The 90+ Study: Cognitive Resilience, Early Life Predictors, & Neuropathological Findings

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Outline

- Background of *The 90+ Study*
- Operational definition of Cognitive Resilience
- Prevalence and Demographics in *The 90+ Study*
- Lifestyle 25 years before Cognitive Resilience
- Dementia-related Pathologies and Cognitive Resilience
The 90+ Study & The Leisure World Cohort Study
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
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

1,931
>90 years
Alive

3,774
>90 years
Deceased

1,071
<90 years
Alive

7,202
<90 years
Deceased

Enrolled
N = 1610
83%

(77% women, 99% Caucasian)
### The 90+ Study Participants

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Participants</strong></td>
<td>1610</td>
<td></td>
</tr>
<tr>
<td><strong>College grad or more</strong></td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td><strong>% Caucasian</strong></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td><strong>% of Women</strong></td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>94 (90 - 106)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing or group home</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Home alone</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Home with others</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Impaired no Dementia</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Unspecified Dementia</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>AD/Other</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>AD/VaD</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Alzheimer Disease</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

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![Pie chart showing distribution of cognitive diagnoses and other characteristics.](chart.png)
Assessments

- Demographics & Medical History
- Neuropsychological Tests
  - Memory, language, executive function
- Neurological & Physical Examination
- Informant Questionnaires
- Genetic studies
  - Stored DNA (n=850)
- Brain Imaging (n=211)
- Brain Donation (n=312)
Age-Specific Incidence of Dementia in Studies with Participants Aged 90+

Doubling Time = 5.5 years

Pathological Diagnoses by Dementia Status

Dementia (N=111)

- AD Pathology: 59%
- None or Insufficient AD Pathology: 41%
Pathological Diagnoses by Dementia Status

Dementia (N=111)

- None or Insufficient AD/Vascular Pathology: 23%
- AD Pathology: 45%
- Microinfarcts and Vascular: 32%

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

Dementia (N=111)

- AD Pathology: 29%
- Hippocampal Sclerosis: 22%
- Microinfarcts and Vascular: 32%
- None or Insufficient AD/Vascular/HS Pathology: 17%

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

Dementia (N=111)

- None or Insufficient Pathology: 12%
- Microinfarcts and Vascular: 32%
- Only AD Pathology: 26%
- Other Pathologies: 10%
- Hippocampal Sclerosis: 22%

AD=Intermediate/High NIA Reagan Criteria; Vascular = lacunes, large infarcts, subcortical leukoencephalopathy; HS = Hippocampal Sclerosis; Other = LBD, CAA, glioblastoma, cortical basal degeneration
Pathological Diagnoses by Dementia Status

No Dementia (N=103)

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

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

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

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

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
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Centenarian with Superior Cognitive Performance

- Followed from Age 92 to 101
- Cognitive scores at or above 90th percentile for her age
Cognitive Resilience
Cognitive Resilience: Operational Definition

- 2 or more visits (median=6, range 2-26)
- Average MMSE ≥ 28
- Last MMSE ≥ 28 & within 12 months of death or last f/u

Dementia 49%
Resilient 13%
Not Resilient 38%

N = 760
Cognitive Resilience in The 90+ Study

<table>
<thead>
<tr>
<th></th>
<th>Dementia (N=376)</th>
<th>Not Resilient (N=289)</th>
<th>Resilient (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age @ last f/u (years)</td>
<td>97.1 (90-110)</td>
<td>96.7 (90-107)</td>
<td>96.4 (91-102)</td>
</tr>
<tr>
<td>MMSE @ last f/u</td>
<td>14.5</td>
<td>24.9</td>
<td>28.8</td>
</tr>
<tr>
<td>Interval between LW &amp; last 90+ f/u (years)</td>
<td>26.9 (18-35)</td>
<td>26.8 (17-35)</td>
<td>28.5 (19-35)</td>
</tr>
</tbody>
</table>
Hypotheses

- Education is related to resilience
- APOE ε2 is related to resilience
- Lifestyle is related to resilience
Cognitive Resilience in the Oldest-Old: Demographics & APOE

**% Women**

- Demented
- Not Resilient
- Resilient

**% Any Grad school**

- Demented
- Not Resilient
- Resilient

$\text{p}<0.10$

**% APOE e4**

- Demented
- Not Resilient
- Resilient

**% APOE e2**

- Demented
- Not Resilient
- Resilient
Lifestyle Factors Measured Two Decades Earlier & Resilience

- **Active** (1+ hrs/day)
- **Leisure** (5+ hrs/day)
- **Watch TV** (3+ hrs/day)
- **Sleeping** (8+ hrs/day)
- **Alcohol** (2+ drinks/day)
- **Attitude** (top tertile)

**Dementia**

**Not Resilient**

**Resilient**

<table>
<thead>
<tr>
<th>Activity</th>
<th>% in Upper Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (1+ hrs/day)</td>
<td>30%</td>
</tr>
<tr>
<td>Leisure (5+ hrs/day)</td>
<td>30%</td>
</tr>
<tr>
<td>Watch TV (3+ hrs/day)</td>
<td>40%</td>
</tr>
<tr>
<td>Sleeping (8+ hrs/day)</td>
<td>50%</td>
</tr>
<tr>
<td>Alcohol (2+ drinks/day)</td>
<td>30%</td>
</tr>
<tr>
<td>Attitude (top tertile)</td>
<td>20%</td>
</tr>
</tbody>
</table>
Cognitive Resilience & Dementia Related Pathologies
Hypotheses

- Cognitive resilience is related (in part) to the absence of dementia-related pathologies (brain resilience).

- Non-demented individuals with AD pathology will be more likely to have faster cognitive decline than those without.

- Resilient individuals will be more likely to have little or no amyloid, fewer neurofibrillary tangles, or less vascular disease.
Cognitive Resilience in the Oldest-Old: Alzheimer’s Pathology

**% Plaques None/Rare**

- Demented
- Not Resilient
- Resilient

**% Tangles 0-II**

- Demented
- Not Resilient
- Resilient

**% AD Intermediate/High**

- Demented
- Not Resilient
- Resilient

$p<0.10$
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)
Cognitive Resilience in the Oldest-Old: Vascular Pathologies

- **% Large Infarcts/Lacunes**
  - Demented
  - Not Resilient
  - Resilient

- **% Arteriolosclerosis (mod/sev)**
  - Demented
  - Not Resilient
  - Resilient

- **% microinfarcts (1+)**
  - Demented
  - Not Resilient
  - Resilient

- **% Atherosclerosis (mod/sev)**
  - Demented
  - Not Resilient
  - Resilient

Note: All differences are statistically significant at p<0.10.
Pathology Index & Resilience (N=270)

Dementia  Not Resilient  Resilient

Pathology Index

Dement0a  Not Resilient  Resilient

Pathology Index & Resilience

(tangles (0-II, III-IV, V-VI) + plaques (0, sparse/mod, frequent) + microinfarcts (0, 1-2, 3+) + macroinfarcts (0, 1, 2+) + LB + HS + WM disease)
Hypotheses

Cognitive Resilience in the presence of AD pathology is (in part) related to:

- APOE genotype
- Education
APOE, Dementia, and AD Pathology

Dementia

AD Neuropathology

% demented

% with Neuropathological AD

APOE Genotype

D Berlau, M Corrada, E Head, C Kawas Neurology 2009; 72:829:834
Two Amyloid Positive Participants with Normal Cognition
Odds of Cognitive Impairment in Relation to Amyloid PET

- 103 participants with amyloid PET
- 67 normal, 36 with impaired cognition
- Mean age: 96 years
- Education: < college (47%) vs. > college degree (53%)

![Odds Ratio Chart]

Higher education may confer resilience in the presence of amyloid deposition.
Resilience and PET Amyloid Deposition

Amyloid deposition (SUVR) does not distinguish resilience vs non-resilient or demented individuals (N=143)
Some Final Thoughts ...
Alzheimer Disease
amyloid cascade hypothesis

Secondary Prevention Trials in amyloid + individuals

Is this preclinical AD or resilience?
Summary

- Oldest-old, ideal group for studying resilience
- Sleep, Attitude and other lifestyle factors may be associated with cognitive resilience in the oldest-old
- Cognitive resilience does not appear to be due to a paucity of dementia-related pathologies, except perhaps for mod/severe atherosclerosis, and large or lacunar infarcts
- APOE ?

2 and education are associated with good cognitive performance in the presence of AD-type pathology
- When we observe AD pathology in cognitively normal individuals, is it resilience or preclinical AD?
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Cognition, Education and Amyloid PET

Higher education confers resilience

- 103 participants with amyloid PET
- 67 normal, 36 with impaired cognition
- Mean age = 96 years
- Education: > college degree (53%) vs. < college (47%)

<table>
<thead>
<tr>
<th>Odds Ratio for Cognitive Group (normal vs. impaired) as outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Aβ negative                OR (95% CI)</td>
</tr>
<tr>
<td>&lt; College Degree</td>
</tr>
<tr>
<td>≥ College Degree</td>
</tr>
</tbody>
</table>

SA Sajjadi et al, AAIC 2017
Rate 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)

AB Balasubramanian, 2011
The Leisure World Cohort Study

- Demographics & personal info
  - Marital status, height, weight, weight at age 21

- Medical history
  - Hospitalizations, illnesses, medications

- Personal/lifestyle habits
  - Exercise, sleep habits, alcohol use, smoking, diet, vitamin intake

- ‘Attitude’ scale (selected items from Zung)

- Medical screening
  - Hemoccult, blood pressure, PAP smear, mammogram, breast self-exam

- Menstrual & reproductive history
The 90+ Study
(Co-PIs: Claudia Kawas & María Corrada)

- Epidemiological longitudinal study of aging and dementia
- Survivors of the Leisure World Cohort Study (USC, A Paganini-Hill)
- Aged 90 and older as of:
  - January 1, 2003
  - On or after January 1, 2008
- ~1,600 enrolled