Lessons from the Oldest old: The 90+ Study

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90study.org
If increases in life expectancy continue,

….more than half of all children born today in developed countries can expect to celebrate their 100\textsuperscript{th} birthdays


Jeanne-Louis Calment
Arles, France

1875 – 1997
Age 122
Overview

I. Background of the Oldest Old and The 90+ Study

II. Successful Aging: factors related to longevity related to cognition

III. Findings from The 90+ Autopsy Study

IV. Projections : dementia in 90+ year olds

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

Population Projections U.S. Census Bureau 2002, Middle Series
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+
The Relative Frequency of “Dementia of Unknown Etiology” Increases With Age and Is Near 50% in Nonagenarians

- Series of 128 subjects
- “Dementia of unknown etiology”
  - 5% of all cases dying in their 70’s
  - 21% of all cases dying in their 80’s
  - 48% of all cases dying in their 90’s

H Crystal et al., Arch Neurol, 2000
Unknown in 90+ Year Olds

- Risk/Protective Factors Related to Longevity
- Prevalence and Incidence of Dementia
- Risk/Protective Factors Related to Dementia
- Types of Dementia
The Leisure World Cohort Study

A. Paganini-Hill and colleagues, USC

- Prospective Cohort Study Design
- Residents of Southern California Retirement Community
- 13,978 Enrolled 1981-1985
  - Median age at enrollment: 73 years
  - Primarily white
  - 2/3 female
  - Well-educated
- Follow-up Surveys
Studies of Factors Associated with Longevity

- Vitamin C (diet + supplements)
- Vitamin A (diet + supplements)
- Vitamin E (supplements)
- Calcium (diet)
- Soft drinks (cola & other)
- Tea (black or green)
- Alcohol (wine, beer, other)
- Caffeine
- Body Mass Index
- Activities - Exercise
- Activities - Leisure

Corrada, et al, AAN 2004
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%

1/1/03
1980s
Assessments

- Demographics & Medical History
- Neuropsychological Tests
  - Memory, language, executive function
- Neurological & Physical Examination
- Informant Questionnaires
- Genetic studies
  - DNA and cell lines
- Brain Imaging
- Brain Donation
# The 90+ Study Participants Baseline Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Participants</strong></td>
<td>1603</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>College grad or more</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>77%</td>
</tr>
<tr>
<td>Married</td>
<td>14%</td>
</tr>
<tr>
<td><strong>% of Women</strong></td>
<td>76%</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>95.8</td>
</tr>
<tr>
<td><strong>Type of Residence</strong></td>
<td></td>
</tr>
<tr>
<td>Nursing or group home</td>
<td>40%</td>
</tr>
<tr>
<td>Home alone</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Neurological Exam Cognitive Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>32%</td>
</tr>
<tr>
<td>Cognitively Impaired, not Demented</td>
<td>34%</td>
</tr>
<tr>
<td>Demented</td>
<td>34%</td>
</tr>
</tbody>
</table>
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+

## Clinical Pathological Correlations

### The 90+ Autopsy Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dementia</th>
<th>No Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>MMSE</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Brain Weight (g)</td>
<td>1100</td>
<td>1157</td>
</tr>
</tbody>
</table>

- Alzheimer’s Plaques & Tangles
- Microinfarct
- Hippocampal Sclerosis
- White Matter Disease

N = 212 participants
Pathological Diagnoses by Dementia Status

Dementia (N=98)

- AD Pathology: 59%
- None or Insufficient AD Pathology: 41%

No Dementia (N=85)

- AD Pathology: 39%
- None or Insufficient AD Pathology: 61%

AD=Intermediate/High NIA Reagan Criteria
Rates of Cognitive Decline and Alzheimer’s Disease Neuropathology

**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)

**Results**
- No difference in rate of cognitive decline in **Low** vs. **High** plaque groups ($p = 0.20$)

Mean Regression Slope: -1.15

Mean Regression Slope: -0.94

Archana B. Balasubramanian
Odds of Dementia For Different Pathologies
(vs not having that pathology)

the effect of Multiple Pathologies
Frequency of Dementia by Number of Pathologies

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

Pathological Diagnoses by Dementia Status

Dementia (N=98)
- AD Pathology: 59%
- None or Insufficient AD Pathology: 41%

No Dementia (N=85)
- AD Pathology: 39%
- None or Insufficient AD Pathology: 61%
AD = Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, WM gliosis
Pathological Diagnoses by Dementia Status

Dementia (N=98)
- AD Pathology 29%
- Microinfarcts and Vascular 32%
- None or Insufficient AD/Vascular/HS Pathology 17%
- Hippocampal Sclerosis 22%

No Dementia (N=85)
- AD Pathology 38%
- None or Insufficient AD/Vascular/HS Pathology 53%
- Hippocampal Sclerosis 3%
- Microinfarcts and Vascular 6%

AD=Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, WM gliosis; HS = Hippocampal Sclerosis
Pathological Diagnoses by Dementia Status

Dementia (N=98)

- Hippocampal Sclerosis: 22%
- AD Pathology: 24%
- Other Pathologies: 10%
- None or Insufficient Pathology: 12%
- Microinfarcts and Vascular: 32%

No Dementia (N=85)

- Only AD Pathology: 28%
- None or Insufficient Pathology: 51%
- Other Pathologies: 12%
- Microinfarcts and Vascular: 6%
- Hippocampal Sclerosis: 3%

AD=Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, WM gliosis; Other = LBD, CAA, glioblastoma, cortical basal degeneration
MMSE Score by Number of Pathologies in people with Dementia

What are the risk factors for dementia in the oldest old?
Investigations of Risk Factors and Dementia

- Vitamin E (supplementation)
- Vitamin C (diet and supplementation)
- BMI
- Alcohol
- Caffeine
- Activities
- Homocysteine levels
- Thyroid function
- ApoE E4
the effect of Vascular Risk Factors
Cardio- and Cerebrovascular Disease & Risk of Dementia (N=625)

Hazard Ratio (95% CI) (log scale)

Prevalence

- CHF: 10%
- Stroke: 9%
- HVD: 6%
- Diabetes: 7%
- TIA: 17%
- MI: 12%
- Arrhythmia: 28%
- CAD: 15%
- High Cholest: 35%
- HTN: 59%

Medical History

Cox regression adjusting for age, gender, & education
Hypotension and Increased Risk of Dementia

• Gothenburg H-70 & Rotterdam
  – Ruitenberge et al., Dement Geriatr Cogn Disord, 2001

• East Boston Study
  – Morris et al., Arch Neurol, 2001

• Bronx Aging Study

• 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 would be the effect in 90+ year olds if we had successful treatment/prevention of AD?
## Impact of Interventions to Reduce AD Pathology on USA Dementia Prevalence in the Oldest-old

<table>
<thead>
<tr>
<th>Intervention Scenario</th>
<th>AD Pathology (NIA Reagan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modest Reduction</td>
<td>High → Intermediate</td>
</tr>
<tr>
<td>Moderate Reduction</td>
<td>High → Intermediate  Intermediate → Low</td>
</tr>
<tr>
<td>Substantial Reduction</td>
<td>High, Intermediate → Low</td>
</tr>
<tr>
<td>Complete Elimination</td>
<td>High, Intermediate, Low → None</td>
</tr>
</tbody>
</table>
Impact of Interventions to Reduce AD Pathology on USA Dementia Prevalence in the Oldest-old

No Intervention
- Modest Reduction
- Moderate Reduction
- Substantial Reduction
- Complete Elimination

Brookmeyer, Kawas, Corrada, et al Under review
Summary

• Remarkable increase in longevity and numbers of oldest old worldwide

• Risk of dementia is exceptionally high in these individuals, with AD accounting for half the dementia at most

• Classifying the etiology of dementia in the oldest old is very difficult particularly given the presence of multiple pathologies

• Risk and protective factors will be different for the different pathologies and need to be identified

• The oldest-old hold the secrets to successful aging
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