Preventing late life dementia
What are we waiting for?

Healthy Aging Alliance Conference
September 30, 2014
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Portland VA Medical Center
What are we waiting for?

Figure 1: The growth in numbers of people with dementia (in millions) in high income countries, and low and middle income countries.
Most dementia is Alzheimer’s disease:
The National Institute of Health opinion on dementia prevention:
"Alzheimer's disease is a feared and heart-breaking disease," said Dr. Martha L. Daviglus, conference panel chair and professor of preventive medicine and medicine at Northwestern University, Chicago. "We wish we could tell people that taking a pill or doing a puzzle every day would prevent this terrible disease, but current evidence doesn't support this....."

Preventing Alzheimer's Disease and Cognitive Decline – NIH State-of-the-Science Conference

Many preventive measures for cognitive decline and for preventing Alzheimer's disease—mental stimulation, exercise, and a variety of dietary supplements—have been studied over the years. However, an independent panel convened this week by the National Institutes of Health determined that the value of these strategies for delaying the onset and/or reducing the severity of decline or disease hasn't been demonstrated in rigorous studies.

“...Evidence is insufficient to support the use of pharmaceutical agents or Dietary supplements to prevent cognitive decline or Alzheimer’s disease...”
what are we waiting for?

• Clinical trials?
  – Expensive, time-consuming
  – Field is dominated by anti-amyloid strategies
what are we waiting for?

• Clinical trials?
  – Expensive, time-consuming
  – Field is dominated by anti-amyloid strategies
  
  – Are there contributors to late life dementia other than amyloid?
# Brain Infarction and the Clinical Expression of Alzheimer Disease

The Nun Study

*JAMA. 1997;277:813-817*

<table>
<thead>
<tr>
<th>Type and Location of Infarct</th>
<th>Proportion Demented (No. Demented/No. at Risk)</th>
<th>Multivariate-Adjusted Odds Ratio for Dementia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 Lacunar infarcts in basal ganglia, thalamus, or deep white matter</td>
<td>0.93 (14/15)</td>
<td>20.7 (1.5-288.0)</td>
</tr>
<tr>
<td>≥1 Large infarcts in lobes of neocortex</td>
<td>0.75 (9/12)</td>
<td>6.7 (0.9-48.3)</td>
</tr>
<tr>
<td>No brain infarcts</td>
<td>0.57 (21/37)</td>
<td>...</td>
</tr>
</tbody>
</table>

*All 61 participants met the neuropathologic criteria for Alzheimer disease. Variables adjusted were age at the...*
Interpreting the nun study: version 1

Amyloid plaques + stroke → Dementia
Interpreting the nun study: version 2:

Vascular disease → Amyloid plaques → Dementia
Testing interpretation #2:

• If:
  – vascular risk factors promote AD pathology

• Then:
  – measurements of vascular risk should be associated with markers of AD pathology before patients exhibit cognitive decline
Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults

*Neurology® 2013;81:2024–2027*

**ABSTRACT**

**Objective:** The current study examined the association between pulse pressure (PP) and CSF-based biomarkers for Alzheimer disease, including β-amyloid 1–42 (Aβ₁-₄₂) and phosphorylated tau (P-tau) protein, in cognitively normal older adults.

**Methods:** One hundred seventy-seven cognitively normal, stroke-free older adult participants (aged 55–100 years) underwent blood pressure assessment for determination of PP (systolic – diastolic blood pressure) and lumbar puncture for measurement of CSF Aβ₁-₄₂ and P-tau. Pearson correlations and multiple linear regression, controlling for age, sex, APOE genotype, and body mass index, evaluated the relationship between PP and Alzheimer disease biomarkers.
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Cor. = 0.228; p < 0.001
Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults

ABSTRACT

Objective: To determine arterial stiffness and β-amyloid (Aβ) deposition in the brain of dementia-free older adults.

Methods: We studied a cohort of 91 dementia-free participants aged 83-96 years. In 2009, participants completed brain MRI and PET imaging using Pittsburgh compound B (PiB; a marker of amyloid plaques in human brain). In 2011, we measured resting blood pressure (BP), mean arterial pressure (MAP), and arterial stiffness by pulse wave velocity (PWV) in the central, peripheral, and mixed (e.g., brachial ankle PWV [baPWV]) vascular beds, using a noninvasive and automated waveform analyzer.

Results: A total of 44/91 subjects were Aβ-positive on PET scan. Aβ deposition was associated with mixed PWV, systolic BP, and MAP. One SD increase in baPWV resulted in a 2-fold increase in the odds of being Aβ-positive (p = 0.007). High white matter hyperintensity (WMH) burden was associated with increased central PWV, systolic BP, and MAP. Compared to Aβ-negative individuals with low WMH burden, each SD increase in PWV was associated with a 2-fold to 4-fold increase in the odds of being Aβ-positive and having high WMH.

Conclusions: Arterial stiffness was associated with Aβ plaque deposition in the brain, independent of BP and APOE ε4 allele. The associations differed by type of brain abnormality and vascular bed measured (e.g., WMH with central stiffness and Aβ deposition and mixed stiffness). Arterial stiffness was highest in individuals with both high Aβ deposition and WMH, which has been suggested to be a “double hit” contributing to the development of symptomatic dementia. Neurology® 2013;81:1711-1718
Table 3  Least square means for measures of arterial stiffness by tertiles of Aβ deposition

<table>
<thead>
<tr>
<th></th>
<th>Low Aβ deposition (n = 30)</th>
<th>Middle Aβ deposition (n = 30)</th>
<th>High Aβ deposition (n = 31)</th>
<th>p Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LSmean</td>
<td>95% CI LL</td>
<td>95% CI UL</td>
<td>LSmean</td>
</tr>
<tr>
<td>baPWV, cm/s</td>
<td>1,765</td>
<td>1,654</td>
<td>1,877</td>
<td>1,826</td>
</tr>
<tr>
<td>cfPWV, cm/s</td>
<td>1,551</td>
<td>1,318</td>
<td>1,784</td>
<td>1,593</td>
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<tr>
<td>hfPWV, cm/s</td>
<td>1,411</td>
<td>1,301</td>
<td>1,521</td>
<td>1,299</td>
</tr>
<tr>
<td>faPWV, cm/s</td>
<td>1,021</td>
<td>954</td>
<td>1,088</td>
<td>1,110</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>63</td>
<td>59</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>133</td>
<td>126</td>
<td>140</td>
<td>135</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>69</td>
<td>65</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>98</td>
<td>93</td>
<td>104</td>
<td>96</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ = β-amyloid; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; CI = confidence interval; DBP = diastolic blood pressure; faPWV = femoral-ankle pulse wave velocity; hfPWV = heart femoral pulse wave velocity; LL = lower limit; LSmean = least square mean; MAP = mean arterial pressure; SBP = systolic blood pressure; UL = upper limit.
Conclusions:

• Two recent studies support the idea that vascular risk factors directly promote Alzheimer pathology.
But...
regardless of which model you believe:

• Reducing stroke may reduce dementia

• Reducing stroke risk factors should reduce stroke
The projected effect of risk factor reduction on Alzheimer’s disease prevalence

Lancet Neurol 2011; 10: 819–28

Deborah E Barnes, Kristine Yaffe

Figure: Potential number of AD cases that could be prevented through risk factor reduction
what are we waiting for?

• Clinical trials?
  – How do you do a placebo-controlled trial of BP control? diabetes control? cholesterol control?
what are we waiting for?

• Clinical trials?
  – How do you do a placebo-controlled trial of BP control? diabetes control? cholesterol control?
  – If we are to do more clinical trials, we have to focus on those that will not deny the current standard to care to placebo subjects
Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging

ABSTRACT

Objective: To examine the cross-sectional relationship between nutrient status and psychometric and imaging indices of brain health in dementia-free elders.

Methods: Thirty plasma biomarkers of diet were assayed in the Oregon Brain Aging Study cohort (n = 104). Principal component analysis constructed nutrient biomarker patterns (NBPs) and regression models assessed the relationship of these with cognitive and MRI outcomes.

Results: Mean age was 87 ± 10 years and 62% of subjects were female. Two NBPs associated with more favorable cognitive and MRI measures: one high in plasma vitamins B (B1, B2, B6, folate, and B12), C, D, and E, and another high in plasma marine ω-3 fatty acids. A third pattern characterized by high trans fat was associated with less favorable cognitive function and less total cerebral brain volume. Depression attenuated the relationship between the marine ω-3 pattern and white matter hyperintensity volume.

Conclusion: Distinct nutrient biomarker patterns detected in plasma are interpretable and account for a significant degree of variance in both cognitive function and brain volume. Objective and multivariate approaches to the study of nutrition in brain health warrant further study. These findings should be confirmed in a separate population. Neurology® 2012;78:241–249
Low omega 3’s associated with subclinical cerebrovascular disease: Do omega 3’s reduce dementia risk by keeping brain blood vessels healthy?
NIA-funded dementia prevention study:

Start with non-demented patients over 80 with high WMH on MRI
(“WMH” is an MRI indicator of damage to small blood vessels in the brain)
NIA-funded dementia prevention study:

Start with non-demented patients over 80 with high WMH on MRI

Memory testing and interview with family to ensure they are not demented
NIA-funded dementia prevention study:

- Start with non-demented patients over 80 with high WMH on MRI
- Memory testing and interview with family to ensure they are not demented
- Randomize to omega 3 fatty acid vs placebo for 3 years
NIA-funded dementia prevention study:

Start with non-demented patients over 80 with high WMH on MRI

Memory testing and interview with family to ensure they are not demented

Randomize to omega 3 fatty acid vs placebo for 3 years

Primary outcome measure is rate of increase in WMH on MRI
Clinical trials actively recruiting:

- Bowman/Shinto R01: omega 3 fatty acids for prevention of cognitive decline in the elderly

- Shinto: omega 3 fatty acids + lipoic acid for prevention of cognitive decline in middle-aged people with hypertension

- Craft NIA funded multi-center trial (OHSU PI Erten-Lyons) : intranasal insulin study
What are we waiting for?

• Ethical placebo-controlled clinical trials to modify vascular risk are possible in some limited areas.
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• Ethical placebo-controlled clinical trials to modify vascular risk are possible in some limited areas.

• *Addressing other vascular risk factors in the elderly should begin now in order to promote brain health*
American Heart Association = American Stroke Association

R Sacco: First neurologist to serve as President of American Heart Association (2010-11)
Heart Health Factors

- American Heart / Stroke Association
  - Aerobic exercise
  - Control cholesterol
  - Eat according to AHA guidelines
  - Manage blood pressure
  - Lose weight
  - Reduce blood sugar
  - Stop smoking
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Only 2% of the American population meets all 7 guidelines.
(www.AHA.org)
OHSU Alzheimer’s Center commitment to Life’s Simple 7 and “Brain TLC”

- Based on community interest:
  - We have launched a quarterly educational program for people interested in adopting Life’s Simple 7
  - Working on the logistics of an online program to promote participation and to measure adherence.
  - We hope to expand beyond the “simple 7” to mental exercise, stress management, optimal sleep, others
“Life’s Simple 7” scorecard:

<table>
<thead>
<tr>
<th></th>
<th>target</th>
<th>Status 2012-2103</th>
</tr>
</thead>
<tbody>
<tr>
<td>smoking</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>hypertension</td>
<td>&lt;120/80</td>
<td>130/80</td>
</tr>
<tr>
<td>Diabetes (fasting glucose)</td>
<td>&lt;100</td>
<td>??</td>
</tr>
<tr>
<td>cholesterol</td>
<td>&lt;200 mg/dl</td>
<td>185</td>
</tr>
<tr>
<td>diet</td>
<td>4/5 AHA guidelines*</td>
<td>Not meeting</td>
</tr>
<tr>
<td>Physical exercise</td>
<td>150 minutes per week</td>
<td>Barely meeting</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;25</td>
<td>26.4</td>
</tr>
</tbody>
</table>

*Fruits and vegetables: At least 4.5 cups a day
Fish (preferably oily fish): At least two 3.5-ounce servings a week
Fiber-rich whole grains: At least three 1-ounce-equivalent servings a day
Sodium: Less than 1,500 mg a day
Sugar-sweetened beverages: No more than 450 calories (36 ounces) a week
Preventing late life dementia: What are we waiting for?

• **We should not be waiting**
  – Encourage patients to embrace wellness
  – Use the structure of Life’s Simple 7 or find other options.
  – Do it yourself.
  – Refer patients to clinical trials so we expand wellness recommendations beyond those already in place.
Thank you for your attention...