Lessons from the Oldest Old: The 90+ Study
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Aging Life Care Association
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Madame Jeanne-Louise Calment
Arles, France

1875 – 1997
Age 122
If increases in life expectancy continue, more than half of all children born today in developed countries can expect to celebrate their 100th birthdays.

Christensen, Aging Populations: The Challenges Ahead, Lancet, 2009

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. Describe the Relationship between Exercise and Falls in 90+ year olds
U.S. Projected Population Growth Among 90+ Year Olds

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, J Am Med Assoc 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
USC

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

The 90+ Study
The 90+ Study

• 2003: ~1,140 survivors of the Leisure World Cohort (13,978 were enrolled) aged 90 years old and older were invited.

• Today we have a total of 1,882 participants enrolled.

• Participants evaluated every 6 months:
  • neuropsychological tests
  • physical and neurological examinations
  • Neuroimaging – Brain PET scans & MRIs

• Many enrolled in The 90+ Autopsy Study

Assessments

• Intake
  – Demographics & Medical History

• Neuropsychological Tests
  – Memory, Language, Executive function

• Neurological Examination
• Informant Questionnaires
• Genetic studies
  – DNA

• Brain Donation
## Physical Performance Measures

### The 90+ Study Participants Baseline Results

<table>
<thead>
<tr>
<th># of Participants</th>
<th>1882</th>
</tr>
</thead>
<tbody>
<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>96</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>Assisted Living</td>
<td>30%</td>
</tr>
<tr>
<td>Home alone</td>
<td>30%</td>
</tr>
</tbody>
</table>

### Neurological Exam Cognitive Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>Cognitively Impaired, not Demented</td>
<td>26%</td>
<td>33%</td>
</tr>
<tr>
<td>Demented</td>
<td>41%</td>
<td>24%</td>
</tr>
</tbody>
</table>

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- 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
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.

35 States Traveled To Visit Participants

Frequency of Medical Histories at Baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP</td>
<td>43</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>29</td>
</tr>
<tr>
<td>Cancer</td>
<td>29</td>
</tr>
<tr>
<td>Macular Degener</td>
<td>27</td>
</tr>
<tr>
<td>High Chol</td>
<td>22</td>
</tr>
<tr>
<td>Thyroid</td>
<td>21</td>
</tr>
<tr>
<td>Atrial Fib / Arryth</td>
<td>20</td>
</tr>
<tr>
<td>TIA</td>
<td>18</td>
</tr>
<tr>
<td>Depression</td>
<td>15</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>14</td>
</tr>
<tr>
<td>CHF</td>
<td>11</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
</tr>
<tr>
<td>CAD</td>
<td>9</td>
</tr>
<tr>
<td>MI</td>
<td>8</td>
</tr>
<tr>
<td>Rheum Arth</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
</tr>
</tbody>
</table>
What is Related to Longevity?

Vitamins, Beverages and Longevity

• Vitamin C (diet + supplements)
• Vitamin A (diet + supplements)
• Vitamin E (supplements)
• Calcium (diet)
• Soft drinks (cola & other)
• Tea (black or green)

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)
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
Causes of Dementia in the Elderly

- Alzheimer's Disease: 52%
- Vascular Dementia: 17%
- Mixed Dementia (both AD and minor strokes): 14%
- Lewy Bodies: 4%
- Fronto-temporal: 2%
- Parkinson's disease: 2%
- Other: 8%

Age-Specific Incidence of Dementia in Studies with Subjects Aged 90+

Incidence (per 1000 person-years) vs. Age

- Incidence increases with age
- Highest incidence observed in studies with subjects aged 90+

Diagrams show the trend of incidence over age categories for different 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

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 and Prevalent Dementia

46% Hypertension
13% Coronary Artery Disease
13% Myocardial Infarction
17% Congestive Heart Failure
22% Atrial Fibrillation

Vascular risk factors did not distinguish demented and non-demented participants except hypertension
Background

- Cardiovascular diseases in midlife are commonly associated with an *increased* risk of dementia later in life. (Kivipelto, Brit Med J 2001; Whitmer, Neurology 2001; Launer, Neuroscience Aging 2000)
- In contrast, history of *hypertension* in the oldest-old is associated with a *decreased* risk of dementia. (Li, JAGS 2007; Ruitenberg, Geriatr Cogn Disord 2001; MM Corrada, Alzheimers Dement. 2014)
- Whether the apparent change in risk with age is unique to *hypertension*, or other cardiovascular risk factors behave in a similar manner, is not known.

Prevalence of Cardiovascular Risk Factors at Baseline

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>44</td>
</tr>
<tr>
<td>High Cholesterol</td>
<td>36</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>27</td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
<td>15</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>15</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>12</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>10</td>
</tr>
<tr>
<td>Heart Valve Disease</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
</tr>
</tbody>
</table>

Association between Cardiovascular Risk Factors & Risk of Dementia in the Oldest-Old (N=559)

Medical Histories Analyzed Separately
Conclusions

- In people who reach age 90+ without dementia:
  - *Decreased risk* - Hypertension
  - *Increased risk* - Congestive heart failure, stroke, and heart valve disease

- The association with dementia changes with age for some but not all vascular diseases.
Discussion

- Our results are consistent with other studies.

- Hypertension at older ages may be necessary to sustain adequate cerebral perfusion in the oldest-old.

- Survival bias is an unlikely explanation for the association between hypertension and a decreased risk of dementia; finding is specific to hypertension and not other vascular diseases.


Risk of Dementia in Relation to Age of Onset of Hypertension

<table>
<thead>
<tr>
<th>Age of Onset of Hypertension</th>
<th>Relative Risk (95% CI, log scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.88 (0.68-1.13)</td>
</tr>
<tr>
<td>80-89</td>
<td>0.59 (0.45-0.79)</td>
</tr>
<tr>
<td>90+</td>
<td>0.45 (0.32-0.65)</td>
</tr>
</tbody>
</table>

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 tortuous 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

- Enrolled 506
- Longitudinal follow-up every 6 months
- 305 have come to autopsy

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: 42%
- None or Insufficient Pathology: 58%

Dementia (N=98)
- AD Pathology: 60%
- None or Insufficient Pathology: 40%

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 arrow) 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 (meningeal arteries vs. deep penetrating cerebral arteries). Scale bar is approximately 70 microns.

Microinfarcts

Hippocampal Sclerosis

Neuronal cell loss and gliosis in the CAI and subiculum of the hippocampus
OBJECTIVE

To explore the relationship between risk of falling at age 90+ and physical activity at ages 60-70s
Methods

• Time spent exercising (at ages 60 -70s) was self-reported in 1980s and categorized as none, 15 minutes, 30-45 minutes, or 1+ hour / day.

• 1536 participants (or their informant) of The 90+ Study provided information on falls in the previous year.

• Mean age = 94 years; 78% female; 99% Caucasian

RESULTS

• 52% had fallen in the prior year
• 32% had fallen more than once
• 21% had had a severe fall
• Falling at age 90+ was significantly related to:
  – Medical hx: heart disease, TIA/stroke, arthritis, vision disease, dementia, depression
  – Medications: hypnotics, anti-psychotics, anti-depressants
  – Assistive Devices: cane, walker, wheelchair

RESULTS

• Regular physical activity (30+ minutes /day) at ages 60 -70s was associated with a 35% lower odds of falling in the previous year at age 90+.

• Regular physical activity (30+ minutes /day) at ages 60 -70s was associated with a 45% lower odds of repeated falls in the previous year at age 90+.
Conclusion and Relevance

- Falls are extremely common among the oldest-old and often lead to serious injury.

- Prior exercise of 30+ minutes/day was related to a decreased risk of falling at age 90+ even the presence of co-morbidities, certain medications and assistive devices.

- This work is the first to show an association between exercise at ages 60-70s and lower risk of falling at age 90+.

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

Did you hear? 95 is the new 65!

The Laguna Beach Independent - O'Malley - 2/1/08
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60 Minutes - May 4, 2014

The 90+ Study Team