Prospects for Prevention of Dementia in our Increasingly Aging Society: Good News on the Horizon?

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• Previous: As mortality decreased demographers and actuaries assumed we were approaching an upper limit of life expectancy. At the upper limit "old age" set in; nothing could be done

• More recent evidence indicates POSTPONEMENT OF MORTALITY is widespread

• Rather than sensecence being inevitable in multi-cellular species, biodemography suggests greater variations in patterns of aging.

• No evidence for an upper limit of life expectancy
Overview: Widespread aging of populations in both developed and developing world has resulted in dramatic increases in persons with AD and related dementias. These trends will challenge social and economic welfare for most countries. The trends may also be seen as welcome for individuals and what they can contribute.

Widespread variation in patterns of aging exist. This widespread variation is a challenge to clinicians but can also be a clue to opportunities for optimization and suggest that senescence need not be considered inevitable.

Primary prevention trials have been disappointing but at least three epidemiologic studies suggest there may already be delayed onset of dementia.

AD or Multi-infarct dementia? Not the dichotomy typical of early onset dementia but variation is key with the complex "ecology" of the aging brain being an individually varying complex convergence of clinical and subclinical diseases (AD, vascular and Lewy Body diseases).

No treatment to date has been proved effective at reducing or removing plaques and tangles. Multiple risk factors for dementia have been identified, many of which are modifiable.

The burden of aging is great for individuals and for societies. Better health of our aging populations may have already relieved the burdens of aging and could be mobilized for further good.
Postponement of Mortality

• More people living to 100 - Sweden: 3 in the 1860; 750 in 2008 and of those born in 2007 50-60,000 expected to live to 100

• More people living to each progressive old age milestone: 85, 90, 95. This is driven by progressive increases in survival past age 65, 75 and beyond

• Overall we see a postponement of senescence, occurring later in life

• "Two scourges of old age are cognitive impairment, often due to Alzheimer's disease and Sensory deprivations" (Vaupel, 2010)
Historical trends in $X_5$ and $X_{10}$, the ages at which remaining life expectancies are, respectively, five and ten years for females in Sweden (1861-2008), the USA (1933-2006) and Japan (1947-2008). For Swedish women, since 1950 senescence as measured by $X_{10}$ has been postponed by about eight years. For Japanese women, since 1950 $X_{10}$ has risen about 12 years. Note that for all three countries, the curve for $X_5$ follows the same general trajectory as the curve for $X_{10}$ but at a roughly constant gap of about a decade of age. This indicates that senescence, as captured by these two measures, is being postponed rather than lengthened.

James W. Vaupel; Biodemography of human ageing; Nature 2010;464, 536-42; doi:10.1038/nature08984
Figure 3. Age and the incidence of Alzheimer disease in 6 studies compared with the Adult Changes in Thought (ACT) cohort study. EURODEM indicates European Studies of Dementia, MoVIES CDR >0.5, MoVIES Clinical Dementia Rating 0-5 or greater, Monongahela Valley Study, Rochester, Rochester, Minn, study; Framingham, Framingham, Mass, study; East Boston, East Boston, Mass, study; and Baltimore Longitudinal Aging Study, the Baltimore Longitudinal Study of Aging, Baltimore, Md.
<table>
<thead>
<tr>
<th>Age</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 - 69</td>
<td>.8 %</td>
</tr>
<tr>
<td>70 - 74</td>
<td>1.4 %</td>
</tr>
<tr>
<td>75 - 79</td>
<td>6.3 %</td>
</tr>
<tr>
<td>80 - 84</td>
<td>12.7 %</td>
</tr>
<tr>
<td>85 - 89</td>
<td>29.7 %</td>
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<tr>
<td>90 - 94</td>
<td>50.2 %</td>
</tr>
<tr>
<td>95+</td>
<td>74.3 %</td>
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</table>
Alzheimer’s Prevalence – 7 Studies
Alzheimer’s Disease and Related Dementias
Are Diseases of Old Age

- Population with ADRD is becoming older.

- Our early work (1978-80): Mean age of persons with dementia was 79 years and median duration of symptoms was over four years.

- In our current research the mean age is getting older - probably exceeds 85 with duration of symptoms typically 1-2 years.

- Two trends:
  1. Dramatic increase in incidence of ADRD with age (< 5/1000 at 65 vs- > 50/1000 ages 85-89 and 85/1000 age 90+)
  2. Postponement of mortality in later life
  3. Research results may “change”
Forecast of Dementia Prevalence Worldwide

Prevalence: 24.3 Million

2001: 7.7
North America: 3.4
South America: 1.8
Europe: 9.9
Africa: 1.5
Asia: 2.8

2020: 42.3 Million
North America: 10.8
South America: 5.1
Europe: 19.5
Africa: 4.1
Asia: 2.8

2040: 81.1 Million
North America: 15.9
South America: 6.2
Europe: 40.6
Africa: 9.1
Asia: 6.3

Ferri, et al. Lancet, 2005

Legend:
- Europe
- North America
- South America
- Africa
- Asia
Disappointing primary prevention trial results

- Antioxidants: AREDS, Women’s Health Study, Physicians Health study, Health Protection Study: no consistent benefit
- Estrogen: HERS, WSHIMS, COGENT: neutral or harmful
- Ginkgo Biloba: GEMS, GuidAge: neutral
- NSAIDS: ADAPT (naprosyn and celebcoxib): stopped due to harm
• Are we already seeing cohort effects of potentially modifiable risk factors: better education, greater wealth, reduced vascular risk?

• Manton (2005): National Long Term Care Survey Data (1982-1999) Decline in Severe Cognitive impairment - 5.7-2.9%


Early efforts, especially when we saw a "younger" population with dementia, were to distinguish AD from vascular dementia (VD).

Key observation: Skoog's 1993 paper describing causes of dementia in 85 yo in Sweden: almost 50% had VD (higher rates in older persons observed originally by Blessed, Tomlinson, and Roth (1970).

Our neuropathologic study (Lim 1999) described community-based autopsy results for persons with AD. NINCDS clinical criteria were quite accurate but of the 95 of 135 cases with neuropathologic AD only 34 had "pure" AD, with remainder having coexisting vascular or Lewy body lesions.

The general trend is for increasing recognition of the importance of "mixed dementias" in late-life dementias even though our efforts in research are to categorize persons into one or the other disease entity.
Unique study: "Ecology of the Aging Human Brain" (Sonnen, 2011)

Montine/Sonnen neuropathology lab accumulated 1672 brain autopsies from ACT, HAAS, Nun Study and Oregon Brain Aging Study); 424 met criteria for being cognitively normal at time of death.

Results: 47% had moderate to frequent NP density (6% had Braak stage V or VI for NFTs; 15% had medullary Lewy Body disease; 8% and 4% respectively had nigral and isocortical LBD; Cerebral microinfacts were identified in 33% with a high level in 10%. Overall burden of lesions in each individual and their co-morbidity varied widely within each study but was similar among studies.

Conclusion: The data show an individually varying complex convergence of subclinical diseases in the brains of older cognitively normal adults. This ecology should help guide biomarker, neuroimaging studies as well as clinical trials that focus on community, and population-based cohorts.
Brain Autopsy Results in 336 Cognitively Normal Subjects Expressed as Summary Neuropathology Slopes
• Mortality is being postponed; populations are older.

• Senescence is not inevitable; biodemography suggests great(er) variations in patterns of aging.

• Several neurodegenerative processes commonly occur (together) in late life: in persons without impairment and in those with dementing disorders - another source of variation.

• Sources of variation can be basis for prospects for prevention.

• What is the evidence for potentially modifiable risk factors for late life dementias?
Potential impact of risk factor reduction

Since no treatment to date has yet been proved effective for reducing plaques and tangles, there may be no "magic bullet" for aging and dementia.

What about projected impact of Risk factor reduction?

7 modifiable risk factors analyzed (Barnes and Yaffe, Lancet Neurology 2011):

• Cardiovascular disease risk factors (hypertension, lipids, smoking)

• Obesity/metabolic dysregulation:

• Depression

• Physical activity

• Low education
## PARs for AD, US

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population Prevalence</th>
<th>Relative Risk (95% CI)</th>
<th>PAR % (Range)</th>
</tr>
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<tbody>
<tr>
<td>Physical inactivity</td>
<td>33%</td>
<td>1.8 (1.2, 2.8)</td>
<td>21% (6-37%)</td>
</tr>
<tr>
<td>Depression</td>
<td>19%</td>
<td>1.9 (1.6, 2.3)</td>
<td>15% (10-20%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>21%</td>
<td>1.6 (1.2, 2.2)</td>
<td>11% (3-20%)</td>
</tr>
<tr>
<td>Mid-life hypertension</td>
<td>14%</td>
<td>1.6 (1.2, 2.2)</td>
<td>8% (2-15%)</td>
</tr>
<tr>
<td>Mid-life obesity</td>
<td>13%</td>
<td>1.6 (1.3, 1.9)</td>
<td>7% (4-11%)</td>
</tr>
<tr>
<td>Low education</td>
<td>13%</td>
<td>1.6 (1.4, 1.9)</td>
<td>7% (4-10%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9%</td>
<td>1.4 (1.2, 1.7)</td>
<td>3% (2-5%)</td>
</tr>
<tr>
<td>Combined (max.)</td>
<td></td>
<td></td>
<td>54%</td>
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## PARs for AD, Worldwide

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population Prevalence</th>
<th>Relative Risk (95% CI)</th>
<th>PAR % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low education</td>
<td>40%</td>
<td>1.6 (1.4, 1.9)</td>
<td>19% (12-26%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>27%</td>
<td>1.6 (1.2, 2.2)</td>
<td>14% (4-25%)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>18%</td>
<td>1.8 (1.2, 2.8)</td>
<td>13% (3-24%)</td>
</tr>
<tr>
<td>Depression</td>
<td>13%</td>
<td>1.9 (1.6, 2.3)</td>
<td>11% (7-15%)</td>
</tr>
<tr>
<td>Mid-life hypertension</td>
<td>9%</td>
<td>1.6 (1.2, 2.2)</td>
<td>5% (1-10%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6%</td>
<td>1.4 (1.2, 1.7)</td>
<td>2% (1-4%)</td>
</tr>
<tr>
<td>Mid-life obesity</td>
<td>3%</td>
<td>1.6 (1.3, 1.9)</td>
<td>2% (1-3%)</td>
</tr>
<tr>
<td>Combined (max.)</td>
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<td></td>
<td>51%</td>
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Implications

- Up to half of AD cases may be attributable to modifiable risk factors
- Public health interventions to ↑education and physical activity and ↓smoking and depression could have dramatic impact on AD prevalence
- Intervention studies needed to test impact of prevention strategies
ACT study results n = 1740 over age 65 who scored above 25th percentile in cohort of non-demented persons in 1994-96, followed 6.2 years.

Age specific incidence:

- 13.0 per 1000 person years in persons exercising 3+ times per week.
- 19.7 per 1000 person years in those exercising less than 3 times per week. HR = .62 (.44-.86).

Risk reduction greatest in those with lower performance levels.

Results similar for incident AD.
Randomized Trials of Exercise in Community (Lautenschlager et al 2008):

Older persons complaining of cognitive impairment at 18 month f/u had mean ADAS-COG difference of .69 point, no significant side effects of walking exercise: Greater than effect size or treatment effects of cholinesterase inhibitors (Cochrane Review)
The hippocampus “shrinks” in late adulthood; reduced volume especially in anterior hippocampus is associated with impaired memory and increased risk of dementia; A decades-old hypothesis called AD a "hippocampal" dementia because of earliest changes appearing in the hippocampus and centrality of hippocampus to memory function.

A recent RCT of aerobic exercise training showed an increased size of the anterior hippocampus leading to improved spatial memory. Hippocampal volume increased by 2% compared with declines in the control group. Volumes in other areas were unaffected (caudate and thalamus). Increased volume associated with Brain Derived Neurotrophic Factor (BDNF).

Conclusion: Aerobic exercise training is effective in reversing hippocampal volume loss in late adulthood.

Other Vascular Risk Factors

Vascular risk factors have been linked to all incident dementia as well as to AD and vascular dementia individually.” (UpToDate – 2012)

- Hypercholesterolemia: Likely stronger association in late midlife, early old age

- Hypertension: Consistent association that declines and disappears in old old age, "U" shaped

- Diabetes Mellitus: 50-100% increased risk of AD; 100-150% increase in all cause dementia mainly in persons over 70

- Smoking: RR risk for AD about 1.3 and all cause dementia 1.8

- Atrial Fibrillation: OR = 1.4 for all cause dementia; 1.5 for AD (Dublin, 2012)
Some Conclusions of Prospects for Prevention in the 21st century

General improvement in midlife health and especially better control of vascular risk factors, combined with effective treatments of vascular diseases and maintenance of physical activity, healthy diets have great potential to further promote cognitively healthier long lives.

These conclusions are based on descriptive research predominantly. Time trend and descriptive research will continue, more clinical trials (traditional and pragmatic) will be informative but face logistic challenges.

Strongest evidence supports value of habitual exercise. Evidence will continue to appear over next decade.
1. **Mental Retirement** *(Rohwedder and Willis 2010)*

   Cross national comparable surveys of older persons in the US, England and 11 European Countries to analyze effects of social policies on retirement and cognitive performance.

   Retirement policies are associated with cognitive performance suggesting: “Estimated effect of retirement on cognition proxied by performance on word recall is very large indeed” (for persons in their early 60s).

2. **Worldwide obesity epidemic**

   Threatens to reverse gains related to better control of vascular risk.
More people are living longer and absent disasters (war and social dissolution, nuclear, intractable infectious diseases, etc.).

Current trends indicate there will be large population of very old persons at very high risk of AD and late life dementias.

Absolute prevention of late-life dementias is not likely. If anything more people may have dementia when they die if current longevity trends persist (Brayne 2006). This is true, even though delay of onset is possible and overall exceptional longevity does not result in excessive levels of disability in cohorts of the very old (Christensen (2008)

Nonetheless, social policies that promote adequate education, strong communities characterized by social and economic well being and absence of disparities and extreme poverty, and do not discourage but encourage work into later life may allow for continued postponement of onset of late life dementias
Biodemographic trends predict that "senescence has (already) been postponed by about 10 years" and further postponement will continue.

The "Baby Boom" generation has at various times had huge effects on the societies in which they were numerous. Now as they enter so-called retirement age, there is great fear of the burden their anticipated long life will have, especially since epidemiologic trends change more slowly than biomedical science does.
Reducing the disease burden of late-life dementias will be critical to societal well being in most advanced countries. A global approach to improving personal and public health, especially as suggested by the modifiable factors that affect cognition in old age could be the BOOMERS’ loudest boom of all. It will, however, require major changes in social policies, behavior and the priorities driving health care.

Discovery through prevention trials of effective ways to delay onset by design, not by accident – key to a LONG BABY BOOM.
The good news on the horizon related to prevention of dementia is that there may already be some postponement of cognitive morbidity and dementia consequent to overall better health in our aging populations, and the emergence of multiple risk factors that, if modifiable, may reduce the burden of these diseases. Widespread prevention trials are needed to better establish whether this “possible” good news is indeed going to realized.
Questions?