Lessons from the Oldest Old: *The 90+ Study*

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Madame Jeanne-Louise Calment
Arles, France

1875 – 1997
Age 122
Madame Jeanne-Louise Calment
Supercentenarian
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

Millions of People

Year

2001  2010  2020  2030  2040  2050

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

Crystal, et al, Arch Neurol 2000
Why Study the Oldest-Old?
The Oldest-old

- Fastest growing segment of the population
- Excluded from many aging and dementia studies
  - NINCDS-ADRDA criteria for AD
  - Alzheimer’s Disease Neuroimaging Initiative
- Many population-based studies have low numbers of oldest-old
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
Overview

1. *The 90+ Study*
2. Factors that promote longevity
3. Incidence and Risk Factors for Dementia in the Oldest Old
4. Clinical Pathological Correlations for Dementia
5. Our latest efforts
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
Study population
UCI Clinic for Aging Research and Education
Laguna Woods, CA
• 60 minutes Australia May 2015
• CBS 60 minutes May 2014
• Good Day LA 2014
• OC Register Jan, Oct & Nov 2013
• KCAL 9 TV 2013
• NPR Radio 2012
• Italian Public TV 2012
• Laguna Woods Globe 2012
• Russia-2 TV Documentary 2012
• Newport Beach Daily Pilot 2010
• Bottom Line Health magazine 2010
• New York Times front page 2009
• Louie B. Free radio program 2009
• Los Angeles Times front page 2004
• KCET Life & Times 2003
• My Generation Magazine 2015
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 = 1757

1980s
1/1/03
The 90+ Study

• 2003: ~1,140 survivors of the Leisure World Cohort aged 90 years old and older were invited

  • Total of ~1,757 participants enrolled
  • Participants evaluated every 6 months
    • neuropsychological tests
    • physical and neurological examinations
    • neuroimaging
  • Many enrolled in The 90+ Autopsy Study
35 States Traveled To Visit Participants

# of participants
- 719
- 16
- 9
- 6
- 5
- 3
- 2
- 1
Research Goal

To study potentially modifiable risk factors that may contribute to the prevention or the delay of the development of Alzheimer’s disease and dementia
Assessments

• Intake - Demographics & Medical History
• Neuropsychological Tests - Memory, language, executive function
• Neurological Examination
• Informant Questionnaires
• Brain PET / MRI scans & overnight B/P and Oxygen measurements
• Genetic studies - DNA
• Brain Donation
Physical Performance Measures
Frequency of Medical Histories at Baseline

- HBP: 51%
- Osteoarthritis: 43
- Cancer: 39
- Macular Degen: 29
- High Chol: 29
- Thyroid: 27
- Atrial Fib / Arryth: 22
- TIA: 21
- Depression: 20
- Glaucoma: 18
- CHF: 15
- Stroke: 13
- CAD: 14
- MI: 11
- Rheum Arthr: 8
- Diabetes: 7

12/2012
What is Related to Longevity?
Vitamins, Beverages and Longevity
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)
- Body Mass Index
- Activities - Exercise
- Activities - Leisure
- Caffeine
- Alcohol (wine, beer, other)

Body Mass Index and Mortality

[Image of BMI categories for women and men with corresponding BMI values (17, 18, 20, 22.5, 24, 24.5, 26.5, 31.5, 35, 37).]

Source: Reprinted from material of the Dietitians of Canada.
BMI and All-Cause Mortality
Leisure World Cohort: 1981-2004

Activities and Longevity
‘Active’ Activities and Mortality
Leisure World Cohort: 1981-2004

\[ N = 13,601 \]
‘Other’ Activities and Mortality
Leisure World Cohort: 1981-2004

N = 13,601
Intake of Alcohol and Caffeine

Alcohol (wine, beer, other)

- 1-2 glasses of alcohol a day reduction in mortality up to 18%

Caffeine

- Equivalent to ~2 cups of coffee a day reduction in mortality of 10%

What is related to Dementia in the Oldest-Old?
What is Dementia?

• A decline in mental ability severe enough to interfere with daily life
Dementia

• Loss of cognitive abilities including:
• 2 Domains:
  – Memory and
  – One or more of the following domains:
    - Visual-Spatial, Language, Constructions, Calculations, Attention deficits, Executive function

• And Functional Loss (ADLs)
Causes of Dementia in the Elderly

- Alzheimer’s Disease: 62%
- Vascular Dementia: 17%
- Lewy Bodies: 4%
- Fronto-temporal: 2%
- Parkinson’s disease: 2%
- Mixed Dementia: 10%
- Other: 3%
## The 90+ Study Participants
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td># of Participants</td>
<td>1757</td>
<td></td>
</tr>
<tr>
<td>% of Women</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td>94 (90 - 106)</td>
<td></td>
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<tr>
<td>Type of Residence</td>
<td></td>
<td></td>
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<tr>
<td>Nursing or group home</td>
<td>36%</td>
<td></td>
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<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>Cognitive Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Cognitively Impaired not Demented</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Demented</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>

**Education**
- College grad or more: 39%

**Marital Status**
- Widowed: 75%
- Married: 15%
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+
Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+
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
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 did not distinguish demented and non-demented participants except **hypertension**

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

*Reduced odds of dementia in B/P above normal vs. normal B/P*

Corrada, et al, AAN 2010
Risk of Dementia in Relation to Age of Onset of Hypertension

Adjusted for age & education

Corrada, et al. AAIC 2014
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
The 90+ Autopsy Study

- In collaboration with UCI ADRC
- Enrolled 439 from in-person exams
- Longitudinal follow-up every 6 months
- 270 Autopsies (92% autopsy rate)
## 90+ Autopsy Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Not Demented</th>
<th>Demented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>MMSE</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Brain Weight (g)</td>
<td>1150</td>
<td>1117</td>
</tr>
</tbody>
</table>
Alzheimer’s Brain  
Normal Brain
AD Pathological Features

Neuritic Plaques
Extracellular deposits of beta-amyloid

Neurofibrillary Tangles
Intracellular deposits of hyperphosphorylated tau
Pathological Diagnoses by Dementia Status

No Dementia (N=85)
- AD Pathology: 39%
- None or Insufficient Pathology: 61%

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

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

CA1/Subiculum

Berlau et al., Arch Neurol, 2007
Other pathologies that may contribute to dementia in the oldest old
Lewy Body
H&E stained sections of frontal cortex at 200x magnification. A single microinfarct is shown (black 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 (pink arrow) due to a different arterial supply (meningal arteries vs. deep penetrating cerebral arteries). Scale bar is approximately 70 microns.
Hippocampal Sclerosis

Neuronal cell loss and gliosis in the CA1 and subiculum of the hippocampus
Frequency of Dementia by Number of Pathologies (N=183)

Kawas, et al. (under revision)
Important Studies

- Brain Donation - The 90+ Autopsy Study
- Amyloid PET & MRI imaging
- 24-hour blood pressure and oxygen
- Blood draw for DNA genetic studies
Brain PET Scan

- Positron Emission Tomography
- A new radiotracer that enables researchers see amyloid plaques during life
- Amyloid plaques are accumulations of proteins found in Alzheimer’s disease
Brain MRI

- Magnetic Resonance Imaging
- Allows researchers see a variety of abnormalities related to cognitive problems
  - Brain volume
  - White matter disease
  - Gray matter disease
  - Strokes
  - Hippocampal volume
Summary

- Remarkable increase in longevity and numbers of oldest old world-wide
- Risk of dementia continues to increase with age
- 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
- Old people are not bad versions of younger people!
Did you hear?  95 is the new 65!
To Volunteer for Research at UCI:

*The 90+ Study*

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