Prevention of Alzheimer’s disease and dementias

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Prevalence of dementia increases with age

Alzheimer’s disease is the first cause of loss of autonomy

- More than 70% of institutionalizations are due to Alzheimer’s disease and other dementia

- Cost: $173 billion in US (up to 1 trillion in 2050), €18 billion in France

- Prevention of Alzheimer is one of the most important challenges that scientists, researchers, gerontologists, geriatricians have to meet, facing the Longevity revolution.
Is there evidence that AD could be a preventable disease?

• According to the NIH State-of-the-Science Conference: “Preventing Alzheimer’s Disease and Cognitive Decline” held on April 26–28, 2010

The answer is NO

Is it possible to challenge this assertion?
Prevention Approaches

1 Approaches based on epidemiologic studies
   - Estrogens
   - Anti-inflammatory agents
   - Anti-oxidants
   - Cholesterol lowering agents: Statins
   - Blood pressure lowering agents

2 Approaches aimed at increasing the cognitive “reserve”
   - Cognitive stimulation
   - Physical activity
   - Social network, professional activity

3 Brain lesions modifying approaches
   - Anti-Amyloid approach (Vaccin, secretase inhibitors)
   - Anti-Tau approach
Many cardiovascular diseases have been related to the incidence of VD or AD

- Vascular dementia
  - Atrial fibrillation
    Ott 1996
  - Coronary diseases
  - Atherosclerosis
    Hofman 1997
  - White matter lesions
    Leys 1998, Breteler 2000
  - Smoking
    Meyer 1998

- Alzheimer disease
  - Atrial fibrillation
    Ott 1996
  - Coronary diseases
    Spark 1990, Soneira 1996
  - Atherosclerosis
    Hofman 1997
  - White matter lesions
    Leys 1998, Breteler 2000
Diabetes and cognitive impairment
Diabetes and dementia
Longitudinal surveys

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hisayama Study (n=828)</td>
<td>2.2 (1.0-4.9)</td>
</tr>
<tr>
<td>Arvanitakis (n=824)</td>
<td>1.65 (1.10-2.47)</td>
</tr>
<tr>
<td>Rochester Study (n=1455)</td>
<td>1.7 (1.3-2.1)</td>
</tr>
<tr>
<td>Medicare (n=1138)</td>
<td>3.8 (1.8-8.2)</td>
</tr>
<tr>
<td>Rotterdam Study (n=6370)</td>
<td>1.9 (1.2-3.1)</td>
</tr>
<tr>
<td>Kaiser medical care (n=8845)</td>
<td>1.46 (1.2 – 1.8)</td>
</tr>
</tbody>
</table>
N=11 140, HBA1C < 6.5% vs standart care VS optimal care
66 years old, Follow-up : 4.3 ans,

### Table: Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=5571)</th>
<th>Standard Control (N=5569)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Relative Risk Reduction (95% CI) percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary End Points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>498 (8.9)</td>
<td>533 (9.6)</td>
<td></td>
<td>7 (-6 to 17)</td>
</tr>
<tr>
<td>Major coronary events</td>
<td>310 (5.6)</td>
<td>337 (6.1)</td>
<td></td>
<td>8 (-7 to 21)</td>
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<tr>
<td>All coronary events</td>
<td>560 (10.1)</td>
<td>572 (10.3)</td>
<td></td>
<td>2 (-10 to 13)</td>
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<tr>
<td>Major cerebrovascular events</td>
<td>238 (4.3)</td>
<td>246 (4.4)</td>
<td></td>
<td>3 (-16 to 19)</td>
</tr>
<tr>
<td>All cerebrovascular events</td>
<td>352 (6.3)</td>
<td>327 (5.9)</td>
<td></td>
<td>-8 (-26 to 7)</td>
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<tr>
<td>Heart failure</td>
<td>220 (3.9)</td>
<td>231 (4.1)</td>
<td></td>
<td>5 (-14 to 21)</td>
</tr>
<tr>
<td>Peripheral vascular events</td>
<td>343 (6.2)</td>
<td>366 (5.9)</td>
<td></td>
<td>6 (-9 to 19)</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>1232 (22.1)</td>
<td>1249 (22.4)</td>
<td></td>
<td>1 (-7 to 9)</td>
</tr>
<tr>
<td>New-onset microalbuminuria</td>
<td>1318 (23.7)</td>
<td>1434 (25.7)</td>
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<td>9 (2 to 5)</td>
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<tr>
<td>Visual deterioration</td>
<td>3033 (54.4)</td>
<td>3015 (54.1)</td>
<td></td>
<td>0 (-5 to 5)</td>
</tr>
<tr>
<td>New or worsening neuropathy</td>
<td>2353 (42.2)</td>
<td>2311 (41.5)</td>
<td></td>
<td>-4 (-10 to 5)</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>895 (16.1)</td>
<td>911 (16.4)</td>
<td></td>
<td>2 (-7 to 11)</td>
</tr>
<tr>
<td>Dementia</td>
<td>61 (1.1)</td>
<td>48 (0.9)</td>
<td></td>
<td>-27 (-86 to 13)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2501 (44.9)</td>
<td>2381 (42.8)</td>
<td></td>
<td>-7 (-13 to -1)</td>
</tr>
</tbody>
</table>

Cholesterol and Alzheimer’s disease

Conflicting results between the observational studies and the randomized controlled trials
<table>
<thead>
<tr>
<th>Référence</th>
<th>nombre</th>
<th>Âge (ans)</th>
<th>Suivi (ans)</th>
<th>Dosage</th>
<th>Diagnostic</th>
<th>Associa</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moroney, 1999</td>
<td>111</td>
<td>75</td>
<td>7</td>
<td>LDL-C</td>
<td>VaD</td>
<td>+</td>
<td>3.1 (1.5-6.1)</td>
</tr>
<tr>
<td>Reitz 2004</td>
<td>2820</td>
<td>78</td>
<td>4.8</td>
<td>LDL-C</td>
<td>VaD</td>
<td>+</td>
<td>2.45 (1.05-5.70)</td>
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<tr>
<td>Notolka 1998</td>
<td>444</td>
<td>40-59</td>
<td>30</td>
<td>CT</td>
<td>MA</td>
<td>+</td>
<td>3.1 (1.2-8.5)</td>
</tr>
<tr>
<td>Kivipelto 2002</td>
<td>1449</td>
<td>53</td>
<td>21</td>
<td>CT</td>
<td>MA</td>
<td>+</td>
<td>2.8 (1.2-8.5)</td>
</tr>
<tr>
<td>Kalminjn 2000</td>
<td>8006</td>
<td>52.7</td>
<td>26</td>
<td>CT</td>
<td>démence</td>
<td>ns</td>
<td>1.10 (0.95-1.26)</td>
</tr>
<tr>
<td>Tan, 2003</td>
<td>1023</td>
<td>76</td>
<td>8</td>
<td>CT</td>
<td>MA</td>
<td>ns</td>
<td>0.97 (0.90-1.05)</td>
</tr>
<tr>
<td>Mielke 2005</td>
<td>392</td>
<td>70</td>
<td>18</td>
<td>CT</td>
<td>démence</td>
<td>-</td>
<td>0.31 (0.11-0.85)</td>
</tr>
</tbody>
</table>
Statins and cognitive health

- Growing body of epidemiological and biological evidence that statins may reduce dementia
  - *Rodriguez et al. JAGS* 2002; 50: 1852-56
  - *Refoalo LM Neurobiology of Disease* 2000; 7:21
Statins and dementia: Randomised trials

- **MRC/HBF Heart Protection Study** of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled study
  
  *Lancet* 2002; 360:7-22

- Pravastatin in elderly individuals at risk of vascular disease (**PROSPER**): a randomised controlled trial
  
  *Lancet* 2002; 360:1623-30

  No reduction of dementia or cognitive deficit

  Limitations:  
  - Short follow-up in PROSPER
  - No patients > 82 years
  - Cognition=secondary outcome

- Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: **LEADe**.
  
  *Neurology*. 2010 23;74:956-64. **Negative results** (cognition)
Statins and Alzheimer’s disease

• There is no evidence up to now that statins be effective in the prevention or treatment of AD

• Given the biological data, more research is needed with other outcomes

• Statins are nevertheless a powerful approach to reduce incidence of cardiovascular diseases.
Estrogens and Alzheimer’s disease

• This issue raises two questions: How and when an estrogen treatment should be considered?: The timing hypothesis
There was a considerable amount of evidence that estrogens could maintain Cognitive Health

Figure. Results of Meta-analysis of Dementia Studies

- Waring et al., 1999
- Harwood et al., 1999
- Kawas et al., 1997
- Tang et al., 1996
- Paganini-Hill and Henderson, 1996
- Mortel and Meyer, 1995
- Henderson et al., 1994
- Brenner et al., 1994
- Broe et al., 1990
- Graves et al., 1990
- Amaducci et al., 1986
- Heyman et al., 1984

Pooled Relative Risk

RR 0.66 (0.53-0.82)

Leblanc ES, JAMA 2001; 285:1489-99
Women’s Health Initiative
4,532 women ≥ 65 years, 4 year follow-up

Probable Dementia

Cumulative Hazard

Estrogen + Progestin (E+P)
Placebo

HR, 2.05
95% CI, 1.21-3.48

23 additional dementia cases / 10 000 patient years

Shumaker S JAMA 2003 289:2651-62
The timing hypothesis may explain the discrepancy between observational and RCTs

- Rocca WA (Neurodegener Dis. 2010;7:163-6)
  - Case control and cohort studies show a neuroprotective effect in the early menopause phase
  - Estrogen treatment in the late postmenopause phase is associated with an increased risk of dementia and cognitive decline
  - The neuroprotective effects of estrogen depend on age, type and stage of menopause

- Henderson V W (Biochim Biophys Acta. 2009)
  - Estrogen exposure in the early menopause raises the possibility of cognitive benefit later in life
  - After about the age of 65 years, hormone therapy increases dementia risk

  - Further research is needed to understand short term and long term effects but estrogen therapy should not be initiated after age 65 to prevent dementia or remediate cognitive aging.
Hypertension seems a more plausible candidate
### Hypertension and cognitive decline longitudinal studies

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Age (ans)</th>
<th>Suivi</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkie 1971</td>
<td>202</td>
<td>68</td>
<td>10 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Elias 1993</td>
<td>1702</td>
<td>55-88</td>
<td>12-14 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Launer 1995</td>
<td>3735</td>
<td>50</td>
<td>20-28 years</td>
<td>Cognitive decline /dementia</td>
</tr>
<tr>
<td>Starr 1997</td>
<td>603</td>
<td>&gt; 69</td>
<td>4 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Kilander 1998</td>
<td>999</td>
<td>50</td>
<td>20 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Swan 1998</td>
<td>717</td>
<td>45</td>
<td>25-30 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Tzourio 1999</td>
<td>1373</td>
<td>59-71</td>
<td>4 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Knopman 2001</td>
<td>10 963</td>
<td>47-70</td>
<td>6 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Kivipelto 2001</td>
<td>1 449</td>
<td>53</td>
<td>21 years</td>
<td>Dementia</td>
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<tr>
<td>Reinprecht 2003</td>
<td>186</td>
<td>68 years</td>
<td>13 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Piguet 2003</td>
<td>377</td>
<td>≥ 75 years</td>
<td>6 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Qiu 2003</td>
<td>1 270</td>
<td>81</td>
<td>6 years</td>
<td>Dementia</td>
</tr>
<tr>
<td>Whitmer 2005</td>
<td>8 845</td>
<td>44-44</td>
<td>30 years</td>
<td>Dementia</td>
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<tr>
<td>Luchshinger 2005</td>
<td>1 138</td>
<td>76</td>
<td>6 years</td>
<td>Dementia</td>
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## Relationship between hypertension and Alzheimer’s disease

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Type of study</th>
<th>Correlation</th>
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</thead>
<tbody>
<tr>
<td>Kokmen 1991</td>
<td>415</td>
<td>Cross sectional study</td>
<td>+</td>
</tr>
<tr>
<td>Prince 1994</td>
<td>1545</td>
<td>Cross sectional study</td>
<td>+</td>
</tr>
<tr>
<td>Sparks 1995</td>
<td>231</td>
<td>Histopathological study</td>
<td>+</td>
</tr>
<tr>
<td>Skoog 1996</td>
<td>382</td>
<td>Longitudinal study /15 years</td>
<td>+</td>
</tr>
<tr>
<td>Launer 2000</td>
<td>3703</td>
<td>Longitudinal study /25 years</td>
<td>+</td>
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<tr>
<td>Kivipelto 2001</td>
<td>1449</td>
<td>Longitudinal study /21 years</td>
<td>+</td>
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<tr>
<td>Yoshikate 1995</td>
<td>828</td>
<td>Longitudinal study /7 years</td>
<td>0</td>
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<tr>
<td>Landin 1993</td>
<td>71</td>
<td>Cross sectional study</td>
<td>-</td>
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<tr>
<td>Guo 1999</td>
<td>1642</td>
<td>Longitudinal study / 3 years</td>
<td>-</td>
</tr>
</tbody>
</table>
Antihypertensive treatment and dementia: observational studies

- Reduced risk of cognitive impairment or dementia in treated hypertensive patients
  - Guo et al. (Kungsholmen project)
    *Arch Neurol* 1999; 56: 991–6
  - Tzourio et al. (EVA study)
    *Neurology* 1999; 53: 1948–52
  - Launer et al. (Honolulu–Asia Aging study)
  - Richards et al. (African–American study)
  - In’t Veld et al. (Rotterdam study)
Prevention of dementia in controlled hypertension trials

• SHEP (Applegate et al.)
  *Arch Intern Med* 1994; 154: 2154–60

• MRC (Prince et al.)
  *BMJ* 1996; 312: 801–5

• Syst-Eur (Forette et al.)
  *Lancet* 1998; 352: 1347–51

• PROGRESS (C Tzourio)
  *Arch Intern Med* 2003; 163:1069-1075

• SCOPE (Hansson et al)
  *J Hypertens* 2003;21:875-886

• HYVET(Peters et al)
  *LANCET* 2008. 7:683-89
Blood pressure-lowering agents and dementia

- Two randomised placebo-controlled studies demonstrated a reduction in the incidence of dementia

  - Syst-Eur
    Based on calcium-channel blocker nitrendipine possibly associated with ACE-inhibitor enalapril and/or diuretic


  - PROGRESS
    Run on post-stroke patients and based on ACE-inhibitor perindopril and diuretic indapamide

    *Tzourio et al Collaborative Group. Arch Intern Med 2003; 163:1069-1075*
Syst-Eur 2: Incidence of dementia

Median follow-up: 3.9 years

BP difference: 7/3.2 mmHg

Forette Arch Intern Med. 2002 14;162:2046-52
### Dementia and cognitive decline

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Favors treatment</th>
<th>Favors placebo</th>
<th>Odds ratio (95 % CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td></td>
<td></td>
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<tr>
<td><strong>Dementia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With recurrent strokes</td>
<td>43</td>
<td>65</td>
<td></td>
<td>0.66 (0.40-0.87)</td>
</tr>
<tr>
<td>Other dementias</td>
<td>150</td>
<td>152</td>
<td></td>
<td>0.99 (0.78-1.24)</td>
</tr>
<tr>
<td>bitherapie</td>
<td>106</td>
<td>136</td>
<td></td>
<td>0.77 (0.59-1.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>193</td>
<td>217</td>
<td></td>
<td><strong>0.88 (0.72-1.08)</strong></td>
</tr>
<tr>
<td><strong>Cognitive decline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With recurrent strokes</td>
<td>43</td>
<td>88</td>
<td></td>
<td>0.65 (0.39-0.79)</td>
</tr>
<tr>
<td>Without recurrent strikes</td>
<td>233</td>
<td>246</td>
<td></td>
<td>0.91 (0.78-1.10)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>276</td>
<td>334</td>
<td></td>
<td><strong>0.81 (0.68-0.88)</strong></td>
</tr>
</tbody>
</table>
HYVET

HYVET COG (n=3336 > 80 years without dementia)

- **Dementia:**
  - HR 0.86 [95% CI 0.67-1.09], (p=0.21).

- **Dementia (adjusted):**
  - HR 0.85 [95% CI 0.67-1.09]

Potentialisation of vascular and degenerative lesions

By treating the vascular component of cognitive impairment antihypertensive treatment might delay the onset of dementia
No evidence that other pharmacological approaches prevent Alzheimer’s disease

- Anti-inflammatory agents
- Aspirin
- Anti-oxidant
- Folates
Anti-inflammatory agents do not prevent Alzheimer’s disease

- Epidemiological evidence (Skezely 2010)
  - Observational studies found an association of NSAID use and a reduced risk of AD
  - By contrast RCTs are not effective in treating or preventing AD

- Aisen P (JAMA 2003;21: 2819-26). RCT with rofecoxib or naproxen does not slow cognitive decline in AD patients

- ADAPT trial. (Arch Neurol 2008;65:896-905) RCT with naproxen or celecoxib does not improve cognitive function

- It is hypothesized that NSAIDs may be beneficial in normal brain but detrimental when the Abeta deposition process has started because of their inhibiting activity on microglia which mediates Abeta clearance. Imbimbo 2009:
Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial

Jackie F Price, Marlene C Stewart, Ian J Deary, Gordon D Murray, Peter Sandercock, Isabella Butcher, F Gerald R Fowkes and on behalf of the AAA Trialists

N=2295, 62 ys, follow up 5 yrs

<table>
<thead>
<tr>
<th>Test of cognition</th>
<th>Aspirin group (n=1139)</th>
<th>Placebo group (n=1186)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of participants</td>
<td>Mean (SD) score; 95% CI</td>
<td>No of participants</td>
</tr>
<tr>
<td>General cognitive factor score (summary cognitive score)†</td>
<td>1109</td>
<td>0.00 (1.01); −0.06 to 0.06</td>
<td>1153</td>
</tr>
<tr>
<td>Raven’s progressive matrices (5 sets of 12 item tests; maximum possible score 60)</td>
<td>1110</td>
<td>34.3 (9.5); 33.8 to 34.9</td>
<td>1153</td>
</tr>
<tr>
<td>Auditory verballearning, trialsI-V (sum of five trials with same list; maximum possible 75 words)</td>
<td>1118</td>
<td>63.0 (16.7); 62.1 to 64.0</td>
<td>1159</td>
</tr>
<tr>
<td>Digit symbol (total No of symbols matched correctly in 90 second test; maximum possible score 93)</td>
<td>1126</td>
<td>40.0 (11.7); 39.3 to 40.7</td>
<td>1170</td>
</tr>
<tr>
<td>Verbal fluency (total No of words generated in three 1 minute tests)</td>
<td>1117</td>
<td>37.6 (12.8); 36.9 to 38.4</td>
<td>1156</td>
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<tr>
<td>Trail making (seconds to completion)‡</td>
<td>1122</td>
<td>4.6 (0.4); 4.6 to 4.6</td>
<td>1167</td>
</tr>
<tr>
<td>Mini-mental state examination (total score, maximum possible 30)</td>
<td>1131</td>
<td>28.6 (1.7); 28.5 to 28.7</td>
<td>1178</td>
</tr>
</tbody>
</table>

*BMJ 2008;337:a1198*
Selegiline Vit E
341 randomized AD patients, 2 year follow up, placebo, selegiline (10mg/j), vit E (2000 IU/j), les 2

<table>
<thead>
<tr>
<th></th>
<th>selegiline</th>
<th>Vit E</th>
<th>Vit E + seg</th>
<th>placebo</th>
</tr>
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<tbody>
<tr>
<td>MMSE</td>
<td>12.7</td>
<td>11.3</td>
<td>12.9</td>
<td>13.3*</td>
</tr>
<tr>
<td>Time to institution, ADL, CDR deterioration</td>
<td>655 days (p=0.012)</td>
<td>670 days (p=0.001)</td>
<td>585 days (p=0.049)</td>
<td>440 days</td>
</tr>
</tbody>
</table>

Sano M NEJM 1997;336:1216-22
# Honolulu Asia Aging Study

3385 subjects 71 - 93 years; 3 - 5 year FU

<table>
<thead>
<tr>
<th></th>
<th>DV</th>
<th>D Mixtes</th>
<th>MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit E</td>
<td>1.28 (0.35-4.69)</td>
<td>0.86 (0.25-2.92)</td>
<td>0.84 (0.19-3.77)</td>
</tr>
<tr>
<td>Vit C</td>
<td>0.83 (0.27-2.57)</td>
<td>0.75 (0.29-1.96)</td>
<td>1.61 (0.67-3.87)</td>
</tr>
<tr>
<td>Vit E + C</td>
<td>0.12 (0.02-0.88)</td>
<td>0.31 (0.11-0.89)</td>
<td>1.81 (0.91-3.62)</td>
</tr>
</tbody>
</table>

*Masaki KH Neurology 2000;54:1265-72*

3734 subjects 71 - 93 years old, 5 year FU

<table>
<thead>
<tr>
<th></th>
<th>DV</th>
<th>D Mixtes</th>
<th>MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit E + C</td>
<td>0.95 (0.43-2.13)</td>
<td>0.91 (0.59-1.41)</td>
<td>1.05 (0.64-1.75)</td>
</tr>
</tbody>
</table>

*Laurin D JAMA 2002;288:2266-8*
May Life Style prevent dementia?

- Physical Activity
- Diet
“Preliminary evidence suggests a beneficial association of physical activity with the preservation of cognitive function” (NIH 2010)

- A six month program of physical activity provided a modest improvement of cognition over a 18 month follow up period in 170 adults with subjective memory impairment. *Lautenshlager*. *JAMA* 2008
- Exercise at midlife may reduce the odds of dementia in older adulthood in a case control analysis. *Andel J Gerontol* 2008
- Aerobic exercise improves executive control process in 33 older adults at risk of cognitive impairment. *Baker Arch Neurol* 2010
- In a case-control study any frequency of exercise performed in midlife or later life was associated with a reduced odds of having MCI. *Geda Arch Neurol* 2010.
- However in a recent prospective study on Italian cohort, physical activity is associated with a lower risk of vascular dementia but not *AD* (*Ravaglia G and coll. Neurology* 2008;70(19 Pt 2):1786-94).
Nutrition and lifestyle: Are they able to decrease the risk of Alzheimer's disease?

- A number of studies have shown that consumption of fish and adequate intake of fruits and vegetables might be associated with a decreased risk of developing the disease. (Morris Arch Neurol 2003;60(7):940-6. - Larrieu J Nutr Health Aging 2004;8(3):150-4., Barberger-Gateau Neurol. 2007; 69:1921-30, Hughes Am geriat psychiatry 2010;18:413-20))

- Combination of higher physical activity and Mediterranean type of diet are independently associated with reduced risk for AD. (Scarmeas JAMA 2009;302:627-37)
## Alcohol and AD

3 777 subjects ≥ 65 years  3 year follow up  
PAQUID study (Bordeaux, France)

<table>
<thead>
<tr>
<th>Wine intake</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>absence</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>light (1 to 2 verres/j)</td>
<td>0.55</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>moderate (3 to 4 verres/j)</td>
<td>0.25</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

*Orgogozo JM Rev Neurol 1997;153:185-92*
Alcohol consumption and risk of dementia

983 subjects ≥ 55 years, 6 year follow up
Rotterdam Study

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>RR (95% IC)</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 glass/week</td>
<td>0.82 (0.56-1.22)</td>
<td>-</td>
</tr>
<tr>
<td>1-3 glasses/week</td>
<td><strong>0.58 (0.38-0.90)</strong></td>
<td>- 42%</td>
</tr>
<tr>
<td>≥ 4 glasses/week</td>
<td>1.00 (0.39-2.59)</td>
<td>-</td>
</tr>
</tbody>
</table>

All dementias: AD/ Vascular dementia

*Ruitenberg A Lancet 2002;359:281-86*
Approaches aimed at increasing the cognitive “reserve”

- Cognitive stimulation
- Leisure activities
- Social interaction
- Professional activities
Cognitive stimulation and AD

(Petrosini et al. 2009 for a review)

• A number of studies have shown the importance of early cognitive enrichment to maintain cognitive performances later in life (Borenstein 2006, Mc Dowell 2007, Roe 2007)

• Formal education is a positive predictor of age-associated cognitive decline (Bennet 2003, Bruander 2008, Katzman 1993, ….)

• Education does not prevent the onset of AD but provides protection against the expression of clinical symptoms. With the same lesions highly educated subjects become demented later (Letenneur 1999, Snowdown 1996, Stern 1994)

• Post mortem analyses report marked neuropathological features of AD in individuals who have never shown signs of cognitive impairment (Del Ser 1999, katzman 1993, Neuropathology group 2001 ….)

• These data provide the foundation for the reserve theory (Fratiglioni 2007, Stern, 2002, 2003, 2006)
Neuroplasticity, Cognitive Reserve and Cognitive Training

• The Concept of Cognitive reserve was proposed to explain epidemiological data indicating that individuals engaged in higher level of mental and physical activity were at lower risk of developing AD and other dementia. *(Nithianantharajah, Prog Neurobiol 2009)*

• Neuroplasticity refers to the physiological ability of the brain to strengthen and form dendritic connections, produce beneficial morphologic changes and increases brain reserve. *(Vance, J Psychosoc Nurs Ment Health Serv 2010)*
Cognitive training may preserve the cognitive functioning and ADL abilities

- The five year, randomized, controlled, single-blind ACTIVE study supports the effectiveness and durability of the cognitive training interventions in improving targeted cognitive abilities in older independent-living adults (Ball et al. JAMA 2002; 288:2271-81).

- The ACTIVE study also confirmed that reasoning training resulted in less functional decline in self-reported IADL. Compared with the control group, cognitive training resulted in improved cognitive abilities that continued 5 years after the initiation of the intervention. (Willis et al. JAMA 2006; 296:2805-14)
Leisure activities seem as well promising

- The three city study in community-dwelling elders of 65+ free of dementia shows that:
- stimulating leisure activities at least twice a week such as:
  - crosswords,
  - playing cards,
  - attending exhibitions,
  - going to a show,
  - doing artcraft,
- decreases by 50% the incidence of dementia and by 40% AD compared with the incidence in people engaged in such activities less than once a week,

Social activities, environment and AD


- Individuals living alone with no friends or relatives seem more at risk of developing dementia (Fratiglioni L and coll. Lancet 2000;355(9212):1315-9.)

- In the Honolulu Study only the decreased social engagement from mid life to late life was associated with an increased risk of dementia (Saczynski JS and coll. the Honolulu-Asia Aging Study. Am J Epidemiol 2006;163(5):433-40.)
Influence of the professional activities
This is one of the new very promising approaches

• A recent study, only in men observed a significant effect of delaying the age of retirement: each additional year in employment delayed by 0.13 year the onset of AD. (Lupton. Int J Geriatr Psychiatry;25(1):30-6.)

• Moreover, mentally demanding occupations have a direct and relatively early effect on the neuropathology of Alzheimer's disease. (Smyth KA and coll. Neurology 2004;63(3):498-503.)
ORLANDO Study
“Is Older age Retirement related to delayed clinical Dementia Onset?”

• The study is based on 400,000 men and women from the databases of RSI that allow to cross “disease” data and "retirement" data managed by the same organization.

• This work determines if there is a difference in the age of retirement between people with AD and a control population, matched on age, gender, socio-professional category.

• The very promising results will be published soon.
Brain lesions modifying approaches
Brain lesions modifying approaches

- The future disease-modifying treatments of Alzheimer’s diseases will constitute the very prevention treatment.

- This will necessitate a very early diagnosis, years before the onset of symptoms.

- Hence, the importance of the development of biological and neuroimaging markers

- The disease-modifying treatments offer serious hope of considerable progress in preventing pre-symptomatic AD but none of them is close to be released.
Disease-modifying treatments

• **Anti-amyloid?**
  • Secretase modulators
  •  - beta or gamma secretase inhibitors
  •  - alpha secretase enhancers
  •  Immunotherapy:
  •  - Amyloid« vaccin »
  •  - monoclonal antibodies
  •  - Inhibitors of Aβ fibrillisation
  •  - GAG mimétiques : « alzheimed »
  •  - Clioquinol »Negative

• **Anti-Tau?**
  • Inhibitors of Tau phosphorylation
  •  - Kinases inhibitors : CDK5 et GSK-3β
  •  - Phosphatases activators
  •  - Rember, inhibiteur d’aggrégation de tau, Phase 2

• **Dimebon : Stabilisators of Mitochondries (negative)**
Drugs in preclinical and clinical development for AD

Mangialasche et al. Lancet Neurol 2010
Biomarkers of Alzheimer’s disease are available for research

<table>
<thead>
<tr>
<th>Biomarkers of $A\beta$ deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF $A\beta_{42}$</td>
</tr>
<tr>
<td>PET amyloid imaging</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarkers of neuronal injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF tau/phosphorylated-tau</td>
</tr>
<tr>
<td>Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating</td>
</tr>
<tr>
<td>Rate of brain atrophy</td>
</tr>
<tr>
<td>FDG-PET imaging</td>
</tr>
<tr>
<td>SPECT perfusion imaging</td>
</tr>
</tbody>
</table>

Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures

Associated biochemical change

<table>
<thead>
<tr>
<th>Inflammatory biomarkers (cytokines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative stress (isoprostanes)</td>
</tr>
<tr>
<td>Other markers of synaptic damage and neurodegeneration such as cell death</td>
</tr>
</tbody>
</table>
Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase.

- Aβ as identified by cerebrospinal fluid Aβ42 assay or PET amyloid imaging.
- Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition.
- Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau,
- Brain structure is evidenced by structural magnetic resonance imaging.

Figure adapted with permission from Jack et al.

R.A. Sperling et al. / Alzheimer’s & Dementia - (2011) 1–13
Recommendations

• Estrogens, anti-inflammatory agents and antioxidant cannot yet be recommended to maintain cognitive health in the light of published studies.

• Some other trials are ongoing.
Recommendations

• Statins should be recommended to prevent cardiac diseases since all controlled trials (CARE, LIPID, WOSCOPS, PPP, HPS PROSPER) have demonstrated that the benefit on cardiovascular complications persisted after 60 years.

• Up to now there is no evidence that statins prevent dementias. Other trials on cognition should be encouraged.
Recommendations

- Treatment of hypertension should be strongly recommended at all ages.

- Two controlled trials have demonstrated the effectiveness in preventing dementia in addition to the reduction of strokes and cardiovascular complications.

- Other trials should confirm the specific role of the different classes of antihypertensive drugs on the degenerative process.
Recommendations

• The benefit of cognitive stimulation has been proven by controlled trials.

• Physical activity, leisure activity, social interactions should be encouraged on the grounds of their favourable action on health, fitness, quality of life and cognitive activities.

• Prolongation of professional activities may be the strongest tool to maintain cognition and postpone deterioration.

• **Controlled trials on these approaches should be encouraged.**
Conclusion

• Maintaining cognitive health remains the most stimulating challenge of the Century.

• More research is needed in this field.

• Large information of the public is necessary.
Possible Risk factors for Cognitive Decline and/or Dementia

- Age and sex
- Level of education
- Mild Cognitive Impairment (MCI)
- Genetic factors (ApoE4 Allele)
- Oxidative stress
- Inflammation
- Menopause
- Vascular factors (hypertension)
- Metabolic factors (diabetes, obesity, cholesterol..)
- Depression
- ?
Pathophysiological sequence leading to cognitive impairment. This model postulates that amyloid beta (Aβ) accumulation is an “upstream” event in the cascade that is associated with “downstream” synaptic dysfunction, neurodegeneration, and eventual neuronal loss. Age and genetics, as well as other specific host factors, such as brain and cognitive reserve, or other brain diseases may influence the response to Aβ and/or the pace of progression toward the clinical manifestations of AD.

R.A. Sperling et al. / Alzheimer’s & Dementia- (2011) 1–13
Intellectually demanding work and cognitive reserve

• In a recent study, intellectually demanding work was associated with greater benefit to cognitive performance in later life independently of related factors like education and intelligence.

• This suggests that in individual with lower education and intellectual aptitudes, behavior may enhance intellectual reserve, even years after the peak of intellectual activity.

Alzheimer’s disease in the world

4.6 million of new cases by year
1 case every 7 seconds
One in 85 people by 2050

Lancet. 2005; 366:2112-7
Achieving and maintaining cognitive health with aging: Possible strategies

Early detection of individuals at risk
- Neuropsychological testing
- Neuroimaging
- Biomarkers
- Genetic markers

Lifestyle management
- Build “cognitive reserve” by remaining intellectually and socially active
  - Continue lifelong learning
  - Engage in regular mental exercises
  - Maintain active social networks
  - Remain involved in the community by occupational or voluntary activity
- Engage in regular physical exercise
- Reduce or minimise the effects of stress
- Ensure appropriate nutrition and avoid nutritional deficiencies

Manage medical co-morbidities
- Hypertension
- Diabetes
- Hyperlipidemia
- Depression
- Sleep disorders
- Polypharmacy
- Sensory impairments
- Avoid alcohol, smoking and illicit drug abuse

Pharmaceutical approaches
- Cognitive enhancers
- Neurotrophins
- Anti-inflammatory agents
- Antioxidants
- Hormones

Fillit MH, Butler RN et al. Mayo Clinic Proc 2002
Necessary conditions to consider that a risk factor is a good candidate for prevention

• A statistical association between the exposure to the factor and the risk of dementia is present without bias
• Exposure to the factor occurred before the onset of the disease
• The association must be plausible and coherent with the natural history and biology of the disease
• The preventive effect of the risk factor modification must be confirmed by at least two randomized controlled studies

Diabetes is associated with cognitive impairment

- **Knopman et al. Neurology 2001; 56: 42–8**
  ARIC study: Total n=10,729, follow up=6 years: significant decrease in delayed recall and word fluency

  Total n=9679, follow up=3–6 years. Lower baseline scores and significant decrease in digit symbol test and trail B

- **Wahlin et al. Neuropsychology 2002; 16: 208–16**
  Total n=338; diabetics n=31 vs controls n=307. Lower verbal fluency and episodic memory

  Aware study: case-control study. Total n=579; diabetics n=283 and control subjects n=296. Significant impairment in MMSE score and clock testing
Hypocholestérolémiant et maladie d’Alzheimer

Wolozin B, Arch Neurol 2000;57:1439-43
ADCLT pilot (n=71, AD) (Alzheimer’s Disease Cholesterol Lowering Treatment Trial)

ADCLT: n=600, atorvastatin, 14 countries, follow up 18 months.

Arch Neurol. 2005 May;62(5):753-7
Should research on the hormonal approach be continued?

- Absolute risk for cardiovascular events not very high (7 to 8 additional cases for 10,000 P/years)
- American population “at risk” of cardiovascular diseases:
  - 70% obese (BMI> 25)
  - 35% hypertensive
  - 66% 65 years and over
- Hormones used (conjugated equine estrogens and medroxyprogesterone acetate) and oral route of administration known to increase the thromboembolic risk

Question: should a study using the usual European treatment (natural hormones and patch or spray administration) be set up on a less vulnerable population?
Should research on the hormonal approach be continued?

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Question: should a study using the usual European treatment (natural hormones and patch or spray administration) be set up on a less vulnerable population?
Hypertension risk of vascular Dementia (VaD)

- Positive association
  - Yoshitake et al. (Hisayama study)
    Neurology 1995; 45: 1161–8
  - Skoog et al. (Gothenburg study)
    Lancet 1996; 27; 347: 1141–5
  - Hebert et al. (Canadian study on health and aging)
    Stroke 2000; 31: 1487–93
  - Launer et al. (Honolulu Asia study)
  - Posner et al.
    Neurology 2002; 58: 1175–81
Necessary requirements to consider that hypertension is a good target for prevention trials

• A statistical association between the exposure to the factor and the risk of dementia must be present without bias
• The exposure to the factor occurred before the onset of the disease
• The association must be plausible and coherent with the natural history and biology of the disease
• Is the preventive effect of the risk factor modification proven by a controlled trial confirmed by at least one other study?

Number of new cases 30

Intention-to-treat  Per-protocol

Placebo  Active treatment  Placebo  Active treatment

Vascular dementia
Mixed dementia
Alzheimer’s dementia
The level of education is strongly associated to the level of cognitive function.
Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia (Review)

McGuinness B, Todd S, Passmore P, Bullock R

Cochrane Database of Systematic Reviews 2009,
Prevention of dementia
Meta-analysis of double blind placebo controlled trials

# Disease modifying drug trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Molécule (promoteur)</th>
<th>Type de traitement</th>
<th>Etat d’avancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>V950 (Merck)</td>
<td>Immunothérapie active</td>
<td>Recrutement en cours</td>
</tr>
<tr>
<td></td>
<td>ACC-001 (Wyeth/Elan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMS-708163 (Bristol-Myers Squibb)</td>
<td>Inhibiteur de la gamma secrétase</td>
<td>Recrutement en cours</td>
</tr>
<tr>
<td></td>
<td>CAD106 (Novartis)</td>
<td>Immunothérapie active</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGb 761 (Ipsen)</td>
<td>Ginkgo biloba</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galantamine et donepezil (Janssen-Cilag)</td>
<td>Anticholinestérasique</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mémantine</td>
<td>Inhibiteur des récepteurs NMDA</td>
<td>Recrutement en cours</td>
</tr>
<tr>
<td>II</td>
<td>3APS (Bellus Health)</td>
<td>Inhibiteur de l'agréation de l'AB</td>
<td>Actif, pas de recrutement</td>
</tr>
<tr>
<td></td>
<td>Bapineuzumab (Wyeth)</td>
<td>Immunothérapie passive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galantamine (Johnson &amp; Johnson)</td>
<td>Anticholinestérasique</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LY2062430 (Eli Lilly)</td>
<td>Immunothérapie passive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LY450139 (Eli Lilly)</td>
<td>Inhibiteur de la gamma secrétase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RO5313534 (Hoffmann-La Roche)</td>
<td>Agoniste partiel des récepteurs alpha-7 nicotiniques</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivastigmine (Novartis)</td>
<td>Anticholinestérasique</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone XR (GlaxoSmithKline)</td>
<td>Anti-diabetique (thiazolidinedione)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Donepezil (Eisai)</td>
<td>Anticholinestérasique</td>
<td>Actif, pas de recrutement</td>
</tr>
<tr>
<td>IV</td>
<td>Jus riche en polyphénols</td>
<td>Supplément nutritionnel</td>
<td>Recrutement en cours</td>
</tr>
<tr>
<td>N/A</td>
<td>Supplément d’oméga-3 + intervention multidomaine</td>
<td>Supplément nutritionnel + intervention non pharmacologique</td>
<td>Recrutement en cours</td>
</tr>
</tbody>
</table>
Theoretic illustration of how cognitive reserve may delay the clinical expression but not the rate of decline.

Person with low reserve

Person with high reserve

Point of inflection

Incident Dementia

Diet and Alzheimer’s disease

Dietary intake of OMEGA 3 and weekly consumption of fish may reduce the risk of AD up to 60%.

Table 3. Relative Risks for Incident Alzheimer Disease (AD) by Quintile of Intake of n-3 Fatty Acids, Docosahexaenoic Acid (DHA), and Eicosapentaenoic Acid (EPA) Among 815 Persons After 3.9 Years of Follow-up, Chicago Health and Aging Project, 1993-2000

<table>
<thead>
<tr>
<th>Omega 3</th>
<th>Quintiles of Intake</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P Value for Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n-3 fatty acids</td>
<td>Median, g/d</td>
<td>0.9</td>
<td>1.13</td>
<td>1.30</td>
<td>1.49</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Incident AD cases</td>
<td></td>
<td>32</td>
<td>30</td>
<td>22</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Weighted %†</td>
<td></td>
<td>14.2</td>
<td>16.6</td>
<td>8.1</td>
<td>10.8</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% confidence interval)</td>
<td>Age adjusted</td>
<td>1.0 (Referent)</td>
<td>1.1 (0.4-2.9)</td>
<td>0.5 (0.2-1.4)</td>
<td>0.6 (0.2-1.5)</td>
<td>0.3 (0.1-0.7)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Multivariable‡</td>
<td>1.0 (Referent)</td>
<td>1.2 (0.5-3.0)</td>
<td>0.6 (0.2-1.7)</td>
<td>0.7 (0.3-1.6)</td>
<td>0.4 (0.1-0.9)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Arch Neurol. 2003;60:940-946
Diet and Alzheimer’s disease

The three city cohort study, n=8,085 > 65 years without dementia, 4 year follow up

<table>
<thead>
<tr>
<th></th>
<th>Model 1, n = 7,783</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Fruit and vegetable frequent consumers</td>
<td>0.70 (0.53-0.92)</td>
</tr>
<tr>
<td>Butter</td>
<td>0.87 (0.68-1.12)</td>
</tr>
<tr>
<td>Vegetaline</td>
<td>0.29 (0.04-2.05)</td>
</tr>
<tr>
<td>Goose or duck fat</td>
<td>1.24 (0.69-2.23)</td>
</tr>
<tr>
<td>Olive oil</td>
<td>0.83 (0.64-1.09)</td>
</tr>
<tr>
<td>Omega-3 rich oil</td>
<td>0.41 (0.17-0.995)</td>
</tr>
<tr>
<td>Sunflower or grape seed oil</td>
<td>1.20 (0.94-1.53)</td>
</tr>
</tbody>
</table>

*Neurology 2007;69:1921–1930*
Relation of higher Folate intake to lower risk of AD in the Elderly (Observational study) 
n=965 without dementia, 6 year follow up

Table 2. Relation of Quartiles of Energy-Adjusted Total Folate Intake to Incident AD

<table>
<thead>
<tr>
<th>Quartiles of Folate Intake, μg</th>
<th>No. at Risk</th>
<th>No. of Cases (Rate per 100 Person-years)</th>
<th>Model, HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤292.9</td>
<td>241</td>
<td>54 (3.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>293.0-365.0</td>
<td>241</td>
<td>52 (3.4)</td>
<td>1.1 (0.7-1.6)</td>
</tr>
<tr>
<td>365.1-487.8</td>
<td>241</td>
<td>49 (3.2)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>≥487.9</td>
<td>242</td>
<td>37 (2.6)</td>
<td>0.7 (0.5-1.1)</td>
</tr>
</tbody>
</table>

*Model 1 is adjusted for age and sex. Model 2 is also adjusted for ethnic group, education, and apolipoprotein E ε4 allele. Model 3 is also adjusted for history of diabetes, hypertension, current smoking, heart disease, and stroke. Model 4 is also adjusted for levels of vitamins B₆ and B₁₂.

Abbreviations: AD, Alzheimer disease; CI, confidence interval; HR, hazard ratio.

Arch Neurol. 2007;64:86-92
Antihypertensive treatment and Alzheimer’s disease

- More studies are needed to confirm that the BP lowering agents may prevent Alzheimer’s disease.

- Incidence of dementia should constitute the primary outcome of future long term trials comparing different classes of antihypertensive drugs in order to better determine the mechanism of dementia prevention.