HOW TO PREVENT COGNITIVE DECLINE …
....AT MCI STAGE?

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CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflicts of interest to report:
- Received lecture fees from Nestlé Health Science and Nutricia
Outline

Definition of MCI

Etiology of MCI

Impact of MCI

Interventions to prevent cognitive decline at MCI
Definition of MCI

Cognitive Continuum

- Normal
- Age-related cognitive decline
- Mild cognitive impairment
- Impairment of ADL (10 - 25%)
- Prodromal stage of Dementia
- Dementia
Definition of MCI

• Cognitive complaint, cognitive decline or impairment
• Objective evidence of impairment in cognitive domains: memory, executive function/attention, language, or visuospatial skills (<1.5 SD)
• Essentially normal functional activities
• Absence of dementia

Definition of MCI

MCI phenotype

MCI

- MCI Single domain
  - Amnestic
  - Non-Amnestic

- MCI Multiple domains
  - Amnestic
  - Non-Amnestic

## Etiology of MCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amnestic</th>
<th>Non-amnestic</th>
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<tbody>
<tr>
<td>Etiology</td>
<td>Neurodegenerative disease</td>
<td>Vascular damage</td>
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<tr>
<td></td>
<td>APOE ε4</td>
<td>Cerebrovascular disease</td>
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<td>Pathology</td>
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<td>Cerebrovascular</td>
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<td>Amyloid β plaques</td>
<td>Cortical infarctions</td>
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<td></td>
<td>Neurofibrillary tangles</td>
<td>Subcortical infarctions</td>
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<td></td>
<td>Hippocampal atrophy</td>
<td>White matter hyperintensities</td>
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<td>Reduced brain volume</td>
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<td>Presentation</td>
<td>Memory impairment present</td>
<td>Impairment in non-memory domains</td>
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<td>Long term outcomes</td>
<td>Alzheimer’s dementia (AD)</td>
<td>Non-Alzheimer dementias:</td>
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<tr>
<td></td>
<td></td>
<td>Vascular dementia</td>
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<tr>
<td></td>
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<td>Lewy body, Frontotemporal</td>
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</table>
# Etiology of MCI

## MCI Subtypes

<table>
<thead>
<tr>
<th>Amnestic MCI</th>
<th>Non-amnestic MCI</th>
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<tr>
<td>Single domain</td>
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<tr>
<td>Multiple domain</td>
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<table>
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<tr>
<th>Etiology</th>
<th>Degenerative</th>
<th>Vascular</th>
<th>Psychiatric</th>
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<tr>
<td>AD</td>
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<td>Depr</td>
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<tr>
<td>AD</td>
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<td>VaD</td>
<td>Depr</td>
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</tr>
<tr>
<td>FTD</td>
<td></td>
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<tr>
<td>DLB</td>
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<td>VaD</td>
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</table>
Impact of MCI

Trajectories of MCI

Risk factors
Protective factors

Normal | Age-related cognitive decline | Mild cognitive impairment | Dementia

Risk factors for progression to dementia

20 - 40% 10 - 15 % per year (control 1 - 2%)
Impact of MCI

Prognosis of MCI

Annual rates of conversion from MCI to dementia over 48 months

Impact of MCI

RF for progression to dementia

• Older age
• ApoE4
• Worse baseline cognition
• Stroke
• Hypertension
• T2 Diabetes
• Low education
• **Multi-domain MCI**
• **Amnestic MCI**
• Impairment in IADL
• (Subclinical) Depression
• Neuropsychiatric symptoms
• Anticholinergic drugs

• Lower serum folates
• White matter hyperintensity volume (MRI)
• Atrophy (MRI)
• Hippocampal atrophy (MRI)
• FDG PET pattern of Alzheimer’s disease
• CSF markers compatible with Alzheimer's disease
• Positive amyloid imaging scan

MILD COGNITIVE IMPAIRMENT
▲ risk of DEMENTIA
Public Health Issue
INTERVENTIONS

Interventions to prevent cognitive decline at MCI

Goal of Interventions

- Revert MCI to normal cognition
- Revert MCI to better cognition
- Stop progression of MCI
- Delay progression of MCI
- Stop progression to Dementia
Interventions to prevent cognitive decline at MCI

How to prevent cognitive decline ...at MCI stage?

How to prevent PROGRESSION OF MCI TO DEMENTIA?
Interventions to prevent cognitive decline at MCI

Some facts....

• Most studies about prevention of cognitive decline are in persons with normal cognition baseline

• Main outcome of most studies is cognitive performance (and not dementia incidence)

• Several studies in MCI pts consider as positive result any improvement in cognitive performance at short-term
  • Long term effect?
  • Proxy for delay of MCI progression into dementia?
Interventions to prevent cognitive decline at MCI

- Some studies
- Several interventions
- Small studies
- Short term studies
- High risk of bias
- Inconsistent and changing classifications
Interventions to prevent cognitive decline at MCI

Effectiveness of interventions to prevent or delay cognitive decline

Main outcome: Dementia incidence
Secondary outcomes: Cognitive performance

Randomized & nonrandomized controlled trials
Prospective observational cohort studies (>500 pts)
> 6 months follow-up
excluded high risk of bias studies

Publications until September 2016

Agency Healthcare Research & Quality (US). *Comparative Effectiveness Reviews*, 188. March 2017
Interventions to prevent cognitive decline at MCI

13 interventions

- Cognitive training
- Physical activity
- Nutraceuticals
- Diet interventions
- Multimodal interventions
- Hormone therapy
- Vitamins
- Antihypertensive drugs
- Lipid lowering drugs
- NSAIDs
- Antidementia drugs
- Diabetes treatment
- Other interventions
Interventions to prevent cognitive decline at MCI

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- Other interventions
Cognitive Training

Promotion of neuroplasticity

Building new neuronal pathways

Maintaining existing neuronal pathways
## Interventions to prevent cognitive decline at MCI

### Cognitive Training

<table>
<thead>
<tr>
<th>Trials</th>
<th>n</th>
<th>time</th>
<th>mode</th>
<th>Intervention Trained domains</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buschert, 2012</td>
<td>24</td>
<td>28 months</td>
<td>Small group (12pp) 2 hours/week, 6 weeks</td>
<td>Mnemonic memory</td>
<td>▲ 2/6 cognitive tests ▼ Dementia</td>
</tr>
<tr>
<td>Rapp, 2002</td>
<td>19</td>
<td>6 months</td>
<td>Small group 2 hours/week, 6 weeks</td>
<td>Memory</td>
<td>▲ Self-rated memory ○ cognitive tests</td>
</tr>
<tr>
<td>Vidovich, 2015</td>
<td>160</td>
<td>24 months</td>
<td>Small group (6-9 pp) 3 hours/week 5 weeks</td>
<td>Attention Memory Executive functions</td>
<td>▲ 1/9 cognitive tests</td>
</tr>
<tr>
<td>Kwok, 2012</td>
<td>223</td>
<td>12 months</td>
<td>Small group (3-5 pp) 1,5 hours/week 12 weeks</td>
<td>Attention Processing speed Memory, Reasoning</td>
<td>○ cognitive tests</td>
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<tr>
<td>Herrera, 2012</td>
<td>22</td>
<td>6 months</td>
<td>Individual Computer-based 2 hours/week, 12 weeks</td>
<td>Recognition Working memory Recall</td>
<td>Mixed results ▲ 3/9 cognitive tests</td>
</tr>
</tbody>
</table>
### Cognitive Training

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SIGNIFICANT*</th>
<th>NONSIGNIFICANT*</th>
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<tbody>
<tr>
<td><em>Result favors I</em></td>
<td><em>Results were not statistically significant</em></td>
<td></td>
</tr>
<tr>
<td>Buschert 2012 &amp; Forster 2011, n=24</td>
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<tr>
<td>Biomarkers</td>
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<tr>
<td>Buschert 2012 &amp; Forster 2011, n=24</td>
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<tr>
<td>Brief Cognitive Test Performance</td>
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<tr>
<td>Buschert 2012 &amp; Forster 2011, n=24</td>
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<tr>
<td>Multidomain Neuropsychological Performance</td>
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<tr>
<td>Buschert 2012 &amp; Forster 2011, n=24</td>
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<tr>
<td>Vidovich 2013, n=150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive, Attention, Processing</td>
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<td></td>
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<tr>
<td>Buschert 2012 &amp; Forster 2011, n=24</td>
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</table>

*No improvement of untrained domains*
Physical activity

**Neuroprotection**
- ▲ neuronal connectivity
- ▲ brain volume
- ▼ B amyloid

**Cerebrovascular reserve**
- ▼ blood viscosity
- ▲ brain blood flow

**Chronic & Psychiatric Disorders**
## Interventions to prevent cognitive decline at MCI

### Physical activity

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<thead>
<tr>
<th>Trials</th>
<th>n</th>
<th>time</th>
<th>Mode / Training</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker, 2010</td>
<td>33</td>
<td>6 months</td>
<td>Aerobic exercise</td>
<td>▲ cognitive tests (executive fx, women)</td>
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<tr>
<td>Hildreth, 2015</td>
<td>53</td>
<td>6 months</td>
<td>Aerobic / endurance</td>
<td>No improvement of cognitive tests</td>
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<tr>
<td>Nagamatsu, 2012</td>
<td>86</td>
<td>26 weeks</td>
<td>Resistance (vs aerobic vs balance &amp; tone)</td>
<td>No improvement of cognitive tests</td>
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<tr>
<td>Suzuki, 2013</td>
<td>100</td>
<td>6 months</td>
<td>Multicomponent physical activity</td>
<td>▲ 2/9 cognitive tests at 6 months (MMSE, Memory, Verbal Fluency) (no improvement at 12 months)</td>
</tr>
<tr>
<td>Suzuki, 2012</td>
<td></td>
<td>6 months</td>
<td>Multicomponent physical activity</td>
<td>No improvement of cognitive tests</td>
</tr>
<tr>
<td>Lautenschlager, 2008</td>
<td>100</td>
<td>6 M training</td>
<td>Home-based physical activity</td>
<td>▲ 1/5 cognitive tests (ADAS-Cog at 6&amp;18M) ○ Dementia incidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 M follow-up</td>
<td></td>
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</tr>
</tbody>
</table>

**Benefit of aerobic & resistance training**

AHRQ (US). *Comparative Effectiveness Reviews, 2017. 188*
Interventions to prevent cognitive decline at MCI

Physical activity

Effects of aerobic exercise on mild cognitive impairment
a controlled trial

Improvement of language and executive functions

Interventions to prevent cognitive decline at MCI

**Physical activity**

Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment

**Multicomponent exercise** (n=25) vs **Education control group** (n=25)

Improvement of MMSE, memory and executive functions

Nutraceuticals

- Oxidative stress decreased
- Inflammation decreased
- Vascular function increased

Supplementation of macronutrients of brain tissue and fx
Interventions to prevent cognitive decline at MCI

**Nutraceuticals**

Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI)

a 12-month randomised, double-blind, placebo-controlled trial

- **MCI ≥60 yo**
- **Fish oil group** (daily omega-3 fatty acids)
  - 12 months
- **Placebo**

▲ memory
▲ executive fx
= MMSE

Interventions to prevent cognitive decline at MCI

Nutraceuticals

Efficacy and safety of Ginkgo biloba extract EGb 761® in mild cognitive impairment with neuropsychiatric symptoms

a randomized, placebo-controlled, double-blind, multi-center trial

Figure 5 Change in Trail-Making Test B score from baseline to week 24, means, and 95% confidence intervals, two-sided p-value of analysis of covariance.
Nutraceuticals

Ginkgo biloba for Prevention of Dementia: A Randomized Controlled Trial

Hormone therapy

Epidemiological studies suggest benefit of HRT
Interventions to prevent cognitive decline at MCI

**Hormone therapy**

**Testosterone**

Treatment of men with MCI and low serum testosterone

▲ verbal memory (1/14 tests)


**Soybean in Elderly Japanese Subjects with Memory Complaints**

▲ MMSE (1/6 tests)

Vitamins

Neurotropic vitamins

Lowering of homocysteine levels (B)
Vitamins

**Vitamin E**
- n=516, 3 years follow up
- No effect in dementia incidence

**B Vitamins**
- Folic acid + B12 + B6
- n=266, 2 years follow up
- Improvement of MMSE and memory tests limited to pts w/ hyperhomocysteinemia

**Multivitamin (E + C)**
- Improvement of MMSE in both arms, no difference between multivitamins and placebo


*Vitamin E had no benefit in patients with mild cognitive impairment.*
Antidementia drugs
Interventions to prevent cognitive decline at MCI

**Antidementia drugs**

Donepezil reduces progression to dementia at 1 year but not at 3 years (at 3 years only in ApoE4 carriers)

Interventions to prevent cognitive decline at MCI

**Antidementia drugs**

Rivastigmine failed to reduce progression to dementia at 4 years

Insufficient evidence to prescribe Acetylcholinesterase inhibitors in MCI

• There is very little evidence that AchEI affect progression to dementia or cognitive test scores in MCI.

• AchEI should not be recommended for MCI.
Diabetes treatment
Interventions to prevent cognitive decline at MCI

**Diabetes treatment**

**Pioglitazone** in older adults with MCI and insulin resistance

- n=78, 6 months follow up
- ▲ visual memory (1/10 tests)


**Metformin** in older adults with Amnestic MCI and ▲ BMI

- n=80, 1 year follow up
- ▲ memory (1/10 tests)

Multimodal interventions

Cognitive decline is a multifactorial condition and can be prevented by multifactorial interventions
Interventions to prevent cognitive decline at MCI

Multimodal interventions

Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial

The multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints

Interventions to prevent cognitive decline at MCI

Multimodal interventions

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER) a randomised controlled trial
There is no strong evidence that any intervention can prevent cognitive decline in MCI patients.
Is there really nothing to do to prevent cognitive decline at MCI?

Be careful with trials results...

- Late stage interventions (life cycle approach urgent)
- Short time interventions
- Short follow-up
- Heterogeneity of studies prevent reliable meta-analysis
- Control groups might not be real-life persons
  - More education, healthier behaviors, less comorbidity
  - Received some kind of intervention

Are not trials “underestimating” the effectiveness of interventions ?...
Interventions to prevent cognitive decline at MCI

Wrap up conclusions, into Clinical Practice

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Cognition</th>
<th>Progression to dementia</th>
<th>Clinical Practice</th>
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<tbody>
<tr>
<td>Cognitive Training</td>
<td>Some benefit</td>
<td>???</td>
<td>Promote!</td>
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<tr>
<td>Physical activity</td>
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<tr>
<td>Omega-3</td>
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<tr>
<td>Gingko biloba</td>
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<tr>
<td>Antidementia drugs</td>
<td>Scarce benefit</td>
<td>Scarce benefit</td>
<td>Not to prescribe</td>
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</tbody>
</table>
Take Home Messages

• Mild cognitive impairment is a prodromal stage of dementia

• It is a priority to stop progression to dementia and to revert to normal cognition

• In theory several interventions could work but high risk of bias of trials might underestimate effectiveness

• Prevention of Mild cognitive impairment is the best treatment.
HOW TO PREVENT COGNITIVE DECLINE ... 
....AT MCI STAGE?

Thank you for your attention!

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