Lifestyle Intervention to Prevent Cognitive Impairment

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Are there ways to prevent cognitive impairment and dementia/AD?

- State of the art

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- Future directions: Multi-domain, multinational studies and pragmatic prevention programs
Dementia and Alzheimer disease: importance of life-long exposure to multiple factors

**RISK FACTORS**

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

**PROTECTIVE FACTORS**

- Education
- Physical activity, Cognitive & social activity

**MECHANISMS**

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

**DEMENTIA**

Kivipelto, Mangialasche et al., Oxford Ger Text Medicine 2015, in press
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
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

Principal Investigator:
Prof. Miia Kivipelto
INCLUSION CRITERIA: persons at risk of dementia/cognitive decline

- Dementia Risk score $\geq 6$ 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
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
FINGER intervention
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
- **Control**
- **Intervention**

### Processing speed
- **Control**
- **Intervention**

### Memory (abbreviated score)
- **Control**
- **Intervention**

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

*Kivipelto et al., Lancet 2015*
Risk for cognitive decline

**NTB total score**

- **Intervention**
- **Control**

Control group: 30% increased risk
Cognitive decline

* p<0.05

*Kivipelto, Ngandu, Mangialasche et al., Lancet 2015*
## 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</th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular factors</strong></td>
<td></td>
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<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>**Lifestyle factors **</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*
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
Multimodal preventive trials for Alzheimer’s Disease: towards multinational strategies (MIND-AD)
Ongoing clinical trials in Alzheimer disease (AD)

β amyloid

Cholinergics

Others

† Currently approved for AD treatment

Mangialasche, Kivipelto et al, modified 2013 from Lancet Neurology, 2010
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!