How to prevent cognitive decline?
At dementia stage

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CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report
Outline

- Background
- Risk Factors/Secondary Prevention
- Timely detection
- Interventions
- Take Home Messages
Outline

• **Background**
  • Risk Factors/Secondary Prevention
  • Timely detection
  • Interventions
  • Take Home Messages
Prevalence of dementia in Europe

Figure 1: Number of people with dementia in 28 European countries in 2013

Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe.\footnote{Winblad et al. Lancet Neurol 2016; 15: 455–532}
Age-specific annual incidence

Global impact: one new case every 3 seconds

Burden of dementia

<table>
<thead>
<tr>
<th></th>
<th>WHO GBD (2004)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aggregated estimates – millions of years (% of total burden)</td>
<td>Millions of years, per 1,000 older people</td>
<td>Aggregated estimates – millions of years (% of total burden)</td>
</tr>
<tr>
<td>Years of Life Lost</td>
<td>3.4 (0.9%)</td>
<td>5.2</td>
<td>3.9 (0.9%)</td>
</tr>
<tr>
<td>Years Lived with Disability</td>
<td>15.4 (13.1%)</td>
<td>23.4</td>
<td>6.2 (3.8%)</td>
</tr>
<tr>
<td>Disability Adjusted Life Years</td>
<td>18.8 (4.2%)</td>
<td>28.7</td>
<td>10.0 (1.7%)</td>
</tr>
</tbody>
</table>

## Costs of dementia

Table 6.4
Worldwide costs of dementia in 2010 and 2015 (billion US$), based on World Bank country classification 2010 and adjusted prevalence figures for 2010

<table>
<thead>
<tr>
<th>Year for cost estimates (basis for prevalence estimates)</th>
<th>2010 (WAR 2009)</th>
<th>2015 (WAR 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US$ (billions)</td>
<td>Per cent</td>
</tr>
<tr>
<td>World Bank Country Classification Year</td>
<td>2010</td>
<td>2010</td>
</tr>
<tr>
<td>Low income</td>
<td>5.2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>41.2</td>
<td>6.8%</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>49.4</td>
<td>8.1%</td>
</tr>
<tr>
<td>High income</td>
<td>510.9</td>
<td>84.2%</td>
</tr>
<tr>
<td>Total</td>
<td>606.7</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Costs of dementia

Table 6.6
Sub-category costs of dementia in 2010 and 2015 (billion US$, and percent of total costs), by country income level based on current World Bank country classification

<table>
<thead>
<tr>
<th></th>
<th>Direct medical costs</th>
<th></th>
<th>Direct social sector costs</th>
<th></th>
<th>Informal care costs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US$ (billions)</td>
<td>Per cent</td>
<td>US$ (billions)</td>
<td>Per cent</td>
<td>US$ (billions)</td>
<td>Per cent</td>
</tr>
<tr>
<td>2015 (WAR 2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>0.2</td>
<td>20.4%</td>
<td>0.1</td>
<td>10.4%</td>
<td>0.8</td>
<td>69.2%</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>3.7</td>
<td>23.9%</td>
<td>2.0</td>
<td>13.2%</td>
<td>9.6</td>
<td>62.9%</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>19.3</td>
<td>22.4%</td>
<td>17.7</td>
<td>20.5%</td>
<td>49.3</td>
<td>57.1%</td>
</tr>
<tr>
<td>High income</td>
<td>136.0</td>
<td>19.0%</td>
<td>308.1</td>
<td>43.1%</td>
<td>271.1</td>
<td>37.9%</td>
</tr>
<tr>
<td>Total</td>
<td>159.2</td>
<td>19.5%</td>
<td>327.9</td>
<td>40.1%</td>
<td>330.8</td>
<td>40.4%</td>
</tr>
</tbody>
</table>

Estimated growth of the prevalence

- **High-income countries**
  - 47 millions in 2030
  - 131 millions in 2050

- **Low and middle-income countries**
  - 66 millions in 2030

*Figure 1: Growth in numbers of people with dementia in high-income and low and middle-income countries*

Outline

- Background
- **Risk Factors/Secondary Prevention**
  - Timely detection
  - Interventions
  - Take Home Messages
Risk Factors / Secondary prevention

Livingston et al. Lancet 2017
Outline

• Background
• Risk Factors/Secondary Prevention
• **Timely detection**
• Interventions
• Take Home Messages
**Definition DSM V**

**DSM-5 criteria for major neurocognitive disorder**
*(previously dementia)*

**A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*:
- Learning and memory
- Language
- Executive function
- Complex attention
- Perceptual-motor
- Social cognition

**B.** The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.

**C.** The cognitive deficits do not occur exclusively in the context of a delirium

**D.** The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)
Timely detection of dementia

- Allows people to benefit from treatment
- Screening all older people for dementia is not recommended
- Case-finding
Outline

• Background
• Risk Factors/Secondary Prevention
• Timely detection
• **Interventions**
• Take Home Messages
Interventions

• Drugs

• Cognitive treatments

• Physical Exercise
All cholinesterase inhibitors, show modest benefit on cognition (2.4 point difference on ADAS-cog). They also show a mean difference of 1.37 points on MMSE, which is equivalent to the minimum clinically important difference.
A double-blind, discontinuation study, found that donepezil cessation (replaced by a placebo) in patients with moderate-to-severe Alzheimer’s disease (MMSE <12) was accompanied by a cognitive (MMSE mean difference 1.9) and functional decline, an increase in neuropsychiatric symptoms, and doubling of risk of care home admission in the year after discontinuation.
Drugs - Cholinesterase inhibitors

Inhibition of 19–27% of cerebral cortical acetylcholinesterase activity

Bohnen et al. J Neurol Neurosurg Psychiatry 2005;76:315–319
Drugs - Cholinesterase inhibitors

Effectiveness and Tolerability of High-Dose (23 mg/d) Versus Standard-Dose (10 mg/d) Donepezil in Moderate to Severe Alzheimer’s Disease: A 24-Week, Randomized, Double-Blind Study

Farlow et al Clin Ther. 2010 July; 32(7): 1234–1251

A double-blind RCT of 1371 people with moderate-to-severe Alzheimer’s disease found a score 2.2 points higher on the 100-point Severe Impairment Battery.
Drugs - Cholinesterase inhibitors

- Higher withdrawals compared with placebo
- Diarrhoea, vivid dreams and leg cramps
Analysis 1.2. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer’s disease. 6 month studies. ITT-LOCF data., Outcome 2 Cognitive function: SIB (change from baseline at 24-28 weeks).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Memantine, N</th>
<th>Mean (SD)</th>
<th>Placebo, N</th>
<th>Mean (SD)</th>
<th>Mean difference IV, fixed (95% CI)</th>
<th>Weight %</th>
<th>Mean difference IV, fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9605/Reisberg 2003</td>
<td>124</td>
<td>-4 (11.34)</td>
<td>123</td>
<td>-10.1 (13.5)</td>
<td></td>
<td>17.2%</td>
<td>6.10 (2.99 to 9.21)</td>
</tr>
<tr>
<td>MD-02/Tariot 2004</td>
<td>198</td>
<td>0.9 (9.42)</td>
<td>196</td>
<td>-2.5 (9.66)</td>
<td></td>
<td>46.6%</td>
<td>3.40 (1.52 to 5.28)</td>
</tr>
<tr>
<td>MD-01</td>
<td>170</td>
<td>-1.7 (11.34)</td>
<td>165</td>
<td>-2.6 (8.61)</td>
<td></td>
<td>100%</td>
<td>0.90 (1.25 to 3.05)</td>
</tr>
</tbody>
</table>

Total (95% CI) 492 484

Heterogeneity: $\chi^2 = 7.64$, df = 2 (p = 0.02); $I^2 = 74$

Test for overall effect: $Z = 4.51$ (p=0.00001)

Test for subgroup difference: not applicable

Figure 8: Effect of memantine at optimum dose on cognition

McShane et al. Cochrane Database Syst Rev 2006
**Memantine for dementia (Review)**

**Analysis 2.2.** Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer’s disease. Published, 6 month studies. ITT-LOCF data, Outcome 2 Cognitive function: ADAS-Cog (change from baseline at 24 weeks).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Memantine</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>N/Fixed:95% CI</td>
</tr>
<tr>
<td>99679(Lunebeck)</td>
<td>311</td>
<td>1.69 (7.23)</td>
<td>151</td>
<td>1.03 (6.64)</td>
<td>-</td>
</tr>
<tr>
<td>MD-10/Peskind 2004</td>
<td>195</td>
<td>0.8 (7.81)</td>
<td>198</td>
<td>-1.1 (7.87)</td>
<td>-</td>
</tr>
<tr>
<td>MD-12</td>
<td>212</td>
<td>-0.1 (6.55)</td>
<td>212</td>
<td>-0.8 (6.55)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>718</td>
<td></td>
<td>561</td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.013)
Test for subgroup differences: Not applicable
• No controlled data are available on the efficacy of memantine beyond 6 months

• Memantine is an option for managing moderate Alzheimer’s disease for people who cannot take cholinesterase inhibitors, and for managing severe Alzheimer’s disease. (NICE guidelines)
Drugs - Souvenaid

• medical food product

• includes precursors (uridine monophosphate; choline; phospholipids; eicosapentaenoic acid; docosahexaenoic acid) and cofactors (vitamins E, C, B12, and B6; folic acid; selenium) for the formation of neuronal membranes.
Drugs - Souvenaid

- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- Co-factors facilitate phospholipid synthesis by enhancing precursor bioavailability

Synapse formation requires nutritional precursors and cofactors
Plasma nutrient status of patients with Alzheimer’s disease: Systematic review and meta-analysis

% Cognitive Intact elderly

- DHA: 4 studies
- EPA: 4 studies
- Folate: 30 studies
- Vit B12: 37 studies
- Vit C: 8 studies
- Vit E: 19 studies

Effects of Souvenaid on plasma micronutrient levels and fatty acid profiles in mild and mild-to-moderate Alzheimer’s disease

The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer’s Disease: A Randomised Controlled Study

Mean normalised path length lambda in beta band

- Active
- Control

Time (weeks)
0 12 24
Drugs - Souvenaid

The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease

Shah et al. Alzheimer's Research & Therapy 2013, 5:59

A 24-week, double-masked clinical trial at 48 clinical centers, participants taking AD medications

no significant difference between study groups
Drugs - Souvenaid

The efficacy of supplementation with the novel medical food, Souvenaid, in patients with Alzheimer’s disease: A systematic review and meta-analysis of randomized clinical trials

Other cognitive interventions

- Cognitive stimulation therapy
- Cognitive training
- Cognitive rehabilitation
Cognitive stimulation therapy

- Psychological approach
- It stems from reality orientation and is usually group-based
- Social activity, reminiscence, and simple cognitive exercises
Cognitive stimulation therapy

Cognitive stimulation to improve cognitive functioning in people with dementia (Review)

Woods B, Aguirre E, Spector AE, Orrell M
Cochrane Database Syst Rev 2012

Mean difference of cognitive stimulation therapy vs control of 1.78 points on the MMSE

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hedges g (SE)</th>
<th>Experimental, N</th>
<th>Control, N</th>
<th>Weight %</th>
<th>Hedges g</th>
<th>IV, random (95% CI)</th>
<th>Hedges g</th>
<th>IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oror et al (2007)</td>
<td>0 (0.5)</td>
<td>8</td>
<td>8</td>
<td>2.4%</td>
<td>0.00</td>
<td>(-0.98 to 0.98)</td>
<td>0.00</td>
<td>(-0.98 to 0.98)</td>
</tr>
<tr>
<td>Chapman et al (2004)</td>
<td>0.006 (0.272)</td>
<td>25</td>
<td>28</td>
<td>6.5%</td>
<td>0.01</td>
<td>(-0.53 to 0.54)</td>
<td>0.01</td>
<td>(-0.53 to 0.54)</td>
</tr>
<tr>
<td>Tadaia et al (2007; AD)</td>
<td>0.039 (0.408)</td>
<td>12</td>
<td>17</td>
<td>3.4%</td>
<td>0.02</td>
<td>(-0.08 to 0.82)</td>
<td>0.02</td>
<td>(-0.08 to 0.82)</td>
</tr>
<tr>
<td>Lai et al (2004)</td>
<td>0.339 (0.248)</td>
<td>35</td>
<td>30</td>
<td>7.5%</td>
<td>0.04</td>
<td>(-0.35 to 0.63)</td>
<td>0.04</td>
<td>(-0.35 to 0.63)</td>
</tr>
<tr>
<td>Spector et al (2003)</td>
<td>0.336 (0.144)</td>
<td>115</td>
<td>86</td>
<td>14.2%</td>
<td>0.34</td>
<td>(0.05 to 0.62)</td>
<td>0.34</td>
<td>(0.05 to 0.62)</td>
</tr>
<tr>
<td>Order et al (2005)</td>
<td>0.41 (0.162)</td>
<td>79</td>
<td>79</td>
<td>12.7%</td>
<td>0.41</td>
<td>(0.09 to 0.73)</td>
<td>0.41</td>
<td>(0.09 to 0.73)</td>
</tr>
<tr>
<td>Wang et al (2007)</td>
<td>0.464 (0.201)</td>
<td>51</td>
<td>51</td>
<td>10.9%</td>
<td>0.46</td>
<td>(0.07 to 0.86)</td>
<td>0.46</td>
<td>(0.07 to 0.86)</td>
</tr>
<tr>
<td>Coen et al (2011)</td>
<td>0.557 (0.093)</td>
<td>15</td>
<td>13</td>
<td>3.7%</td>
<td>0.56</td>
<td>(-0.02 to 1.33)</td>
<td>0.56</td>
<td>(-0.02 to 1.33)</td>
</tr>
<tr>
<td>Bottino et al (2006)</td>
<td>0.587 (0.57)</td>
<td>6</td>
<td>7</td>
<td>1.9%</td>
<td>0.59</td>
<td>(-0.52 to 1.70)</td>
<td>0.59</td>
<td>(-0.52 to 1.70)</td>
</tr>
<tr>
<td>Tarraga et al (2006)</td>
<td>0.589 (0.391)</td>
<td>16</td>
<td>12</td>
<td>3.7%</td>
<td>0.59</td>
<td>(-0.18 to 1.35)</td>
<td>0.59</td>
<td>(-0.18 to 1.35)</td>
</tr>
<tr>
<td>Tadaia et al (2007; VD)</td>
<td>0.676 (0.343)</td>
<td>20</td>
<td>18</td>
<td>4.5%</td>
<td>0.68</td>
<td>(0.00 to 1.35)</td>
<td>0.68</td>
<td>(0.00 to 1.35)</td>
</tr>
<tr>
<td>Spector et al (2001)</td>
<td>0.688 (0.355)</td>
<td>71</td>
<td>71</td>
<td>4.3%</td>
<td>0.69</td>
<td>(-0.01 to 1.38)</td>
<td>0.69</td>
<td>(-0.01 to 1.38)</td>
</tr>
<tr>
<td>Breuil et al (1994)</td>
<td>0.716 (0.265)</td>
<td>32</td>
<td>29</td>
<td>6.9%</td>
<td>0.72</td>
<td>(0.20 to 1.24)</td>
<td>0.72</td>
<td>(0.20 to 1.24)</td>
</tr>
<tr>
<td>Baldelli et al (2002)</td>
<td>0.83 (0.284)</td>
<td>71</td>
<td>16</td>
<td>6.2%</td>
<td>0.83</td>
<td>(0.27 to 1.39)</td>
<td>0.83</td>
<td>(0.27 to 1.39)</td>
</tr>
<tr>
<td>Requena et al (2006)</td>
<td>0.884 (0.302)</td>
<td>20</td>
<td>30</td>
<td>5.6%</td>
<td>0.88</td>
<td>(0.29 to 1.48)</td>
<td>0.88</td>
<td>(0.29 to 1.48)</td>
</tr>
<tr>
<td>Halgit et al (2005)</td>
<td>1.252 (0.395)</td>
<td>15</td>
<td>16</td>
<td>3.5%</td>
<td>1.25</td>
<td>(0.48 to 2.03)</td>
<td>1.25</td>
<td>(0.48 to 2.03)</td>
</tr>
<tr>
<td>Baldelli et al (1993)</td>
<td>1.463 (0.477)</td>
<td>55</td>
<td>457</td>
<td>100%</td>
<td>1.46</td>
<td>(0.53 to 2.40)</td>
<td>1.46</td>
<td>(0.53 to 2.40)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>553</td>
<td>457</td>
<td></td>
<td>1.51</td>
<td>(0.35 to 0.66)</td>
<td>1.51</td>
<td>(0.35 to 0.66)</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; χ² = 21.31, df = 16 (p = 0.17); I² = 25%
Test for overall effect: Z = 6.33 (p = 0.00001)

Figure 9: Effect of cognitive stimulation therapy versus usual care on cognition
Cognitive stimulation therapy

- Cognitive stimulation therapy is cost-effective for people with mild-to-moderate dementia
- Few follow-up studies to clarify how long effects last
- Individualised cognitive stimulation therapy has not been found to be effective
Cognitive training

• strategies or exercises targeting specific cognitive domains
Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer’s or vascular type: a review

Bahar-Fuchset al Alzheimer’s Research & Therapy 2013

Abstract
Cognitive impairments, and particularly memory deficits, are a defining feature of the early stages of Alzheimer’s disease and vascular dementia. Interventions that target these cognitive deficits and the associated difficulties with activities of daily living are the subject of ever-growing interest. Cognitive training and cognitive rehabilitation are specific forms of non-pharmacological intervention to address cognitive and non-cognitive outcomes. The present review is an abridged version of a Cochrane Review and aims to systematically evaluate the evidence for these forms of intervention in people with mild Alzheimer’s disease or vascular dementia. Randomized controlled trials (RCTs), published in English, comparing cognitive rehabilitation or cognitive training interventions with control conditions and reporting relevant outcomes for the person with dementia or the family caregiver (or both), were considered for inclusion. Eleven RCTs reporting cognitive training interventions were included in the review. A large number of measures were used in the different studies, and meta-analysis could be conducted for several primary and secondary outcomes of interest. Several outcomes were not measured in any of the studies. Overall estimates of the treatment effect were calculated by using a fixed-effects model, and statistical heterogeneity was measured by using a standard chi-squared statistic. One RCT of cognitive rehabilitation was identified, allowing the examination of effect sizes, but no meta-analysis could be conducted. Cognitive training was not associated with positive or negative effects in relation to any of the reported outcomes. The overall quality of the trials was low to moderate. The single RCT of cognitive rehabilitation found promising results in relation to some patient and caregiver outcomes and was generally of high quality. The available evidence regarding cognitive training remains limited, and the quality of the evidence needs to improve. However, there is still no indication of any significant benefits from cognitive training. Trial reports indicate that some gains resulting from intervention may not be captured adequately by available standardized outcome measures. The results of the single RCT of cognitive rehabilitation show promise but are preliminary in nature. Further well-designed studies of cognitive training and cognitive rehabilitation are required to provide more definitive evidence. Researchers should describe and classify their interventions appropriately by using the available terminology.
Cognitive rehabilitation

- Aims to improve everyday function
- No evidences on cognitive decline
- Evidences on functional decline
Exercise intervention

THE HUMAN BRAIN
IF SEDENTARY FOR AN HOUR
Activity decreases as blood flow and oxygen intake are minimal in a seated position.
**Exercise intervention**

**REVIEW**

The effect of exercise interventions on cognitive outcome in Alzheimer’s disease: a systematic review

*Figure 1.* (Colour online) A forest plot of the meta-analysis of RCT studies that have measured global cognitive outcome. Exercise interventions were found to have a positive effect on global cognitive outcome.

Farina et al Int Psychogeriatr 2014; 26: 9–18
Exercise intervention

Exercise programs for people with dementia (Review)

Outcome: 1 Cognition

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Exercise</th>
<th>Usual care</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition: all trials</td>
<td>12</td>
<td>14.9 (2.2)</td>
<td>17</td>
<td>14.8 (1.3)</td>
<td>11.0 %</td>
</tr>
<tr>
<td>Christoflelli 2008</td>
<td>51</td>
<td>0.24 (0.78)</td>
<td>46</td>
<td>0.2 (0.63)</td>
<td>13.5 %</td>
</tr>
<tr>
<td>Eggermont 2009a</td>
<td>30</td>
<td>0.07 (0.37)</td>
<td>31</td>
<td>0.47 (0.97)</td>
<td>12.7 %</td>
</tr>
<tr>
<td>Eggermont 2009b</td>
<td>10</td>
<td>28.9 (11.36)</td>
<td>8</td>
<td>24 (14.68)</td>
<td>9.5 %</td>
</tr>
<tr>
<td>Hwang 2010</td>
<td>16</td>
<td>30.38 (7.66)</td>
<td>15</td>
<td>22.23 (8.37)</td>
<td>10.9 %</td>
</tr>
<tr>
<td>Kernoun 2010</td>
<td>15</td>
<td>15.33 (4.44)</td>
<td>9</td>
<td>11 (4.3)</td>
<td>10.0 %</td>
</tr>
<tr>
<td>Van de Winckel 2004</td>
<td>11</td>
<td>12 (2)</td>
<td>10</td>
<td>6 (2)</td>
<td>7.2 %</td>
</tr>
<tr>
<td>Venturelli 2011</td>
<td>50</td>
<td>0.14 (0.5)</td>
<td>38</td>
<td>0.38 (0.89)</td>
<td>13.3 %</td>
</tr>
<tr>
<td>Volkers 2012</td>
<td>20</td>
<td>23.9 (5)</td>
<td>19 (7.7)</td>
<td>11.8 %</td>
<td>0.74 [0.10, 1.38]</td>
</tr>
<tr>
<td>Vreugdenhil 2012</td>
<td>215</td>
<td>194</td>
<td>100.0 %</td>
<td>0.43 [-0.05, 0.92]</td>
<td></td>
</tr>
</tbody>
</table>
Outline

• Background
• Risk Factors/Secondary Prevention
• Timely detection
• Interventions
• *Take Home Messages*
Take Home Messages

• It is possible to slow the progression of cognitive decline at dementia stage
• Risk factors should be taken into account for secondary prevention
• Early diagnosis means early treatment
• Cholinesterase inhibitors have a clinically important effect on cognition and function at all Alzheimer’s disease severities but have side-effects.
• Memantine has a smaller effect on cognition in moderate- to-severe Alzheimer’s disease.
Take Home Messages

• Group cognitive stimulation therapy improves cognition in patients with mild-to-moderate dementia
• Engaging in exercise is helpful for a variety of reasons, including cardiovascular and cerebrovascular health, diabetes, obesity, strength, and protection against frailty.
• Exercise offers positive small effects on function for people with dementia, but whether it helps cognition is unclear.
Thank you for your attention

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INFOGRAPHIC
The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015, one every 3 seconds.

46.6 million people worldwide are living with dementia in 2015. This number will almost double every 20 years.

68% in 2050

Much of the increase will take place in low and middle income countries (LMICs). In 2015, 68% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to US$ 2 trillion by 2030.

If global dementia care were a country, it would be the 18th largest economy in the world exceeding the market values of companies such as Apple and Google.

Google $363 billion
Apple $742 billion

We must now involve more countries and regions in the global action on dementia.

This map shows the estimated number of people living with dementia in each world region in 2015.
Amyloid damages neurones and synapses...

Beta Amyloid particles increase oxidation of membranes

This greatly increases membrane turnover
MCI is not primarily a nutritional disorder - but age-related nutritional deficiencies occur.

Reduced plasma levels of folate, Vit B12, Vit C, Vit E

Increased homocysteine

Reduced CSF and brain levels of omega-3 (DHA/EPA)

Reduced mobilisation & synthesis of DHA

These deficiencies reduce capacity to replace membrane.
Preclinical studies from MIT: a strong effort

Addition of DHA, UMP and Choline increases membrane dependent structures, synapses and improves neurotransmission

Synergy of nutrients increases phospholipid production
- DHA, UMP, Choline

Increased membrane dependent structures
- dendritic spines
- neurite outgrowth
- pre and post-synaptic proteins

Improved neurotransmission
- Increased Ach synthesis & release
- Improved receptor function
Take Home Message

• Cognitive impairment (MCI, AD) is a result of multiple process failures, the most significant of which is synapse loss.

• Combined Nutrients (gave by specific and balanced medical nutrition product) support synapse formation and have been shown to improve memory in MCI and early stage of AD.

• This offers a nutritional approach to support patients with brain failure.
Panel 2: Cognitive stimulation therapy

The aim of cognitive stimulation therapy is to actively mentally stimulate participants through cognitive activities and reminiscence, multisensory stimulation, and group social contact. Each session is led by a facilitator. The standard cognitive stimulation therapy model is a group intervention of 14 themed sessions, each lasting approximately 45 min and held twice per week. This standard programme has been manualised and can be potentially administered by anyone working with people with dementia and held in care homes, hospitals, or day centres.

The programme includes:

- A non-cognitive warm-up activity (eg, soft ball game and song)
- Elements of reality orientation including a board displaying personal and orientation information

Sessions then focus on different themes, including childhood, food, current affairs, use of money, faces, scenes, and quizzes or word games.
The evidence from RCTs that exercise interventions improve cognitive and functional outcomes in patients with dementia is highly variable. A systematic review of four RCTs of exercise interventions in Alzheimer’s disease reported a significant overall SMD on cognitive outcomes compared with controls of 0·75 (95% CI 0·32–1·17). By contrast, a Cochrane review of nine studies with 409 participants did not find a significant difference and rated the quality of evidence as very low. The Finnish Alzheimer Disease Exercise Trial reported that a year-long programme improved executive function, measured with a clock drawing test (effect size in the home-based exercise group d=0·25, 95% CI 0·06 to 0·48 vs d=−0·10, −0·27 to 0·16 in the control group), but not verbal fluency, and there were no effects in other domains. However, in the Cochrane review, there was an overall significant benefit of exercise on activities of daily living (SMD=0·68, 95% CI 0·08 to 1·27) in six trials with 289 participants.
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hedges g (SE)</th>
<th>Experimental, N</th>
<th>Control, N</th>
<th>Weight %</th>
<th>Hedges g IV, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onor et al (2007)</td>
<td>0 (0.5)</td>
<td>8</td>
<td>8</td>
<td>2.4%</td>
<td>0.00 (-0.98 to 0.98)</td>
</tr>
<tr>
<td>Chapman et al (2004)</td>
<td>0.006 (0.272)</td>
<td>26</td>
<td>28</td>
<td>6.6%</td>
<td>0.01 (-0.53 to 0.54)</td>
</tr>
<tr>
<td>Tadaka et al (2007; AD)</td>
<td>0.019 (0.408)</td>
<td>12</td>
<td>12</td>
<td>3.4%</td>
<td>0.02 (-0.78 to 0.82)</td>
</tr>
<tr>
<td>Lai et al (2004)</td>
<td>0.139 (0.248)</td>
<td>36</td>
<td>30</td>
<td>7.6%</td>
<td>0.14 (-0.35 to 0.63)</td>
</tr>
<tr>
<td>Spector et al (2003)</td>
<td>0.336 (0.144)</td>
<td>115</td>
<td>86</td>
<td>14.2%</td>
<td>0.34 (0.05 to 0.62)</td>
</tr>
<tr>
<td>Onder et al (2005)</td>
<td>0.41 (0.162)</td>
<td>79</td>
<td>77</td>
<td>12.7%</td>
<td>0.41 (0.09 to 0.73)</td>
</tr>
<tr>
<td>Wang et al (2007)</td>
<td>0.464 (0.201)</td>
<td>51</td>
<td>51</td>
<td>10.0%</td>
<td>0.46 (0.07 to 0.86)</td>
</tr>
<tr>
<td>Coen et al (2011)</td>
<td>0.557 (0.393)</td>
<td>14</td>
<td>13</td>
<td>3.7%</td>
<td>0.56 (-0.21 to 1.33)</td>
</tr>
<tr>
<td>Bottino et al (2005)</td>
<td>0.587 (0.57)</td>
<td>6</td>
<td>7</td>
<td>1.9%</td>
<td>0.59 (-0.53 to 1.70)</td>
</tr>
<tr>
<td>Tarraga et al (2006)</td>
<td>0.589 (0.391)</td>
<td>16</td>
<td>12</td>
<td>3.7%</td>
<td>0.59 (-0.18 to 1.36)</td>
</tr>
<tr>
<td>Tadaka et al (2007; VD)</td>
<td>0.676 (0.343)</td>
<td>18</td>
<td>18</td>
<td>4.6%</td>
<td>0.68 (0.00 to 1.35)</td>
</tr>
<tr>
<td>Spector et al (2001)</td>
<td>0.688 (0.355)</td>
<td>21</td>
<td>14</td>
<td>4.3%</td>
<td>0.69 (-0.01 to 1.38)</td>
</tr>
<tr>
<td>Breuil et al (1994)</td>
<td>0.716 (0.265)</td>
<td>32</td>
<td>29</td>
<td>6.9%</td>
<td>0.72 (0.20 to 1.24)</td>
</tr>
<tr>
<td>Baldelli et al (2002)</td>
<td>0.83 (0.284)</td>
<td>71</td>
<td>16</td>
<td>6.2%</td>
<td>0.83 (0.27 to 1.39)</td>
</tr>
<tr>
<td>Requena et al (2006)</td>
<td>0.884 (0.302)</td>
<td>20</td>
<td>30</td>
<td>5.6%</td>
<td>0.88 (0.29 to 1.48)</td>
</tr>
<tr>
<td>Haight et al (2006)</td>
<td>1.252 (0.395)</td>
<td>15</td>
<td>16</td>
<td>3.6%</td>
<td>1.25 (0.48 to 2.03)</td>
</tr>
<tr>
<td>Baldelli et al (1993)</td>
<td>1.463 (0.477)</td>
<td>13</td>
<td>10</td>
<td>2.6%</td>
<td>1.46 (0.53 to 2.40)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.51 (0.35 to 0.66)</td>
<td>553</td>
<td>457</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; χ² = 21.31, df = 16 (p = 0.017); I² = 25%
Test for overall effect: Z = 6.23 (p < 0.00001)

**Figure 9**: Effect of cognitive stimulation therapy versus usual care on cognition
Reproduced from Huntley and colleagues, by permission of BMJ Publishing Group. Measured by MMSE.
Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer’s Disease: The Effect of Physical Exercise (ADEX Trial): Rationale and Design
Exercise intervention

The functional benefits are illustrated by the FINALEX trial,378 in which 210 home-dwelling patients with Alzheimer’s disease were randomly assigned to group or tailored exercise twice a week for 1 year or to usual treatment control. Although the study was unblinded, the tailored home-based exercise group declined less on the functional independence measure at 12 months (mean change –7·1, 95% CI –3·7 to –10·5) than controls (–14·4, –10·9 to –18·0). Overall, RCTs examining exercise interventions in dementia are few and limited by small sample sizes, lack of masking, inadequate comparator groups, variable form, frequency, duration, and intensity of exercise, and the use of multicomponent interventions masking the effect of an exercise component. It is possible that a dose-response association between exercise and cognition exists, and that high-intensity exercise gives more beneficial cognitive effects.379 It has been hypothesised that there is an intensity threshold beyond which cognitive benefits become more pronounced.380 Supporting this hypothesis, a subanalysis of the ADEX trial381 found that high-intensity training is required for cognitive improvement in patients with mild Alzheimer’s disease. Participants doing higher intensity exercise with more than 70% maximum heart rate (n=66) improved in the primary cognitive outcome versus control, whereas participants doing moderate intensity exercise had no significant improvement.382
Figure 10: Approaches to assessment and management of psychosis in dementia
Figure 11: Approaches to assessment and management of agitation in dementia

*For more on treatment of depression or psychosis see figures 10 and 14.
Technological innovations in dementia care
Panel 6 gives an overview of available and possible future uses of dementia-related devices. The huge advances in the development of health-care devices, including electronic health records, portal technologies, and wireless communications,656 are likely to have a key role in future dementia care. Given the progressive nature of dementia, certain devices might have a window of usefulness to people with dementia and their carers.657 Although somewhat overlapping, dementia health-care technologies can be divided into five general categories. (1) Technologies for diagnosis and assessment, such as computerised neuropsychological assessments and telemedicine to facilitate examinations, testing, and therapy in remote areas.658 (2) Monitoring, including sensors (motion, infrared, video, pressure, moisture, and vital sign measurement) to detect changes in the environment or health status of the person with dementia.656,658,659 (3) Assistive, including cognitive aids (eg, reminder systems for medication management), assistance for activities of daily living, and safety devices (eg, electrical outlet shutoff devices).656,658,659 (4) Therapeutic, including those that address communication, companionship, and activity.656,658 Despite interest in the animal-assisted interventions in long-term care settings, often using social assistive robots, very few well controlled studies have been done.660,661 (5) Carer supportive,658,659 including technology either to help carers with the care of the person with dementia or support their own wellbeing.658,662,663
Panel 6: Possible use for technological innovations in dementia care

Diagnosis and assessment
- Computerised diagnostic assessment: neuropsychological assessments and video-conferenced examinations
- Detecting progression: wearable sensors to detect changes in gait or activities of daily living
- Virtual reality: assessment of activities of daily living, such as meal preparation

Monitoring
- Environmental sensors: detection of changes in movement, such as falls; sensors to detect and intervene in the environment—eg, heat or gas, satellite tracking devices, or remote viewing camera
- Physiological sensors: devices measuring pulse, blood pressure, oxygen saturation, blood glucose, or sleep; or so-called smart garments with sensors that send biometric data

Assistive technology
- Cognitive aids: reminder systems—eg, medication management; activities of daily living prompting—eg, a tool that prompts user through handwashing; cognitive training

- Activities of daily living assistance: robots to help with eating, washing, and mobility
- Safety: electrical outlet shut-off devices, hands-free taps, and water temperature sensors
- Combination: robot to assist with care and monitor physiological or environmental changes and send information to carers

Therapeutic technology
- Communication: support reminiscence-based communication between people with dementia and their carers or chat groups
- Companionship: robotic animals
- Activity: technology to deliver music, messages, images, and video tailored to an individual’s interests

Carer-supportive technology
- Telemedicine: video-conferencing with professionals
- Online information: virtual assistance for managing challenges or web-based tools to support carer decision making
- Peer support: carer online or phone support groups
47 million people live with dementia worldwide
Growth in numbers of people with dementia (millions) in high income (HIC) and low and middle income countries (LMIC)

<table>
<thead>
<tr>
<th>Year</th>
<th>High Income</th>
<th>Low and Middle Income</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>27.28</td>
<td>19.50</td>
</tr>
<tr>
<td>2020</td>
<td>32.30</td>
<td>21.97</td>
</tr>
<tr>
<td>2025</td>
<td>38.72</td>
<td>24.73</td>
</tr>
<tr>
<td>2030</td>
<td>46.74</td>
<td>27.95</td>
</tr>
<tr>
<td>2035</td>
<td>56.16</td>
<td>31.72</td>
</tr>
<tr>
<td>2040</td>
<td>66.45</td>
<td>35.71</td>
</tr>
<tr>
<td>2045</td>
<td>77.63</td>
<td>39.14</td>
</tr>
<tr>
<td>2050</td>
<td>89.28</td>
<td>42.18</td>
</tr>
</tbody>
</table>
Estimated growth of costs of dementia

Figure 6.1
Forecasted global costs of dementia 2015-2030

Cognition

Drugs for cognition

The only approved drug treatments in many countries for cognitive symptoms of dementia are for Alzheimer’s disease, dementia with Lewy bodies, or Parkinson’s disease dementia. They target biochemical abnormalities as a consequence of neuronal loss, but do not modify the underlying neuropathology or its progression. Cholinesterase inhibitors might partly restore the deficit in acetylcholine arising from loss of neurons in the nucleus basalis of Meynert and in the central septal area, projecting to cortical regions. Memantine might attenuate the toxic effects of glutamate released from degenerating neurons, although its exact mechanism of action is uncertain. No drug has shown neuroprotective potential in humans. Few studies of anti-dementia drugs provide placebo-controlled data beyond 6 months. Anti-dementia drugs are not indicated in mild cognitive impairment because people with prodromal Alzheimer’s disease did not show clinically meaningful improvement or slowing of progression in trials of cholinesterase inhibitors, and systematic reviews of mild cognitive impairment trials suggest increased mortality risks.
Drugs - Cholinesterase inhibitors

Cholinesterase inhibitors for Alzheimer’s disease (Review)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cholinesterase inhibitor, n/N</th>
<th>Placebo, n/N</th>
<th>Odds ratio</th>
<th>Weight %</th>
<th>Odds ratio M–H, fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DON-302</td>
<td>37/149</td>
<td>17/152</td>
<td>5.9%</td>
<td>2.62</td>
<td>(1.40–4.91)</td>
</tr>
<tr>
<td>DON-304</td>
<td>60/241</td>
<td>36/257</td>
<td>12.1%</td>
<td>2.03</td>
<td>(1.29–3.22)</td>
</tr>
<tr>
<td>GAL-INT-1 Wilcock</td>
<td>36/206</td>
<td>33/203</td>
<td>12.7%</td>
<td>1.09</td>
<td>(0.65–1.83)</td>
</tr>
<tr>
<td>GAL-USA-1 Raskind</td>
<td>37/186</td>
<td>27/196</td>
<td>9.8%</td>
<td>1.55</td>
<td>(0.90–2.67)</td>
</tr>
<tr>
<td>RIV-B303</td>
<td>80/219</td>
<td>46/230</td>
<td>13.2%</td>
<td>2.30</td>
<td>(1.51–3.52)</td>
</tr>
<tr>
<td>RIV-B304</td>
<td>51/222</td>
<td>41/216</td>
<td>14.8%</td>
<td>1.27</td>
<td>(0.80–2.02)</td>
</tr>
<tr>
<td>RIV-B351</td>
<td>80/318</td>
<td>43/169</td>
<td>19.5%</td>
<td>0.98</td>
<td>(0.64–1.51)</td>
</tr>
<tr>
<td>RIV-B352</td>
<td>47/214</td>
<td>34/224</td>
<td>12.0%</td>
<td>1.57</td>
<td>(0.97–2.56)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1755</strong></td>
<td><strong>1647</strong></td>
<td><strong>100%</strong></td>
<td><strong>1.56</strong></td>
<td><strong>(1.32–1.85)</strong></td>
</tr>
</tbody>
</table>

Total events: 428 (cholinesterase inhibitor), 277 (placebo)
Heterogeneity: $\chi^2 = 14.17, df = 7, (p = 0.05); I^2 = 51$
Test for overall effect: $Z = 5.17 (p < 0.0001)$
Test for subgroup differences: not applicable

Figure 7: Effect of cholinesterase inhibitors at optimum dose on global assessment
Exercise intervention

Effects of aerobic exercise on cognition and hippocampal volume in Alzheimer’s disease: study protocol of a randomized controlled trial (The FIT-AD trial)

Fang Yu1, Ulf G Bronna1, Suma Koney2, Nathaniel W Nelson3, Maurice Dykens4, Clifford Jack Jr5, Jean F Wyman1, David Vock6 and Glenn Smith7

Yu et al. Trials 2014, 15:394

Abstract

Background: Alzheimer’s disease, a global public health issue, accounts for 60 to 80% of all dementias. Alzheimer’s disease primarily causes cognitive impairment and drugs have only modest short-term effects, highlighting a pressing need to develop effective interventions. Aerobic exercise holds promise for treating cognitive impairment in Alzheimer’s disease through biologically sound mechanisms. Nonetheless, aerobic exercise studies in Alzheimer’s disease are limited with mixed findings.

Methods/Design: This pilot randomized controlled trial will investigate the effects of a 6-month, individualized, moderate-intensity cycling intervention (20 to 50 minutes per session, 3 times a week) on cognition and hippocampal volume in community-dwelling older adults with mild-to-moderate Alzheimer’s disease. The specific aims are to: 1) determine the immediate effect of the cycling intervention on cognition in Alzheimer’s disease; 2) examine if the cycling intervention slows cognitive decline in Alzheimer’s disease from baseline to 12 months; and 3) assess the effect of aerobic exercise on hippocampal volume over 12 months. Ninety subjects will be randomized on a 2:1 allocation ratio to cycling or attention control (low-intensity stretching) and followed for another 6 months. Allocations will be concealed to all investigators and outcome assessors will be blinded to group assignments and previous data. Cognition will be measured by the Alzheimer’s disease Assessment Scale-Cognition at baseline before randomization and at 3, 6, 9, and 12 months. Hippocampal volume will be measured by magnetic resonance imaging at baseline and 6 and 12 months. The sample size of 90 will give 80% power to detect a 2.5-point difference in within-group changes in the Alzheimer’s disease Assessment Scale-Cognition at 6 months for the cycling group.

Discussion: Findings from this study will address the critical gap of exercise efficacy in Alzheimer’s disease and use of magnetic resonance imaging as an outcome measure in clinical trials. This study will provide a potential treatment that may increase physical function and quality of life and curb the prohibitive costs for the growing dementia population.

Trial registration: Primary registration: (NCT01954550; date of registration: 20 September 2013). Secondary registration: (NCT01954550; date of registration: 1 October 2013).

Keywords: Exercise, Alzheimer’s disease, Dementia, Physical activity, Cognition, Hippocampal volume, Imaging
Exercise intervention

Moderate-to-High Intensity Physical Exercise in Patients with Alzheimer’s Disease: A Randomized Controlled Trial

Conclusions: This is the first randomized controlled trial with supervised moderate-to-high intensity exercise in patients with mild AD. Exercise reduced neuropsychiatric symptoms in patients with mild AD, with possible additional benefits of preserved cognition in a subgroup of patients exercising with high attendance and intensity.

Exercise intervention

Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial

CONCLUSION: Regular, long-term, customized HE improved the executive function of community-dwelling older people with memory disorders, but the effects were mild and were not observed in other domains of cognition. J Am Geriatr Soc 64:731–738, 2016.