Prevention of dementia:
An overview of European Studies

Laura Fratiglioni

http://www.KI-SU-ARC.se
G8 Dementia Summit: Global action against dementia
London, 11 December 2013

Focus on dementia prevention
→ International collaboration
→ Prevention trials to obtain evidence based conclusions
Outline

1. Evidence from observational studies
2. Temporal trends- indirect confirmation
3. Nordic multi-domain intervention studies
4. European Dementia Prevention Initiative
1. Importance of life-long exposure

2. Life-long exposure to multiple factors

<table>
<thead>
<tr>
<th>Birth</th>
<th>Childhood-2nd decade</th>
<th>Adult life-Middle age</th>
<th>Transition</th>
<th>Old age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>60</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Healthy brain

Alzheimer brain
Risk Factors: biological & contextual

Genetic background

<table>
<thead>
<tr>
<th>Birth</th>
<th>Childhood-2^nd decade</th>
<th>Adult life-transition</th>
<th>Older age</th>
</tr>
</thead>
</table>

Brain Reserve Capacity

Protective Factors
- Psychosocial factors
- Nutrition

Brain lesions

Risk Factors: biological & contextual
- Neurodegeneration
- Vascular mechanisms
- Oxidative stress
- Inflammation
- Toxicity

Genetic background
- Genetic background
- Inflammation
- Toxicity
- Oxidative stress
- Vascular mechanisms
- Neurodegeneration

Protective Factors
- Psychosocial factors
- Nutrition
Risk Factors: biological & contextual

- Neurodegeneration
- Vascular mechanisms
- Oxidative stress
- Inflammation
- Psychosocial factors
- Nutrition

Genetic background

Brain Reserve Capacity

Birth | Childhood-2nd decade | Adult life- | Older
Transition | age

0
Not all old persons get dementia
Why?

Dementia Prevalence per 100

- Fratiglioni et al, 1999; All continents
- Lobo et al, 2000; Europe

Dementia Incidence per 1000 personyears

- Gao et al, 1998; All continents
- Fratiglioni et al, 2000; Europe
Two cohort studies in Stockholm

Kungsholmen District


N=1810, age ≥75 yrs

Swedish National study on Aging and Care (SNAC)-K: 2001–ongoing

N=3363, age ≥60 yrs
Vascular burden

- SBP>180: Low/all 3 8%, High/1-2 10%, High/all 3 12%
- DBP<70: Low/all 3 10%, High/1-2 12%, High/all 3 14%
- Diabetes: Low/all 3 12%, High/1-2 12%, High/all 3 14%
- Heart...: Low/all 3 37%, High/1-2 47%, High/all 3 47%
- Stroke: Low/all 3 8%, High/1-2 8%, High/all 3 8%

Mental, social & physical scores

- Low/all 3: Dementia 40%, Non Dementia 35%
- High/1-2: Dementia 25%, Non Dementia 20%
- High/all 3: Dementia 20%, Non Dementia 15%
Hazard ratios of dementia in subjects with highest \((\text{grey})\) and lowest \((\text{plum})\) risk profiles by genetic background.

- **APOE £4**: HR 0.62
- **Non £4**: HR 0.46

Ferrari et al, Neurobiology of Aging 2013
3. Possible preventive strategies against dementia

- **Promoting healthy lifestyles**
  - non-smoking
  - moderate alcohol intake
  - physical activity

- **Decreasing vascular burden**
  - hypertension
  - heart failure
  - diabetes
  - stroke

- **Increasing brain reserve**
Brain Plasticity

Van Praag et al. (2006) Nat Rev Neurosci

Draganski et al. (2006) J Neurosci


Draganski et al. (2004) Nature
Outline

1. Evidence from observational studies
   Life course
   Multiple interacting factors
   Three possible preventive strategies

2. Temporal trends- indirect confirmation

3. Nordic multi-domain intervention studies

4. European Dementia Prevention Initiative
Given that

- Vascular risk factors and related diseases are implicated in dementia
- Incidence and mortality of major cardiovascular diseases have decreased in high-income countries since the 1980s

Rosengren et al, *Stroke* 2013

Di Cesare et al, *Int J Epidemiol* 2013

Nichols et al, *Eur Heart J* 2013
75+ old Swedish urban population:

Prevalence of dementia in 1987-89 & 2001-04

Stable prevalence, but also longer survival

Decreased incidence

Qiu et al, Neurology 2013
Comparison with other studies
Trends of dementia occurrence

- Two studies from the Netherland and from USA show evidence of declining incidence (Rocca et al, 2011; Schijvers et al, 2012)

- A recent study from UK shows decreased prevalence (Matthew et al, July Lancet 2013)

- K Christensen et al, Lancet July 2013. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart.
Outline

1. Evidence from observational studies
   - Life course
   - Multiple interacting factors
   - Three possible preventive strategies

2. Temporal trends - indirect confirmation
   - Decreasing incidence

3. Nordic multi-domain intervention studies

4. European Dementia Prevention Initiative
The pre-FINGER framework

Observational studies

• FINRISK (Vartiainen et al., Int J Epidem 2010)
• CAIDE (Kivipelto et al., BMJ 2001)

Intervention studies

• NORTH KARELIA PROJECT
• DIABETES PREVENTION STUDY
• DR’S EXTRA (Komulainen, Kivipelto, Rauramaa Neurobiol Learn Mem. 2008)
Finnish Diabetes Prevention Study: effect of 3-year intervention persisted over 13 years!

The DR’s EXTRA Study: effects on cognition (CERAD-TS) by age

Adjusted for CV risk factors, alcohol, depression, age, social support, medication & gender.

Rauramaa, Kivipelto, in progress
Aims to **reduce cognitive impairment** in an at risk population through a 2-year multi-domain life-style intervention including:

→ Nutritional guidance

→ Physical activity

→ Cognitive and social activities

→ Monitoring and management of metabolic and vascular risk factors: hypertension, dyslipidemia, obesity, impaired glucose tolerance

*Kivipelto et al., Alzheimer & Dementia 2013*
Participants:
- N=1260 persons at risk of dementia/cognitive decline
- Age 60-77y
- Randomized into 2 groups

Time schedule:
- Intervention completed February 2014
- Extended 7-year follow-up starts 2015

Kivipelto et al., Alzheimer & Dementia 2013
### INTERVENTION SCHEDULE

#### INTENSIVE INTERVENTION

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NUTRITION:</strong></td>
<td>7 group sessions, 3 individual sessions</td>
</tr>
<tr>
<td><strong>EXERCISE:</strong></td>
<td>1-2x/wk muscle, 2-4x/wk aerobic</td>
</tr>
<tr>
<td><strong>EXERCISE:</strong></td>
<td>2x/wk muscle, 4-5x/wk aerobic</td>
</tr>
<tr>
<td><strong>EXERCISE:</strong></td>
<td>2x/wk muscle strength training, 5-6x/wk aerobic training</td>
</tr>
<tr>
<td><strong>COGNITIVE TRAINING:</strong></td>
<td>9 group sessions, Independent training</td>
</tr>
<tr>
<td><strong>COGNITIVE TRAINING:</strong></td>
<td>2 group sessions, Independent training</td>
</tr>
</tbody>
</table>

#### MONITORING AND MANAGEMENT OF METABOLIC AND VASCULAR RISK FACTORS

- Nurse: Visit every 3 months, Physician: 3 additional visits

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

Primary:

- **Cognitive impairment** (Neuropsychological Test Battery, Trail Making & Stroop tests)

Secondary:

- Dementia (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*
FINGER intervention

"I have friends who are jealous when they hear all that I have been offered to do at this course"
Outline

1. Evidence from observational studies
   Life course
   Multiple interacting factors
   Three possible preventive strategies

2. Temporal trends - indirect confirmation
   Decreasing incidence

3. Nordic multi-domain intervention studies
   Feasibility
   Low drop-outs rate
   High adherence

4. European Dementia Prevention Initiative
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
Outline

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   Life course
   Multiple interacting factors
   Three possible preventive strategies

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   Decreasing incidence

3. Nordic multi-domain intervention studies
   Feasibility
   Low drop-outs rate
   High adherence

4. European Dementia Prevention Initiative
   Multidomain interventions
   Starting early, at risk persons
Is aging without dementia just a dream?

Aging without dementia is already a reality today.

Dementia risk can decrease even more in the future.
Acknowledgements

- Swedish Council for Working Life & Social Research (FAS-FORTE);
- Swedish Research Council (VR);
- SBP, EU, American AD, Private Foundations, etc.

Miia Kivipelto
RELEVANCE OF THE FINGER STUDY

- Will test to what extent a multi-domain intervention may delay cognitive impairment and dementia onset in people at increased risk.

- The broad range of secondary outcomes enables estimation of total benefit and mediating pathways.

- Will provide data urgently needed for health education and community planning.
1) Dietary intervention

Based mainly on Finnish Nutrition Recommendations

The dietary measures recommended:

- High consumption of fruits and vegetables
- Whole grain in all cereal products
- Fish 2-3 portions/week, 1-2 portions being fatty fish
- Low-fat options in milk and meat products
- Vegetable margarine and rapeseed oil instead of butter
- Decrease salt and sucrose intake
- Keep alcohol consumption in moderation
- Adjust the energy level of the diet if needed

Individually tailored counselling

Kivipelto et al., Alzheimer & Dementia 2013
2) Exercise intervention: progression of the resistance and aerobic training program

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0-1</th>
<th>1-3</th>
<th>3-6</th>
<th>6-24</th>
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</thead>
<tbody>
<tr>
<td><strong>Resistance Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise frequency/wk</td>
<td>1-2</td>
<td>1-2</td>
<td>2</td>
<td>2-3</td>
</tr>
<tr>
<td>Duration of exercise, min</td>
<td>30-45</td>
<td>30-60</td>
<td>45-60</td>
<td>60</td>
</tr>
<tr>
<td>Number of muscle groups</td>
<td>8-10</td>
<td>8-10</td>
<td>8-10</td>
<td>8-10</td>
</tr>
<tr>
<td>Repetitions/ set</td>
<td>8-15</td>
<td>10-20</td>
<td>8-20</td>
<td>8-20</td>
</tr>
<tr>
<td>Load % 1RM</td>
<td>40-50</td>
<td>60</td>
<td>70</td>
<td>70-80</td>
</tr>
<tr>
<td>Number of sets</td>
<td>2</td>
<td>2-3</td>
<td>1-3</td>
<td>2-3</td>
</tr>
<tr>
<td><strong>Aerobic Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise frequency/wk</td>
<td>2</td>
<td>2-3</td>
<td>3-4</td>
<td>3-5</td>
</tr>
<tr>
<td>Duration of exercise, min</td>
<td>30-45</td>
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<td>30-60</td>
<td>45-60</td>
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*Kivipelto et al., Alzheimer & Dementia 2013*
3) Cognitive training

- Intervention implementation
  - 10 group sessions lead by study psychologist
  - Individual computer-based training (6 months x 2)
  - Training targets episodic memory, executive function, mental speed, and working memory
Monitoring of metabolic/vascular risk factors

- Regular meetings with study nurses and physicians
- Anthropometric and laboratory measurements
- Discussions of individual results
- Drug treatments - primary care physician

Kivipelto et al., Alzheimer & Dementia 2013
<table>
<thead>
<tr>
<th></th>
<th>FINGER (Finland)</th>
<th>MAPT (France)</th>
<th>Pre-DIVA (Netherlands)</th>
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</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Vascular care, Diet, Exercise, Cognitive training</td>
<td>Multi-domain (Diet, Exercise, Cognitive training), Omega-3</td>
<td>Nurse-lead intensive vascular care</td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td>60 -77</td>
<td>70 +</td>
<td>70-78</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>1260</td>
<td>1680</td>
<td>3535</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Dementia Risk Score &gt;6 and cognitive performance</td>
<td>Frail elderly people (subjective memory complaint, slow walking speed, limitation in IADL)</td>
<td>All elderly within GP practices</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Multi-center, randomized, single-blind, parallel-group</td>
<td>Multi-center, randomized, controlled trial</td>
<td>Multi-cite, open, cluster-randomized parallel group</td>
</tr>
<tr>
<td><strong>Intervention period</strong></td>
<td>2 yrs + 5 yrs extended follow-up</td>
<td>3 yrs + 2 yrs extended follow-up</td>
<td>6 yrs</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Neuropsychological test battery, Trail Making, Stroop, Dementia</td>
<td>Change in cognitive function (Grober and Buschke memory test)</td>
<td>Dementia, Disability</td>
</tr>
<tr>
<td><strong>Study Completion</strong></td>
<td>2014</td>
<td>2014</td>
<td>2015</td>
</tr>
</tbody>
</table>
A 10–25% reduction in all seven risk factors could potentially prevent 1.1–3.0 million AD cases worldwide.
Trends of reduced dementia occurrence

At least five studies provide evidence suggesting that incidence of dementia may have decreased over the last two decades (still the prevalence is increasing):

- Christensen et al. Physical and cognitive function of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *The Lancet* 2013

Why? - Better awareness/”treatment” of vascular/lifestyle related risk factors
Prevention successful!
Brain Reserve

*Bennett, Wilson et al, Neurology 2003*
Religious Order Study, 130 subjects

**Global cognitive function**

Summary measure of AD pathology

Years of schooling
- 90th percentile
- 50th percentile
- 10th percentile