pharmaceuticals

Data and Safety monitoring committees –
  Lilly Pharmaceuticals
  Biogen
Madame Jeanne-Louis Calmet
Arles, France

1875 – 1997
Age 122
If increases in life expectancy continue, more than half of all children born today in developed countries can expect to celebrate their 100th birthdays.

U.S. Projected Population Growth Among 90+ Year Olds

Population Projections U.S. Census Bureau 2002, Middle Series
Aging
The Elephant in the Room!

Age is the biggest risk factor for dementia

Oldest old have the highest rates of dementia

The 90+ Study
Overview

1. Background of The 90+ Study

2. Incidence and Risk Factors for Dementia in the Oldest Old

3. Clinical Pathological and Radiological Correlations: Dementia

4. Preventing AD and Dementia

1. Conclusion
The Leisure World Cohort Study
USC

- Prospective Cohort Study Design
- Residents of California Retirement Community
- 13,978 Enrolled 1981-1985
  - Primarily white
  - 2/3 female
  - Median age at enrollment: 73 years
  - Well-educated
- Follow-up Surveys
The 90+ Study

Population-based study of aging and dementia in persons aged 90 and older

Leisure World Cohort
13,978

- 1,931 ≥90 years Alive
- 3,774 >90 years Deceased
- 1,071 <90 years Alive
- 7,202 <90 years Deceased

Enrolled
N = 1603
83%
Assessments

• Intake
  – Demographics & Medical History

• Neuropsychological Tests
  – Memory, language, executive function

• Neurological Examination

• Informant Questionnaires

• Genetic studies
  – DNA and cell lines

• Brain Donation
## The 90+ Study Participants Baseline Results

<table>
<thead>
<tr>
<th># of Participants</th>
<th>1603</th>
</tr>
</thead>
</table>

### Education

<table>
<thead>
<tr>
<th>Education</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>College grad or more</td>
<td>41%</td>
</tr>
</tbody>
</table>

### Marital Status

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widowed</td>
<td>77%</td>
</tr>
<tr>
<td>Married</td>
<td>14%</td>
</tr>
</tbody>
</table>

### % of Women

<table>
<thead>
<tr>
<th>% of Women</th>
<th>76%</th>
</tr>
</thead>
</table>

### Mean Age

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>95.8</th>
</tr>
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</table>

### Type of Residence

<table>
<thead>
<tr>
<th>Type of Residence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing or group home</td>
<td>40%</td>
</tr>
<tr>
<td>Home alone</td>
<td>31%</td>
</tr>
</tbody>
</table>

### Neurological Exam Cognitive Diagnosis

<table>
<thead>
<tr>
<th>Neurological Exam Cognitive Diagnosis</th>
<th>Women %</th>
<th>Men %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>Cognitively Impaired, not Demented</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td>Demented</td>
<td>41%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+

- Munich, Germany
- Sydney OPS, Australia
- LEILA75, Germany
- CSHA, Canada
- Bronx Aging, NY
- Cache County, UT
- ACT, Seattle WA
- MoVIEs, PA
- Paquid, France
- Kungsholmen, Sweden
- Rochester Epi Proj, MN
- Rotterdam, Netherlands
- Sao Paulo, Brazil
- 90+ Study, CA

Cross-sectional Investigations of Risk Factors and Dementia

- Vitamin E (supplementation)
- Vitamin C (diet and supplementation)
- BMI
- Alcohol
- Caffeine
- Activities
- Homocysteine levels
- Thyroid function
Vascular Risk Factors and Prevalent Dementia

- 46% Hypertension
- 12% Coronary Artery Disease
- 12% Myocardial Infarction
- 17% Congestive Heart Failure
- 22% Atrial Fibrillation
- 23% Stroke

Vascular risk factors did not distinguish demented and non-demented participants – except HTN
Hypertension and Incident Dementia (History)

- 325 non-demented participants
  - 70% women
  - Mean age = 94 (90 – 103)
  - 137 incident cases
- History of hypertension at baseline
  - 53% reported a history

Corrada, et al, ICAD 2010
Hypertension and Prevalent Dementia (BP measurements)

- 609 participants
  - 74% women
  - Mean age = 93 (90 – 107)
  - 32% demented
- BP measurements at baseline
  - 13% normal
  - 36% pre hypertensive
  - 51% hypertensive

Corrada, et al, AAN 2010
Hypotension and Increased Risk of Dementia

- Gothenburg H-70 & Rotterdam
  - Ruitenbergen et al., *Ann Neurol*, 2001

- East Boston Study
  - Morris et al., *Arch Neurol*, 2001

- Bronx Aging Study
  - Verghese et al., *Neurology*, 2003

- OCTO-Twin Study
Blood Pressure & Dementia

Potential Interpretations

1. “Normal” blood pressure may be different for 90+ year olds

2. Elderly torturous cerebral vessels may require increased pressure for adequate perfusion

3. Low blood pressure may be a marker for other diseases

4. Medication effects – ACE-inhibitors, Ca-channel blockers, others

5. Differential medical care
What is Related to Dementia in Oldest-Old?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$O_2$ Saturation &lt;93%</td>
<td>2.3</td>
</tr>
<tr>
<td>Performance Based Physical Function</td>
<td></td>
</tr>
<tr>
<td>Walk Speed</td>
<td>11.8</td>
</tr>
<tr>
<td>Hand Grip</td>
<td>5.3</td>
</tr>
<tr>
<td>History of HTN</td>
<td>0.7</td>
</tr>
</tbody>
</table>
The 90+ Autopsy Study

- 306 people enrolled
- 185 have come to autopsy
- Brain sections are both fixed and frozen
- Mean Post-Mortem Interval 4.9 hours
### 90+ Autopsy Study Participants

<table>
<thead>
<tr>
<th>Median</th>
<th>Not Demented</th>
<th>Demented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>MMSE</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Brain Weight (g)</td>
<td>1157</td>
<td>1100</td>
</tr>
</tbody>
</table>
Pathological Diagnoses by Dementia Status

No Dementia (N=76)
- AD Pathology: 42%
- None or Insufficient Pathology: 58%

Dementia (N=90)
- AD Pathology: 60%
- None or Insufficient Pathology: 40%

AD = Intermediate/High NIA Reagan Criteria
APOE 2/2 Neuropathology

CA1/Subiculum

Non demented subject | Case subject | Demented subject with AD pathology

A | B | C

Senile Plaques

D | E | F

Neurofibrillary Tangles

Berlau et al., Arch Neurol, 2007
Alzheimer Disease Pathogenesis

Abnormal

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/MRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Normal

Preclinical

MCI

Dementia

Clinical Disease Stage

Jack, C, et. al. 2010
Results

• No difference in rate of cognitive decline in Low vs. High plaque groups (p = 0.20)

Subjects
• 68 non-demented at baseline
• Baseline age: 94.7yr (90-102)
• Average # of visits: 7 (3-13)

CERAD Staging
Low Plaques (0-A)
High Plaques (B-C)
PET Amyloid Imaging
florbetapir
Amyvid
Florbetapir Imaging in Non-demented Oldest-old

Cross-sectional Association

Average cortical SUVr correlated significantly with 3MS at baseline (Pearson corr = -0.6, p = 0.03)

Corrada M, et al. ANA 2011
Significantly faster decline in 3MS for High SUVr vs. Low SUVr group (p=0.05)

Corrada M, et al. ANA 2011
Vascular Disease
Frequency of Vascular Pathological Abnormalities in Demented and Non-Demented (N=150)

- Amyloid Angiopathy: 33% (Not Demented), 41% (Demented)
- Atherosclerosis: 32% (Not Demented), 32% (Demented)
- Micro Infarcts: 12% (Not Demented), 19% (Demented)
- Lacunes: 12% (Not Demented), 20% (Demented)
- Large Infarcts: 14% (Not Demented), 5% (Demented)
- White Matter Gliosis: 0% (Not Demented), 15% (Demented)
Vascular Disease

No relationship between cerebrovascular disease and dementia in The 90+ Study
H&E stained sections of frontal cortex at 200x magnification. A single microinfarct is shown (open arrows) characterized by loss of neurons and neuropil, central cavitation with foamy macrophages and linear extension into deeper layers of cortex. There is subpial sparing of cortical layer I (black arrow) due to a different arterial supply (meningal arteries vs. deep penetrating cerebral arteries). Scale bar is approximately 70 microns.
Pilot Data (N=76)

- None: 46%
- 1+: 54%

Collaboration with Josh Sonnen, U Washington
Odds of Dementia by Number of Microinfarcts

Odds of dementia increasing with the number of microinfarcts

J Sonnen collaboration (N=76); Adjusting for Braak tangle stage
Prevalence of Microinfarcts and Risk of Dementia in Epidemiological Studies

- **Honolulu Asia Aging Study (HAAS)**
  - Japanese American men, 85y @ death
  - 1+ MI = 40%
  - OR (1+) = 4.6 (related to dementia independent of AD pathology)

- **Adults Changes in Thought (ACT) Study**
  - 91% Caucasian, 55% women, 86y @ death
  - 1+ MI = 47%
  - OR (3+) = 4.8 (related to dementia independent of AD pathology)

- **The 90+ Study**
  - 99% Caucasian, 71% women, 97y @ death
  - 1+ MI = 16%
  - No relation to cognition
Newer data: Dementia reflects multiple pathologies

- Cerebrovascular Disease
- Hippocampal Sclerosis
- Autopsy-confirmed AD
- Other: FTLD, pure DLB, etc

Average age of Tomlinson, Blessed, & Roth (1967) cohorts
Frequency of Dementia by Number of Pathologies (N=121)

Pathologies: AD (Interm/High), LBD, Hippocampal sclerosis, vascular dementia, CBD

Corrada M (unpub. data)
MMSE Score by No. of Pathologies in Demented Participants

Severity of dementia correlated with number of pathologies

- Non-demented: # of pathologies *not related* to cognitive performance
- Demented: # of pathologies *related* to dementia severity

Corrada M (unpub. data)
2 Hypotheses
Aging and Cognitive Impairment

1. Low BP and vascular cognitive impairment
   In the oldest-old, the risk of hypoperfusion outweighs the risk of mechanical strain from hypertension
   - Stiffness of tissue vasculature
   - Autoregulatory dysfunction

2. Multiple pathologies contribute to cognitive loss in aging

How to Prevent AD?

*Do what your mother told you to do!*

- Challenge your brain
- Exercise
- Eat a heart-healthy diet
- Drink alcohol and coffee in moderation
- Reduce your stress
- Engage in social activities and relationships
Summary

- Risk of dementia continues to increase with age

- Clinical pathological correlations are poor and may provide clues to AD and the expression of dementia at all ages

- Risk factors change with age

- Multiple pathologies (and risk factors specific to each) are likely to be important in the development of dementia in aging
Did you hear? 95 is the new 65!

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