The real potential to prevent Alzheimer’s disease

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CAHS FORUM ON DEMENTIA, September 17, 2015
Are there ways to prevent cognitive impairment and dementia/AD?

- State of the art
- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- Future directions: Multi-domain, multinational studies and pragmatic prevention programs
Dementia as a public health priority

**47 million**: number of people living with dementia worldwide in 2015; this number is expected to almost **double by 2030** and more than **triple by 2050**.

**US $818 billion**: global cost of dementia estimated in 2014.

**AD prevention and adequate care**: worldwide priorities

**AD drug development**: major political, academic and industrial effort

Dementia and Alzheimer disease: importance of life-long exposure to multiple factors

**RISK FACTORS**

- Unhealthy diet, Alcohol misuse, Smoking, Diabetes, Depression
- APOE, other genes
- Familial aggregation
- High blood pressure
- Obesity
- High blood cholesterol

**PROTECTIVE FACTORS**

- Education
- Physical activity, Cognitive & social activity

**MECHANISMS**

- Neuronal damage
- Vascular insults
- Brain reserve
- Cognitive reserve

**DEMENTIA**

- Transition

Kivipelto, Mangialasche et al., Oxford Ger Text Medicine 2015, in press
# Trends of reduced dementia occurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Data Source</th>
<th>Key Findings</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manton et al. (United States)</td>
<td>Prevalence of severe cognitive impairment</td>
<td>National long-term care survey interviews, 1982–1999</td>
<td>Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)</td>
<td>Higher educational level, decline in stroke incidence</td>
</tr>
<tr>
<td>Langa et al. (United States)</td>
<td>Prevalence of cognitive impairment</td>
<td>Ongoing population-based survey of people ≥51 yr of age</td>
<td>Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)</td>
<td>Higher educational level; combination of medical, lifestyle, demographic, and social factors</td>
</tr>
<tr>
<td>Schrijvers et al. (Rotterdam)</td>
<td>Incidence of dementia</td>
<td>Population-based cohort ≥55 yr of age in 1990, extended in 2000</td>
<td>Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)</td>
<td>Higher educational level, reduction in vascular risk, decline in stroke incidence</td>
</tr>
<tr>
<td>Qiu et al. (Stockholm)</td>
<td>Prevalence of DSM-III-R dementia*</td>
<td>Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004</td>
<td>Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence</td>
<td>Favorable changes in risk factors, especially vascular risk; healthier lifestyles</td>
</tr>
<tr>
<td>Matthews et al. (England)</td>
<td>Prevalence of dementia in 3 regions</td>
<td>Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)</td>
<td>Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)</td>
<td>Higher educational level, better prevention of vascular disease</td>
</tr>
</tbody>
</table>

*Abbreviations: CFAS*
To what extent can Alzheimer dementia be prevented?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.9%</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>5.1%</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>2.0%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>12.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>7.9%</td>
</tr>
<tr>
<td>Smoking</td>
<td>13.9%</td>
</tr>
<tr>
<td>Low education</td>
<td>19.1%</td>
</tr>
<tr>
<td>Combined PAR*</td>
<td>28.2%</td>
</tr>
</tbody>
</table>

PAR = population-attributable risk.
*Adjusting for non-independence of the risk factors.

Randomized controlled trials
Long tradition in risk factor monitoring: The FINRISK Study

Intervention studies: North Karelia Project, Finnish Diabetes Prevention Study, Dose-Responses to Exercise Training

Integrating multidomain intervention to prevent cognitive impairment into the existing framework
The Finnish Diabetes Prevention Study (DPS):
Diabetes incidence was decreased by 58%

Goals:
- Weight reduction $\geq 5\%$
- Moderate fat $< 30 \text{ E}\%$
- Low saturated fat $< 10 \text{ E}\%$
- High fibre $\geq 15 \text{g/1000kcal}$
- Physical activity $\geq 30 \text{ min/day}$

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
• Proof-of-concept trial - multidomain approach to cognitive decline prevention

• At-risk segment of the general elderly population (not patients)

• 2-year multi-domain lifestyle intervention:
  → Nutritional guidance
  → Physical activity
  → Cognitive training and social activities
  → Monitoring of metabolic and vascular risk factors: hypertension, dyslipidemia, obesity, impaired glucose tolerance

Clinicaltrials.gov NCT01041989
Protocol in Kivipelto, Solomon et al., Alzheimer & Dementia 2013
Participants:
- Previous national surveys (FINRISK)
- N=1260
- Age 60-77y
- Randomized into 2 groups (1:1)

Time schedule:
- Intervention completed February 2014
- Extended 5-year follow-up starts April 2015
- Extended 7-year follow-up planned
INCLUSION CRITERIA: persons at risk of dementia/cognitive decline

- Dementia Risk score ≥ 6 points
  
  Based on risk factors assessed in earlier population surveys: Age, Education, Sex, SBP, Cholesterol, BMI, Physical Activity (Kivipelto et al., Lancet Neurology 2006)

AND

- Cognitive performance at mean level or slightly lower than expected for age
  (based on CERAD test battery)

  Protocol in Kivipelto et al., Alzheimer & Dementia 2013
INTERVENTION SCHEDULE

INTENSIVE MULTIDOMAIN INTERVENTION

NUTRITION: 7 group sessions, 3 individual sessions

EXERCISE:
- 1-2x/wk muscle
- 2-4x/wk aerobic
EXERCISE:
- 2x/wk muscle
- 4-5x/wk aerobic
EXERCISE:
- 2x/wk muscle strength training
- 5-6x/wk aerobic training

COGNITIVE TRAINING:
- 9 group sessions
- Independent training
COGNITIVE TRAINING:
- 2 group sessions
- Independent training

MONITORING AND MANAGEMENT OF METABOLIC AND VASCULAR RISK FACTORS
- Nurse: Visit every 3 months
- Physician: 3 additional visits

REGULAR HEALTH ADVICE

Kivipelto et al., Alzheimer & Dementia 2013
OUTCOMES

- **Primary:**
  - Neuropsychological Test Battery (NTB) total z score (cognitive change)

- **Secondary:**
  - Dementia/AD (after 7 years)
  - Depressive symptoms (Zung scale)
  - Vascular risk factors, morbidity and mortality
  - Disability (questionnaire, ADL + IADL)
  - Quality of life (RAND-36, 15D)
  - Utilization of health resources
  - Blood markers (i.e. inflammation, redox status, lipid and glucose metabolism, telomere length)
  - Brain MRI measures (n=200) and PET (n=60)

*Kivipelto et al., Alzheimer & Dementia 2013*
Results

Primary efficacy outcome: global cognition
(NTB composite Z score)

Intervention group: 25% higher improvement

Difference between intervention and control groups per year:
Estimate (95% CI) = 0.022 (0.002-0.042)
p=0.03

Lines = estimates for cognitive change from baseline to 12 and 24 months
Higher scores = better performance
Error bars = standard errors
P-values = difference in trajectories over time between groups

Kivipelto, Ngandu, Mangialasche et al., Lancet 2015
Results

Intervention effects on various cognitive domains (secondary outcomes)

Executive functioning

Processing speed

Memory (abbreviated score)

83% higher improvement

150% higher improvement

40% higher improvement

Difference between intervention and control groups per year:

<table>
<thead>
<tr>
<th>Domain</th>
<th>Estimate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functioning</td>
<td>0.027 (0.001-0.052)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.030 (0.003-0.057)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Memory</td>
<td>0.038 (0.002-0.073)</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

Kivipelto et al., Lancet 2015
Risk for cognitive decline

Kivipelto, Ngandu, Mangialasche et al., Lancet 2015

Control group:
30% increased risk
Cognitive decline

* p<0.05
## Intervention effects on secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control Mean change (SE)</th>
<th>Intervention Mean change (SE)</th>
<th>Difference between intervention and control groups per year Estimate (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.33 (0.05)</td>
<td>-0.49 (0.05)</td>
<td>-0.077 (-0.149 - -0.006)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish intake at least twice/week (%)</td>
<td>+0.8</td>
<td>+11.0</td>
<td>10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daily intake of vegetables (%)</td>
<td>-1.0</td>
<td>+2.9</td>
<td>3.9</td>
<td>0.023</td>
</tr>
<tr>
<td>Physical activity ≥2 times/week (%)</td>
<td>-2.1</td>
<td>+7.0</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mixed-model repeated-measures analyses*

** Multinominal logistic regression (change in % units between baseline and 24 months)

*Kivipelto et al, Lancet 2015*
Self-reported adverse events during the study and health care register follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (n=1260)</th>
<th>Intervention (n=631)</th>
<th>Control (n=629)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported adverse events or negative experience of the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>52</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Slight musculoskeletal pain</td>
<td>32</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Stress</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Time-consuming</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Dead during the study</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Health care register information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

No serious adverse events

Kivipelto et al, Lancet 2015
# Self reported adherence

<table>
<thead>
<tr>
<th>Domain</th>
<th>Any participation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>99.7%</td>
</tr>
<tr>
<td>Exercise</td>
<td>90.3%</td>
</tr>
<tr>
<td>Cognitive training</td>
<td>84.9%</td>
</tr>
<tr>
<td>Risk factors monitoring</td>
<td>87.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No of domains</th>
<th>Any participation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>2</td>
<td>6.2%</td>
</tr>
<tr>
<td>3</td>
<td>20.8%</td>
</tr>
<tr>
<td>4</td>
<td>71.6%</td>
</tr>
</tbody>
</table>

Kivipelto et al, Lancet 2015
Prevention of dementia: Future?

Necessary of multi-national studies and pragmatic prevention programs
European Dementia Prevention Initiative

- **FINGER** Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- **Pre-DIVA** Prevention of Dementia by Intensive Vascular Care
- **MAPT** Multidomain Alzheimer Preventive Trial

Data pooling and joint analyses
> 6000 participants
Healthy Aging Through Internet Counseling in the Elderly

- **Main goal**: prevention of dementia and cardiovascular diseases in the elderly
- **Strategy**: motivate and support lifestyle changes to improve management of vascular risk factors
- **Tool**: new easily accessible, interactive internet platform, with readily available nurse-support

www.HATICE.eu
Multimodal preventive trials for Alzheimer’s Disease: towards multinational strategies (MIND-AD)
Ongoing clinical trials in Alzheimer disease (AD)

More than 200 drug development failures in the last 30 years
(Schneider Mangialasche Kivipelto et al., JIM 2014)
Take home points: how to prevent dementia

1. Timing: starting early, at-risk persons

2. Multi-factorial aetiology – multi-domain interventions effective for several cognitive domains

3. FINGER: a pragmatic model that can be tested and adapted in various settings and populations

4. Future: Multi-national prevention RCTs & Pragmatic prevention programs, integrated interventions
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Life matters!