Can Alzheimer’s disease be prevented?

Henry Brodaty
Can we prevent dementia?

- The adult brain weighs about 1.3 kg
- Dementia shrinks it to 1/2 its usual size

Prevention can be....

- Elimination of disease or
- Postponement (delay)
- Targeted ie at people at risk
- Universal ie whole population

Elimination vs Postponement

- Disease elimination
  - eg smallpox vaccination
  - best prospect is AD vaccine
- Disease postponement: delay AD onset by..\(^1\)
  - 2 yrs, ↓ prevalence by 20%
  - 5 yrs, ↓ prevalence by 50%

\(^1\)Brookmeyer et al. (1998)
WHAT are we aiming to prevent: Dementia, AD, VaD, Mixed dementia?

- With ↑age, % of pure AD, VaD or LBD ↓
- 80%+ of older people with dementia had CVD at post mortem
- In older people, mixed dementia > common than AD

WHEN?

Life Course Approach: childhood

- Genetic determinants
- Environmental determinants
  - Foetal maldevelopment
  - Low birth weight for gestational age
  - Low education
  - Parental educat^n & occupat^n
  - Low socio-economic status
  - Dietary history
  - Loss of parent before 11yo

Reduced cognitive reserve

Whalley L et al, Lancet Neurology, 2006;5:87-96; Whalley L et al, IJGP, 28:75-81
Is early life the most important target?

- 70% of world dementia in developing countries
  - Low foetal birth weight
  - Poor or no education
  - Poor socio-economic environment
- 12.4% West Australia’s Kimberley Aboriginal people have dementia = 5.2x non-indigenous

Smith K et al, Neurology, 2008;71: 1470-1473

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Cardiovascular Factors

The human heart
Leonardo Da Vinci

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Your brain matters

- Look after your heart
- Be physically active
- Mentally challenge your brain
- Follow a healthy diet
- Enjoy social activity

yourbrainmatters.org.au
Blood Pressure (BP) and Dementia

- Mid-life hypertension associated with late-life dementia
- BP ↓ before dementia onset
- Hypertension Rx → risk ↓
- Each year of Rx → dementia risk ↓
- 60% ↓ risk of all dementia and AD
- 5 RCTs conflicting results
- Can harm if lower BP too much in older old

Statins to prevent AD

- Epidemiological studies → statins associated with lower rates of AD
- Probably any statin but not other Lipid Lowering Agents
- No benefit in larger studies or reviews
  - Heart Protection Study (N 20,536)
  - Meta-analysis; Cochrane review
- No benefit as treatment of AD

Dosage effect

As CVD risk factors accumulate, AD dementia risk increases

- If we count risk factors…
  - Hypertension
  - Smoking
  - Hypercholesterolemia
  - Obesity
  - Diabetes
  - Physical inactivity

Number of risk factors

Luchsinger et al 2005
Use it or lose it?
Activities & AD
– Physical
– Cognitive
– Leisure

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– Physical
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Physical activity = protective

- Several studies show physical activity protective against cognitive decline, dementia, Alzheimer’s, vascular dementia
- More is better – puffed, weights
- At least 3x per week; > 150 mins/wk
- Check with your doctor

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Physical activity

- Evidence from observational & control studies
- Physical activity benefits older adults to prevent dementia: Never too late to start
- Moderate intensity (brisk walking) 30 min 5d/wk
- No evidence for a specific exercise, but > 1
- > exercise may be better; aerobic + resistance?
- Combine with social and mental activity better?

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2 Lautenschlager et al. (2008). JAMA; 300(9):1027-1037.
3 Ravaglia et al. (2007). Neurology; 4
6 Middleton et al. Plos ONE 2008;3(9):e3124

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Can aerobic exercise protect against dementia?

- Preserve cognition and slow cognitive ↓
- Decreased incident dementia
- 8/11 RCTs in healthy older persons: cognitive & fitness improved
  - especially cognitive speed and attention
- Biomarkers ↑ e.g. brain volume
- Animal studies – growth factors↑, BDNF↑, neurogenesis↑, inflammation↓, AD path. ↓

Graff-Radford NR, Alzheimer's Research and Therapy 2011, 3:6

Walking 150'/wk for cognition


The power of physical activity

Erickson et al., 2011
Physical activity & change in hippocampal volume

- 18 month follow-up of 97 cognitively intact older adults
- Low risk = no APOE e4 allele
- High risk = APOE e4 allele

Smith JC et al. 2014 Frontiers in Aging Neuroscience
doi: 10.3389/fnagi.2014.00061

Mental activity less risk for dementia

- More leisure activities less dementia 5 yrs later
  - > 6/13 leisure activities over last month self-reported eg walking, reading, hobbies, visiting, restaurants, movies or sport 2.9 years later
  - 38% less risk of dementia (RR 0.62, 95%CI 0.46-0.83)

- More reported cognitive activity at baseline delayed the onset of memory decline 5 yrs later, independent of education

Scarmeas et al, Neurology 2001;57:2236-2242

Mental Activity & Dementia

- Meta-analysis of 22 studies, 29,000 individuals
- ↑ complex mental activity in late life = ↓ risk of dementia by half; OR = 0.54 (0.49-0.59)
- Dose - response relationship evident
- Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence
- Results held when covariates in source studies were controlled for

Cognitive interventions healthy older adults & people with MCI

- Systematic review articles 2007-2012
- Majority used memory as outcome measure
- Interventions healthy older adults
  - Metacognitive training, strategy videogame, perceptual discrimination training, computer based memory training.
- Interventions MCI
  - Computer based auditory processing training, training face-name associations, strategy training, memory strategies, cognitive rehab


Cognitive interventions healthy older adults & people with MCI

- 20 RCTs with healthy adults
  - Memory improvements in 17/20
- 6 RCTs with MCI
  - Memory improvements in 4/6
- Unclear whether these improvements generalise to everyday activities


Cognitive training

- Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly\(^1\)
  - 7 RCTs met inclusion criteria, low quality
  - Strong effect size for cognitive exercise intervention vs wait-and-see controls
  - Longer FU duration (>2yrs) ➔ ES no lower
- Review of cog. training or rehab in dementia\(^2\)
  - 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Bahar-Fuchs, Clare, Woods – Cochrane Database Syst Rev. 2013 Jun
Mind your diet
- Mediterranean diet
- Antioxidants

What is Mediterranean diet?
- Abundant plant foods
- Fresh fruit as typical daily dessert
- Olive oil as principal source of fat
- Dairy products (cheese and yogurt)
- Fish and poultry - low to moderate
- 0-4 eggs week
- Red meat - low amounts
- Wine - low to moderate amounts
- Total fat = 25% to 35% of calories
- Saturated fat ≤ 8% of calories

Foods rich in anti-oxidants
- Small red beans
- Blueberries
- Red kidney beans
- Pinto beans
- Cranberries
- Artichoke hearts
- Berries: - black
- Rasp- and Straw-
- Dried prunes
- Apples - Red delicious, Granny Smith, Gala
- Pecans
- Sweet cherries
- Black plum, plum
- Russet potato, cooked
- Black beans
Nutrition / Supplements

- Alcohol \( ? \) moderate
- Fish/Seafood/\( \omega3 \) \( ? \)
- Vitamin D \( ? \)
- Caffeine \( ? \)
- Vitamin E \( ? \)
- Vitamin C \( \times \)

Food sources better than supplements

B Vits reduce rate of brain atrophy

- ↓ homocysteine level
- ↓ brain atrophy rate by 30%
- Effects greater in people with high homocysteine level
- No effect if normal HCy
- Cognition better too

Folic acid 0.8mg/day
Vitamin B6 20mg/d
Vitamin B12 0.5mg/d
In people 70+ w. MCI

Smith AD et al, PLoS ONE, 2010

B Vitamins and atrophy

Over 2 years B-vitamin Rx slows grey matter atrophy in regions associated with AD (areas in blue)

Douaud et al. PNAS 2013;110:9523-9528
Systematic review - negative

- Ford AH\textsuperscript{1}, Almeida OP\textsuperscript{.}
- Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials.

Vitamin D and dementia

- Vit D deficient older adults have increased risk of dementia
- 1,658 65 yo+ in US Cardiovascular Health Study without dementia followed for $\approx$ 6y \textsuperscript{1}
- 171 $\rightarrow$ dementia; (including 102 with AD)
- Those with low vitamin D levels ($<50\text{nmol/L}$) almost 2x as likely to develop dementia & AD
- Assocn betw. Vit D level & cognition, AD risk\textsuperscript{2,3}

\textsuperscript{1}TJ Littlejohns Neurology, 2014
\textsuperscript{2}Balion C, Neurology, 2012; \textsuperscript{3}Annweiler C, Neurology, 2010.

Vitamin D

- Vit D receptors in brain, including hippocampus
- Vit D regulates neurotrophin expression and enhances the survival of brain cells
- Vit D can stimulate brain cells that may play a role in clearing amyloid beta plaques.
- $>50\%$ of Australians and $\leq95\%$ of people in residential aged care are Vit D deficient
- No evidence that taking Vit D improves cognition or reduces risk
Medications for prevention

- Anti-inflammatories – mixed epidemiological evidence
- Fish oil – some evidence (epidemiological)
- Circumin – some evidence (laboratory)
- Alcohol – moderate (epidemiological, not all studies)
  - Contradictory results: interaction with ApoE4

HRT for prevention

- Lab studies & epidemiology ➔ protective
- WHIMS – HRT doubles risk of AD/cog. decline
- Later studies of HRT indicate window of positive effects after menopause (>50 yo)
  - Significantly lower risk of mortality, heart failure, or myocardial infarction, without increase in risk of cancer, DVT or CVA (Schierbeck LL et al. BMJ 2012; 345 doi: http://dx.doi.org/10.1136/bmj.e6409)
- Women who had ovaries removed pre-menopause had better cognition if HRT Rx

Smoking and AD

- Current smoking
  - Increase risk for AD
- Previous smoking
  - Risk not significantly increased

Anstey K. Am J Epidemiol 2008
Alcohol

- Some evidence that moderate alcohol may be beneficial i.e. abstinent higher risk
- Not all studies confirm
- Interaction with genes? Abstinence may be beneficial in some – contradictory results
- Which alcohol – (red) wine?
  - Evidence not strong

Natural therapies

- Ginkgo biloba
- Turmeric, curcumin
- DHA, omega 3
- Fo-ti root
- Soy isoflavone
- Vitamin E, Selenium
- Folate, B6, B12
- Saffron
- Brahmi
- Huperzine A

Can Ginkgo biloba Prevent Dementia?¹

RCT double-blind, 7 years follow-up
1545 Ss on Ginkgo, 1524 on placebo

¹DeKosky et al, JAMA. 2008; 300(19):2253-2262
Attending to environmental factors

- Up to 50% of population attributable risk of AD cases from 7 environmental factors
- If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide

Barnes & Yaffe, 2011

How much AD can be attributed to environmental factors?

- 2% diabetes mellitus (type 2)
- 2% midlife obesity*
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity*
- 14% smoking
- 19% cognitive inactivity/education#

Barnes & Yaffe, 2011

Re-analysis Norton S et al, Lancet 2014

- Highest estimated PAR
  - Global: low education (19.1%, 95% CI 12.3–25.6)
  - USA: physical inactivity (21.0%, 95% CI 5.8–36.6)
    - Europe and UK similar (20.3%, 5.6–35.6)
  - Adjusting for association between risk factors, PAR 49% → 28.2% (95% CI 14.2–41.5) = 9.6/33.9m attributable cases (95% CI 4.8–14.1 million) global
- ≈30% for USA, Europe, UK
Re-analysis Norton S et al, Lancet 2014

- Assuming a causal relation and intervention at correct age for prevention, relative reductions of 10% per decade in the prevalence of each of the seven risk factors could reduce the prevalence of Alzheimer’s disease in 2050 by 8-3% worldwide
- After accounting for non-independence between risk factors, around 1/3 of AD worldwide may be attributable to potentially modifiable risk factors.

Is incidence of dementia/cognitive impairment declining?

Number of people with dementia ↓ ??

- UK: Cohorts 1: c 1990 & 2: c. 2010
  - Based on 1990 Cohort, estimated dementia prevalence in 2010 was 8.3%
  - Actual prevalence 6.5%
- Sweden: Cohorts 1: c 1990 & 2: c. 2005
  - Fewer new cases
- Denmark: Cohorts 1 born 1905 (assessed at 93y) and 2, born 1915 (assessed at 95 yrs)
  - 1915 performed better in cognitive measures

Giu et al. Neurology 2013;80:1888-1894
Implications of reduced prevalence

• Environmental factors
  – Better education?
  – Better attention to lifestyle factors?
    o Cardiovascular?
    o Diet?
    o Perinatal and early childhood?

Developmental & early life

<table>
<thead>
<tr>
<th>Direction of association</th>
<th>Consistency across studies</th>
<th>Evidence type</th>
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<tbody>
<tr>
<td>Nutrition</td>
<td>↓</td>
<td>Moderate</td>
</tr>
<tr>
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<td>↓</td>
<td>Moderate</td>
</tr>
<tr>
<td>Occupational status</td>
<td>↓ ➔</td>
<td>Low</td>
</tr>
<tr>
<td>Early life events</td>
<td>↓</td>
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Developmental & early life

• Nutrition: Indirect evidence for early life nutrition & development
• Education: Consistently protective, in large number cohort studies & across cultures
• Occupational status: Effects attenuated when controlling for education ↓ protective effect may not be causal
• Early life events: Suggestive evidence for death of parent (but few studies)

### Psychological factors - midlife

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</tr>
<tr>
<td>Anxiety</td>
<td>↑</td>
<td>n/a</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>↑</td>
<td>n/a</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>↑</td>
<td>High</td>
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</table>


- Depression: meta-regression indicates smaller effects for longer follow-up periods. Limited evidence for midlife exposure.
- Anxiety: One cohort study suggesting possible risk.
- Sleep disorders: Very few long-term cohort studies
- Psychological distress: Indirect evidence using personality type

### Psychological factors - late life

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Psychological factors – late life

• Depression: strong & consistent association across many studies; reverse causality?
• Anxiety: One case control, one cohort study, no association
• Sleep disorders: suggestive evidence from small number cohort studies. Short follow-up
• Psychological distress:


Lifestyle factors - midlife

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<tr>
<td>Smoking</td>
<td>↑</td>
<td>Low</td>
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<tr>
<td>Alcohol</td>
<td>➞</td>
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<tr>
<td>Nutrient deficiency</td>
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<tr>
<td>Physical activity</td>
<td>↓→</td>
<td>High</td>
<td>Insufficient</td>
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<tr>
<td>Cognitive stimulation</td>
<td>↓</td>
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Lifestyle factors

• Smoking: late life studies support hypothesis. Midlife exposure in cohort studies may underestimate the effect
• Alcohol & nutrition: few studies
• Physical: few long term cohort studies, mixed results
• Cognitive stimulation: supportive case control studies (possible bias). Only 1 long term study

### Lifestyle factors – late life

<table>
<thead>
<tr>
<th>Risk Factor</th>
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- Smoking: Dose effect for AD
  - possible effect for VaD & any dementia
- Alcohol: mod drinkers lower risk AD cf abstainers
  - Unclear if causal.
  - Safe limit of ‘moderate’ drinking unclear
- Nutrition: few RCTs, often poor quality
- Physical: difference in follow-up lengths contributes to contradictory results. Need RCTs to clarify
- Cognitive stimulation: Consistent risk reduction but..
  - …. lack RCTs to determine causality

### Cardiovascular risk factors – midlife

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<tr>
<td>Hypertension</td>
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<td>High</td>
<td>Robust</td>
</tr>
<tr>
<td>Obesity</td>
<td>➔⇐</td>
<td>Low</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>➔</td>
<td>Low</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Diabetes</td>
<td>➔</td>
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<td>Moderate</td>
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Cardiovascular risk factors - midlife

- Hypertension: consistent evidence
  - Stronger for any dementia & VaD than AD
- Obesity: inconsistent for midlife BMI
- Cholesterol: inconsistent. Main support from 2 long-term Finnish studies
- Diabetes: evidence indirect from linkage studies
  Only one long-term cohort study (no association)

Cardiovascular risk factors – late life

<table>
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Cardiovascular risk factors – late life

- Hypertension: decline in BP predicts AD but unlikely to be causal. RCTs suggest no cog benefit/harm to treating hypertension
- Obesity: Several studies, no association.
  - Decline in BMI from mid life predicts dementia but unlikely to be causal
- Cholesterol: no effect of statins on cognition
- Diabetes: consistent evidence for diabetes & incident dementia, AD & VaD. Strong for VaD
Intervention trials
- lifestyle
- pharmacological

FINGER Trial

- 1,260 60-77 yo at risk for cognitive impairment and Alzheimer’s
- Intervention: physical activity, nutritional guidance, cognitive training, social activities and management of heart health risk factors
- Outcomes: improved cognitive performance: overall and in separate measures of executive function (eg planning abilities)

Kivipelto M, AAIC, 2014

Multidomain Alzheimer Prevention Trial (MAPT) frail elderly persons aged ≥ 70 years

<table>
<thead>
<tr>
<th>Experimental 1: Omega-3</th>
<th>Dietary Supplement: omega-3</th>
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<tr>
<td>Experimental 2: Omega-3 + multi-domain intervention</td>
<td>Dietary Supplement: omega-3 Behavioural: multi-domain intervention (Nutrition, physical exercise, cognitive training &amp; social activities; + preventive consultations)</td>
</tr>
<tr>
<td>Placebo Comparator: Placebo group</td>
<td>Drug: Placebo OMEGA-3 placebo</td>
</tr>
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HATICE = Healthy Aging Through Internet Counselling in the Elderly

- Diabetes mellitus, hypertension, obesity, hypercholesterolemia, smoking and physical inactivity are common and increase risk of myocardial infarction, stroke and dementia.
- Develop and evaluate innovative intervention strategy to improve pharmacological and non-pharmacological treatment for cardiovascular disease in elderly patients

1. Data from 3 large ongoing clinical trials on multi-component vascular interventions in elderly → efficacy and feasibility of various treatment regimens
2. Innovative, interactive internet platform for self-management of vascular diseases with interactive support by practice nurses and patient’s own physician
3. RCT, 5400 elderly with multiple cardiovascular diseases

- Primary outcome - optimisation of management of cardiovascular diseases
- Secondary outcomes
  - new cardiovascular events
  - handicap
  - cognition and survival
The A4 trial

- Clinically normal, Aβ positive
- Solanezumab; N = 1000, 70yrs+
- Cognitive tests over three years
- Imaging tests will track structural and functional brain changes
- Outcomes: provide important information about the effectiveness of clearing amyloid from the brain in the early stages of the disease and inform future prevention studies

Principal investigator: Reisa Sperling, M.D., Harvard Medical School, Boston.

Dominantly Inherited Alzheimer Network (DIAN-TU)

- Aimed at AD caused by gene mutation
- Sample: adult children of people with a mutated gene known to cause AD
  - May or may not carry gene themselves
- gantenerumab & solanezumab
- Testing: Clinical interviews, Mental status testing, Brain scans (MRI, PET), Blood assays (genetic, CSF)

http://www.dian-info.org/default.htm

Alzheimer's prevention initiative

- Treatment trials, biomarker studies & registries
- One trial (NCT01998841): Using Crenezumab (vs placebo) for those at risk of early onset AD (genetic mutation)
  - Large extended family in Colombia who share rare genetic mutation (PSEN1 E280A)
  - Likely to develop dementia around 45 yrs

**TOMM40 pioglitazone**

- Clinical trial: NCT01931566 (ongoing)
  - Trial of biomarker risk algorithm for MCI-AD
  - Evaluate pioglitazone (vs placebo) to delay MCI-AD in cognitively healthy participants at high risk for developing MCI within 5 years
- Outcomes: time to MCI Dx by treatment

**ADAPT follow-up study**

- Evaluate efficacy of naproxen & celecoxib for prevention of AD (n = 1537)
- Cumulative incidence of AD did not differ by treatment group


**Computer cognitive training with mild electrical stimulation**

Dr Adith Mohan
Dr Donel Martin

9382 9261
adith.mohan@unsw.edu.au
Can AD be prevented?
May be delayed....

- Look after your heart
- Be physically active
- Mentally challenge your brain
- Follow a healthy diet
- Enjoy social activity

yourbrainmatters.org.au

Thank you

www_cheba_unsw_edu_au
www_dementiaresearch_org_au