RCCN Workshop:
Measuring Biologic Age

Brain Aging: *The 90+ Study*

Jan 18, 2022

Claudia H. Kawas, M.D.
University of California, Irvine

Nothing to Disclose
Aging
The Elephant in the Room!

In the past century we added 27 years to average life expectancy.

Age is the biggest risk factor for cognitive loss and dementia but is rarely studied.

What is Aging?
If increases in life expectancy continue,

more than half of all children born today in developed countries can expect to celebrate their 100th birthdays


Unknown in 90+ Year Olds

- Risk/Protective Factors Related to Longevity
- Prevalence and Incidence of Dementia, Disability and Frailty
- Risk/Protective Factors Related to Dementia
- Types of Dementia
- Excluded from diagnostic criteria for AD (McKhann, 1984)
- Excluded from most studies including ADNI, Clinical trials
The 90+ Study

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

Leisure World Cohort
13,978
Median age 73 years

1,931 ≥90 years
Alive

1,071 <90 years
Alive

3,774 >90 years
Deceased

7,202 <90 years
Deceased

Enrolled
N = 1603
83%
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 and Leisure
- Positive Attitude

Corrada, et al, AAN 2004
90+ Study 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>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, No Dementia</td>
<td>34%</td>
</tr>
<tr>
<td>Dementia</td>
<td>34%</td>
</tr>
<tr>
<td><strong>% of Women</strong></td>
<td>76%</td>
</tr>
</tbody>
</table>
Many putative risk factors for dementia do not appear to be risk factors for dementia at this age:

- Vitamin E (supplementation)
- Vitamin C (diet and supplementation)
- BMI
- Alcohol
- Caffeine
- Apolipoprotein E ε4
- Homocysteine levels
- Thyroid function
- Education and physical performance
Cardio- and Cerebrovascular Disease & Risk of Dementia (N=625)

Cox regression adjusting for age, gender, & education

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Prevalence</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>10%</td>
<td>0.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>9%</td>
<td>0.5</td>
</tr>
<tr>
<td>HVD</td>
<td>6%</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7%</td>
<td>0.5</td>
</tr>
<tr>
<td>TIA</td>
<td>17%</td>
<td>0.5</td>
</tr>
<tr>
<td>MI</td>
<td>12%</td>
<td>0.5</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>28%</td>
<td>0.5</td>
</tr>
<tr>
<td>CAD</td>
<td>15%</td>
<td>0.5</td>
</tr>
<tr>
<td>High Cholest</td>
<td>35%</td>
<td>0.5</td>
</tr>
<tr>
<td>HTN</td>
<td>59%</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Risk of Dementia in Relation to Age of Onset of Hypertension

Adjusted for age & education

Corrada, et al. 2017
What are the causes of dementia in 90+ year olds?

The 90+ Autopsy Study

- 587 people enrolled
- 432 have come to autopsy
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
Pathological Diagnoses by Dementia Status

**Dementia (N=98)**
- AD Pathology: 45%
- None or Insufficient AD/Vascular Pathology: 23%
- Microinfarcts and Vascular: 32%

**No Dementia (N=85)**
- AD Pathology: 39%
- None or Insufficient AD/Vascular Pathology: 55%
- Microinfarcts and Vascular: 6%

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%
- Microinfarcts and Vascular: 6%
- None or Insufficient AD/Vascular/HS Pathology: 53%
- Hippocampal Sclerosis: 3%

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

**Dementia (N=98)**
- AD Pathology: 24%
- Other Pathologies: 10%
- Microinfarcts and Vascular: 32%
- None or Insufficient Pathology: 12%
- Hippocampal Sclerosis: 22%

**No Dementia (N=85)**
- None or Insufficient Pathology: 51%
- Only AD Pathology: 28%
- Other Pathologies: 12%
- Hippocampal Sclerosis: 3%
- Microinfarcts and Vascular: 6%

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

Only ~ 2/3 of dementia cases attributable to neurodegenerative pathologies

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

Odds of Dementia by Combination of Neuropathology

<table>
<thead>
<tr>
<th>Combination of Neuropathology</th>
<th>Odds Ratio (95% CI) (log scale)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
<td>30%</td>
</tr>
<tr>
<td>AD alone</td>
<td>3.5</td>
<td>26%</td>
</tr>
<tr>
<td>non-AD alone</td>
<td>12.4</td>
<td>14%</td>
</tr>
<tr>
<td>AD plus</td>
<td>13.4</td>
<td>24%</td>
</tr>
<tr>
<td>non-AD plus</td>
<td>10.6</td>
<td>7%</td>
</tr>
</tbody>
</table>

N=183 From logistic regression adjusting for age at death and sex
Some questions relevant to brain aging

- Is amyloid deposition (and other pathologies) in non-demented nonagenerians *Resilience or Preclinical disease*?

- Is apparent *resilience to AD*, in part, merely the absence of other pathologies?

- What does age have to do with it and how do we measure it?

- In the absence of neurodegenerative disease, what are the biological underpinnings of age-related cognitive declines?
Thank you!
90+ Study participants and families

90+ Investigators & Staff

Maria Corrada – co-Principal Investigator
Annlia Paganini-Hill
Dana Greenia
Ahmad Sajjadi
Farah Mozaffar
Jaime DeMoss
Christina Whittle
Zara Melikyan
Tina Liu
Thomas Trieu
Ryan Bohannan
Chad Caraway
Sarah Ashrafnia

Colette Aguirre
Montez Hester
Maria Kirkwood
Dan Hoang
Pinar Coskun
Natalie Bryant
Kristin Nguyen
Zeinah Al-darsani
Sara Sabeti

Our Collaborators

Ronald Brookmeyer - UCLA
Charles DeCarli - UC Davis
Tom Montine - Stanford
John Trojanowski - U Penn
Josh Sonnen - U of Utah

UCI

Ronald Kim
David Cribbs
Charles Glabe
Malcolm Dick
Carl Cotman

Frank LaFerla
Aimee Pierce
Dan Gillen
Mark Mapstone
Ed Monuki

Supported by:

NIH: R01AG21055, R01AG042444, P50AG016573, T32AG000096
Alzheimer’s Association: NIRG-10-173916
90+ Study Sharable Resources
mcorrada@uci.edu

Longitudinal Clinical Data
- Demographics
- Neuropsych scores
- Cognitive diagnosis
- Medical hx, medications
- Physical performance
- etc, etc, etc.

Neuropathology Data
- NACC form - UCI, Stanford
- Digital pathology images
- Microinfarcts - Sonnen
- Aβ area, synaptic markers, etc. – UPenn (Trojanowski)

The 90+ Study Data and Tissue Resources

NeuroImaging – UC Davis
- MRI antemortem  N=239
- MRI postmortem  N=55
- Amyloid PET  N=317
- Tau PET  N=86

Genetics
- DNA storage, ApoE genotype
- Lymphoblastic cell lines
- NCRAD

Post-Mortem Tissue Samples
- Frozen / fixed brain tissue
- Plasma /serum
- CSF
- Extracted DNA

The 90+ Study: R01AG021055, MPIs: C. Kawas, M. Corrada