How to prevent cognitive decline: At normal cognitive ageing stage

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CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report

Except...
I’d rather not develop dementia (*potential for confirmation bias*)
I’m one of the 48% (*potential for pro-EU bias*)
Take home messages

A third of dementia may be preventable by addressing modifiable risk factors

Observational evidence is not translating into RCTs, but many difficulties

Treating hypertension, and encouraging physical activity may prevent cognitive decline and dementia
What is normal cognitive ageing?

What is normal cognitive ageing?

**A** Prevalence of Alzheimer disease and amyloid positivity

- **Prevalence of amyloid positivity in normal cognition**
- **Prevalence of AD-type dementia**

**B** Lifetime risk of Alzheimer disease and amyloid positivity by APOE genotype

- *Amyloid positivity in normal cognition*
- *Lifetime risk for AD-type dementia*

- **ε4ε4**
- **ε2ε4**
- **ε3ε4**
- **ε3ε3**
- **ε2ε3**
Preventing what?

Dementia

Cognitive decline

Improve cognition
Risk factors through the life course:

Modifiable and non-modifiable
Early and mid life: Added health and societal benefits?
Late life: Added health and societal benefits?
So, let’s modify them!

Halve prevalence if delay onset by five years

10% reduction in prevalence of modifiable risk factors, reduce global burden by 1 million

All fairly sensible with known benefits otherwise, and good observational evidence

A healthy lifestyle will keep dementia at bay | Daily Mail Online
www.dailymail.co.uk/health/article-4895426/Don-t-want-dementia-Turn-TV.html
20 hours ago - Astonishingly half of the dementia-free patients had the hallmark brain ... what they can do to prevent cognitive decline from the standpoint of ...

Orange a day cuts the risk of dementia by a quarter | Daily Mail Online
www.dailymail.co.uk/news/article-4676178/Orange-day-cuts-risk-dementia-quarter.html
7 Jul 2017 - Eating an orange a day could slash the risk of dementia, a major study ... campaigns to raise awareness of how to prevent the brain disorder, ...

Swedish study reveals benefits of a Nordic diet | Daily Mail Online
www.dailymail.co.uk/health/article.../Why-Viking-diet-best-way-brain-healthy.html
17 Jul 2017 - ‘Eating healthily helps us [prevent dementia], as all the antioxidants clear out the brain and give it the good nutrients to give it the mechanisms ...

NIH says staying fit in middle age slashes dementia risk | Daily Mail ...
www.dailymail.co.uk/health/article.../Don-t-want-dementia-Exercise-eat-healthy.html
8 Aug 2017 - This study supports the importance of controlling vascular risk factors like high blood pressure early in life in an effort to prevent dementia as ...

Extra-virgin olive oil prevents dementia and memory loss | Daily Mail ...
www.dailymail.co.uk/health/.../Extra-virgin-olive-oil-prevents-dementia-memory-loss.ht...
21 Jun 2017 - Extra-virgin olive oil prevents dementia by prompting the brain to clear ... Extra-virgin olive oil preserves memory and protects the brain from dementia, ...... pick up at the gym – and how to avoid deadly bacteria lingering on.

Going to university 'helps to prevent dementia' | Daily Mail Online
www.dailymail.co.uk/news/article.../Going-university-helps-prevent-dementia.html
21 Apr 2017 - Going to university or taking on leadership roles at work 'helps to prevent dementia'. Young people who stay in education or climb career ...

Encouraging elderly to play Wii could prevent dementia | Daily Mail ...
www.dailymail.co.uk/health/.../Encouraging-elderly-play-Wii-prevent-dementia.html
3 May 2017 - They recommend just a quarter of an hour a day, three times a week to ... elderly to play Wii and Xbox could prevent dementia, study reveals.
Treating hypertension does?

P- 3336 >80 yr olds with hypertension and no dementia
I- BP control with indapamide +/- perindopril to 150/80
0- 33 vs 38 per 1000 ptn/ys (HR 0·86, 95% CI 0·67–1·09);

HYVET-COG

Treating hypertension does?

HYVET-COG

Treating hypertension does?

But in meta-analysis HR 0.87 (0.76–1.00, p=0.045) with other hypertension trials with dementia as a secondary outcome

 Probably... 7 meta-analyses!

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log[Hazard ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, random, 95% CI</th>
<th>Hazard ratio IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst-Eur trial 1998 [3]</td>
<td>-0.713</td>
<td>0.364</td>
<td>2.0%</td>
<td>0.49 [0.24, 1.00]</td>
<td></td>
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<tr>
<td>BLSA 2005 [43]</td>
<td>-0.462</td>
<td>0.362</td>
<td>2.0%</td>
<td>0.63 [0.31, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Cache County Study 2006 [44]</td>
<td>-0.446</td>
<td>0.227</td>
<td>4.4%</td>
<td>0.64 [0.41, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Kungsholmen1999 [40]</td>
<td>-0.357</td>
<td>0.08</td>
<td>13.2%</td>
<td>0.70 [0.60, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Rotterdam 2001 [41]</td>
<td>-0.274</td>
<td>0.194</td>
<td>5.5%</td>
<td>0.76 [0.52, 1.11]</td>
<td></td>
</tr>
<tr>
<td>US Veteran 2010 § [46]</td>
<td>-0.269</td>
<td>0.051</td>
<td>15.9%</td>
<td>0.76 [0.69, 0.84]</td>
<td></td>
</tr>
<tr>
<td>SHEP 1991 [6]</td>
<td>-0.174</td>
<td>0.225</td>
<td>4.4%</td>
<td>0.84 [0.54, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Hyvet-Cog 2008 [7]</td>
<td>-0.116</td>
<td>0.13</td>
<td>9.0%</td>
<td>0.89 [0.69, 1.15]</td>
<td></td>
</tr>
<tr>
<td>CSHA 2002 [42]</td>
<td>-0.094</td>
<td>0.179</td>
<td>6.1%</td>
<td>0.91 [0.64, 1.29]</td>
<td></td>
</tr>
<tr>
<td>US Veteran 2010* [46]</td>
<td>-0.061</td>
<td>0.017</td>
<td>18.1%</td>
<td>0.94 [0.91, 0.97]</td>
<td></td>
</tr>
<tr>
<td>CHS 2009 [45]</td>
<td>0.0099</td>
<td>0.076</td>
<td>13.6%</td>
<td>1.01 [0.87, 1.17]</td>
<td></td>
</tr>
<tr>
<td>SCOPE 2003 [5]</td>
<td>0.08</td>
<td>0.186</td>
<td>5.8%</td>
<td>1.08 [0.75, 1.56]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)                     100.0%  0.84 [0.75, 0.93]  
Heterogeneity: Tau² = 0.02; Chi² = 36.43, df = 11 (P = 0.0001); I² = 70%
Test for overall effect: Z = 3.25 (P = 0.001)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison group</th>
<th>Placebo</th>
<th>CCBs</th>
<th>ACE inhibitors</th>
<th>β-blockers</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs</td>
<td>Placebo</td>
<td>0.60 ± 0.18 (P = 0.02)</td>
<td>0.57 ± 0.24 (P = 0.06)</td>
<td>0.47 ± 0.17 (P = 0.01)</td>
<td>0.67 ± 0.18 (P = 0.04)</td>
<td>0.54 ± 0.19 (P = 0.04)</td>
</tr>
<tr>
<td></td>
<td>CCBs</td>
<td>0.02 ± 0.19 (P = 0.91)</td>
<td>–</td>
<td>–</td>
<td>0.10 ± 0.17 (P = 0.58)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td>0.13 ± 0.17 (P = 0.49)</td>
<td>–</td>
<td>–</td>
<td>0.21 ± 0.15 (P = 0.23)</td>
<td>0.07 ± 0.17 (P = 0.70)</td>
</tr>
<tr>
<td></td>
<td>β-blockers</td>
<td>–</td>
<td>–</td>
<td>0.08 ± 0.13 (P = 0.59)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>0.06 ± 0.17 (P = 0.76)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Indirect comparisons exclusively.
All antihypertensives improved cognitive decline (effect size 0.05 only)

For preventing dementia:

RCTs and observational (n=14)

HR 0.91 (0.89-0.94)

ARBs > β blockers > diuretics > ACEi

But no effect in just RCTs (n=4)

But...Vascular health interventions didn’t work

**P-** 3526 70-79 yr olds with normal cognition

**I-** Nurse-led CV intervention

**O-** No significant change in 6 year incidence of dementia, 7% vs 7%

What drugs don’t work...

**Statins**
- 2 large RCTs (152)
- 26340 40-82 yrs
- Unable to do meta-analysis

**NSAIDs**
- ADAPT, 2117 >70, FHx of dementia
- Naproxen, celocoxib
- No diff to 7 year follow-up (2013)

MsGuiness 2016 Cochrane review
What drugs don’t work...

**Oestrogen HRT**
- WHIMS study
  - Poss in ‘healthy’ women, harm in ‘unhealthy’

**Ginko Biloba**
- GEM study, to 6.1 years
  - No difference in Dementia or cognition

**Folic acid + B12**
- Mild effect on memory only in 1 of 2 studies (n=3811, 2 yrs Tx)

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Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies

Sarah J Blondell, Rachel Hammersley-Mather and J Lennert Veerman

Received: 1 April 2014 | Accepted: 8 May 2014 | Published: 27 May 2014
Physical activity may protect

Dose dependent, neuroprotective effect of physical activity on cognitive performance
The more you do, the better the effect
47 studies, >100,000 people

BUT

6-12 months
A Mediterranean diet? That must work surely?

P - 447 healthy 67 yr old at high CV risk
I - Med diet + IL olive oil/week or 30g/day mixed nuts
0 - 4 yr, less cog decline in intervention
MCI incidence the same
No dementia incidence

PREDIMED

A Mediterranean diet? That must work surely?

Brain training probably doesn’t work

Good observational evidence
Study 157, improvements in cognitive domains trained, functional benefits to 10 years, but no effect on dementia incidence or cognitive decline
Need PICO
Brain training probably doesn’t work

Good observational evidence (again)
n=2,832,
10 sessions, boosters at 18 and 36 months
Followed up to 10 years
Improvements in cognitive domains trained, functional benefits to 10 years, but no effect on dementia incidence or cognitive decline

Multicomponent intervention in Finland?

- 600 69 yrs 4·7), education 10·0 years (SD 3·4), and mini mental state examination score 26·8 points (SD 2·0). mean x)

I- 4 lifestyle based strategies (300h/3yrs!)
- Diet
- Exercise
- Cognitive training
- Vascular risk factors

0- 2 yr, mean improvement in cognition effect size 0.13

Executive function, processing, NOT memory

Multicomponent intervention in Finland?

Attrition: Worse cognition, more ApoE ε4, more in control group...

Multicomponent intervention here in France?

- 1525 >70, ‘memory complaints’
- Omega 3 and/or multidomain intervention
- Physical activity
- Cognitive training
- Nutritional advice
- 2 yr, no difference in cognition
- Beneficial if high CV risk or pathology on imaging, possibly in intervention vs control

So where to go from here?

For who?
Healthy or ‘at risk’
Young, middle aged, or older

What?
Individual risk factors, or multicomponent
To improve cognition, halt decline, or prevent dementia

For how long?
Life course, or short
High or low intensity
Overall, ...currently limited evidence to support any preventive strategy.... However, studies to date *suggest* that a multifactorial intervention comprising regular exercise and healthy diet, along with the amelioration of vascular risk factors, psychosocial stress, and major depressive episodes *may be most promising* for the prevention of cognitive decline

Rakesh 2017

*We recommend* active treatment of hypertension in middle aged and older people without dementia to reduce dementia incidence. Interventions for other risk factors.......*might have the potential* to delay or prevent a third of dementia cases

Livingstone 2017

...mostly low-strength evidence that a wide variety of interventions had little to no benefit for preventing or delaying age-related cognitive decline, MCI, or CATD...

...Signals seem more promising for physical activity and vitamin B12 plus folic acid...

...Methodological problems in the available literature were widespread and should be addressed in future studies, including use of consistent cognitive outcome measures, longer follow ups, and recognizing that attrition is a major problem in longer studies. More work is needed...

Kane 2017

Take home messages

A third of dementia may be preventable by addressing modifiable risk factors

Observational evidence is not translating into RCTs, but many difficulties

Treating hypertension, and encouraging physical activity may prevent cognitive decline and dementia
Thank you

Dr Thomas Jackson
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t.jackson@bham.ac.uk
Improving social isolation..
(UK needs some of that!)

Again, good observational evidence
Only 2 pilot RCTS (172, 173)
Improved executive function
Book club didn’t (sadly)

Well older adults >50, 8 weeks, no Aes!


<table>
<thead>
<tr>
<th></th>
<th>Yoga</th>
<th>Control</th>
<th>ANCOVA</th>
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<tbody>
<tr>
<td></td>
<td>Pre n=61</td>
<td>Post n=58</td>
<td>Pre n=57</td>
</tr>
<tr>
<td>Task switching</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Single RT (ms)</td>
<td>724.01</td>
<td>714.97</td>
<td>730.29</td>
</tr>
<tr>
<td></td>
<td>=100.47</td>
<td>=121.53</td>
<td>=111.10</td>
</tr>
<tr>
<td>Single AC (%)</td>
<td>.94</td>
<td>.98</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>=.10</td>
<td>=.05</td>
<td>=.09</td>
</tr>
<tr>
<td>Mixed RT (ms)</td>
<td>1171.3</td>
<td>1084.52</td>
<td>1151.29</td>
</tr>
<tr>
<td></td>
<td>=176.88</td>
<td>=163.48</td>
<td>=182.78</td>
</tr>
<tr>
<td>Mixed AC (%)</td>
<td>.87</td>
<td>.94</td>
<td>.84</td>
</tr>
<tr>
<td></td>
<td>=.16</td>
<td>=.08</td>
<td>=.22</td>
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<tr>
<td>Repeat RT (ms)</td>
<td>998</td>
<td>941.48</td>
<td>1003.33</td>
</tr>
<tr>
<td></td>
<td>=169.35</td>
<td>=147.51</td>
<td>=191.02</td>
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<tr>
<td>Repeat AC (%)</td>
<td>.89</td>
<td>.95</td>
<td>.86</td>
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<tr>
<td></td>
<td>=.14</td>
<td>=.07</td>
<td>=.22</td>
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<tr>
<td>Running span</td>
<td></td>
<td></td>
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<tr>
<td>Partial recall</td>
<td>15.61</td>
<td>17.97</td>
<td>16.89</td>
</tr>
<tr>
<td></td>
<td>=6.86</td>
<td>=6.68</td>
<td>=5.85</td>
</tr>
<tr>
<td>Total recall score</td>
<td>29.48</td>
<td>31.64</td>
<td>29.3</td>
</tr>
<tr>
<td></td>
<td>=8.93</td>
<td>=8.71</td>
<td>=8.32</td>
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<tr>
<td></td>
<td>Relative risk for dementia (95% CI)</td>
<td>Prevalence</td>
<td>Communality</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td><strong>Early life (age &lt;18 years)</strong></td>
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</tr>
<tr>
<td>Less education (none or primary school only)</td>
<td>1.6 (1.26–2.01)</td>
<td>40.0%</td>
<td>64.6%</td>
</tr>
<tr>
<td><strong>Midlife (age 45–65 years)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>1.6 (1.16–2.24)</td>
<td>8.9%</td>
<td>57.3%</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.6 (1.34–1.92)</td>
<td>3.4%</td>
<td>60.4%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>1.9 (1.38–2.73)</td>
<td>31.7%</td>
<td>46.1%</td>
</tr>
<tr>
<td><strong>Later life (age &gt;65 years)</strong></td>
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<tr>
<td>Smoking</td>
<td>1.6 (1.15–2.20)</td>
<td>27.4%</td>
<td>51.1%</td>
</tr>
<tr>
<td>Depression</td>
<td>1.9 (1.55–2.33)</td>
<td>13.2%</td>
<td>58.6%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>1.4 (1.16–1.67)</td>
<td>17.7%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Social isolation</td>
<td>1.6 (1.32–1.85)</td>
<td>11.0%</td>
<td>45.9%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5 (1.33–1.79)</td>
<td>6.4%</td>
<td>70.3%</td>
</tr>
</tbody>
</table>