Dementia in the Oldest-Old: Lessons from The 90+ Study

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

* % of US elderly population (65+)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of People</th>
<th>% of US elderly population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2,000,000</td>
<td>4.7%</td>
</tr>
<tr>
<td>2020</td>
<td>4,000,000</td>
<td>4.9%</td>
</tr>
<tr>
<td>2030</td>
<td>6,000,000</td>
<td>4.6%</td>
</tr>
<tr>
<td>2040</td>
<td>7,000,000</td>
<td>7.0%</td>
</tr>
<tr>
<td>2050</td>
<td>9,000,000</td>
<td>9.6%*</td>
</tr>
</tbody>
</table>

The 90+ Study

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

(Co-PIs: Claudia Kawas & María Corrada)

Leisure World Cohort

13,978 (63% women)

1,931 >90 years Alive

The 90+ Study

1,931 >90 years Alive

3,774 >90 years Deceased

1,071 <90 years Alive

7,202 <90 years Deceased

Enrolled

N = 1608

83%

(77% women)
What is the Risk of Developing Dementia in the Oldest-Old?
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+

The graph shows the age-specific incidence of dementia in various studies with subjects aged 90+. Each line represents a different study location:
- 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
- Zaragoza, Spain

The x-axis represents age, ranging from 65 to 100, and the y-axis represents incidence (% per year) from 0 to 40.
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+

Doubling Time = 5.5 years

What is Related to Dementia in the Oldest-Old?
Risk/Protective Factors for Dementia in Oldest-old

- Vitamin E (supplementation)
- Vitamin C (diet and supplementation)
- BMI
- Alcohol
- Activities
- Homocysteine levels
- Thyroid function
- Inflammatory marker (CRP)
- ApoE e4
Cox regression adjusting for age, gender, & education

Higher Risk – CHF, Heart valve disease, Stroke

Lower Risk - High cholesterol, Hypertension
Risk of Dementia in Relation to Age of Onset of Hypertension

Developing hypertension after age 80 associated with a lower risk of dementia

The 90+ Autopsy Study

▷ In collaboration with UCI ADRC
▷ Enrolled 492 from in-person exams
▷ Longitudinal follow-up every 6 months
▷ 300 Autopsies (92% autopsy rate)
Pathologies that contribute to dementia in the oldest-old
Brain Pathologies

Alzheimer’s Plaques & Tangles

Hippocampal Sclerosis

Microinfarct

White Matter Disease
Odds of Dementia For Different Pathologies (vs not having that pathology)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Odds Ratio (95% CI) (log scale)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's</td>
<td>2.2 (1.3, 3.6)</td>
<td>50%</td>
</tr>
<tr>
<td>Micro-infarcts</td>
<td>3.7 (1.9, 6.9)</td>
<td>17%</td>
</tr>
<tr>
<td>Hippocampal Sclerosis</td>
<td>10.7 (5.6, 20.7)</td>
<td>17%</td>
</tr>
<tr>
<td>White Matter Disease</td>
<td>13.3 (6.2, 28.7)</td>
<td>8%</td>
</tr>
<tr>
<td>Amyloid Angiopathy</td>
<td>1.9 (0.5, 6.0)</td>
<td>13%</td>
</tr>
<tr>
<td>Large Infarcts</td>
<td>4.5 (2.2, 9.3)</td>
<td>4%</td>
</tr>
<tr>
<td>Lewy Body Disease</td>
<td>6.3 (3.3, 12.1)</td>
<td>4%</td>
</tr>
</tbody>
</table>

N=183   From logistic regression adjusting for age at death and sex

Pathological Diagnoses by Dementia Status

Dementia (N=111)
- AD Pathology: 59%
- None or Insufficient AD Pathology: 41%

No Dementia (N=103)
- AD Pathology: 39%
- None or Insufficient AD Pathology: 61%

AD=Intermediate/High NIA Reagan Criteria
Pathological Diagnoses by Dementia Status

**Dementia (N=111)**
- AD Pathology: 45%
- None or Insufficient AD/Vascular Pathology: 23%
- Microinfarcts and Vascular: 32%

**No Dementia (N=103)**
- AD Pathology: 38%
- None or Insufficient AD/Vascular Pathology: 56%
- Microinfarcts and Vascular: 6%

AD=Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, subcortical leukoencephalopathy
Pathological Diagnoses by Dementia Status

### Dementia (N=111)
- AD Pathology: 29%
- None or Insufficient AD/Vascular/HS Pathology: 17%
- Microinfarcts and Vascular: 32%
- Hippocampal Sclerosis: 22%

### No Dementia (N=103)
- AD Pathology: 38%
- None or Insufficient AD/Vascular/HS Pathology: 53%
- Microinfarcts and Vascular: 6%
- Hippocampal Sclerosis: 3%

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

**Dementia (N=111)**
- Only AD Pathology: 26%
- None or Insufficient Pathology: 12%
- Other Pathologies: 10%
- Microinfarcts and Vascular: 32%
- Hippocampal Sclerosis: 22%

**No Dementia (N=103)**
- None or Insufficient Pathology: 51%
- Only AD Pathology: 28%
- Other Pathologies: 12%
- Microinfarcts and Vascular: 6%
- Hippocampal Sclerosis: 3%

AD = Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, subcortical leukoencephalopathy; HS = Hippocampal Sclerosis; Other = LBD, CAA, glioblastoma, cortical basal degeneration
The Effect of Multiple Pathologies

Pathologies: AD NIA Reagan, 3+ microinfarcts, 2+ larger infarcts, LBD, Hippocampal sclerosis, Lewy Body Disease, subcortical arteriolosclerotic leukoencephalopathy, other (CBD, glioblastoma)

The oldest-old with preserved cognition and the full range of Alzheimer pathology (SFN 2016)

Rezvanian, Ohm, Kilreja, Gefen, Weintraub, Rogalski, Kim, Aguirre, Corrada, Mesulam, Kawas, & Geula

8 participants from The 90+ Study aged 95-100
Selected for superior performance on memory tests and preserved performance on other domains

Ranged from very sparse pathology (diffuse amyloid / tangle stage I) to two cases with pathological AD dx (frequent plaques / tangle VI)
Summary

- Risk of dementia is exceptionally high in oldest-old individuals
- Risk and protective factors change with age
- Studies hampered by limitation of only studying people who survived to age 90 (survival bias)
- Pathologies other than AD are important for dementia in oldest-old, but most cannot be identified during life
- Risk/protective factors different for different pathologies and largely unknown
- WHI ideal setting!
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