Prevention of dementia

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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
- Posptonement (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%

¹Brookmeyer et al. (1998)
Iceberg Phenomenon

- 5-10 yrs
- 25 yrs
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 PM \(^1\)
- In OP, mixed dementia > common than AD

\(^1\) MRC CFAS Study (2003)
For prevention need to understand risk and protective factors
Risk factors

Genetic risk factors
- High education
- Rich social network
- Mental activities
- Physical activities

SES-related factors
- Life habits (eg, smoking)
- Vascular risk factors
- Vascular diseases
- Depression
- Head trauma
- HRT(?)

Occupational exposure
- Antihypertensive drugs
- Diet: fish, vegetables
- Moderate alcohol
- Antihypertensive drugs, statins, NSAID, HRT(?)

Protective factors

Years
Life Course Approach

- Foetal maldevelopment
- Low birthweight for gestational age
- Low educational attainment
- Occupation
- Low socio-economic status
- Dietary history

Whalley L et al, Lancet Neurology, 2006;5:87-96
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
Strong risk factors for AD

- Age
- Family history
- Familial AD

- Down’s syndrome
- ApoE4
Less Strong Evidence

Risk factors
- Cardiovascular factors – hi BP, AF, high cholesterol
- Other genetic factors
- Diabetes
- Obesity, inactivity

Protectors
- Education
- Medications?
- Diet/Supplements?
- Lifestyle
  - Physical exercise
  - Diet
  - Alcohol?
Cardiovascular Factors

- High blood pressure
- High cholesterol
- High homocysteine

The human heart, Leonardo Da Vinci
Blood Pressure (BP) and Dementia

• Mid-life hypertension associated with dementia in late-life ¹, ², ³, ⁴, but not ⁵
• BP ↓ before dementia onset ¹

¹Skoog et al (Lancet 1996;347:1141-45)
²Notkola et al (Neuroepidem, 1998;17:14-20)
³Launer et al (Neurol Aging 2002;21:49-55)
⁴Kivipelto et al (BMJ 2001;322:1447-51)
⁵Morris et al (Arch Neurol 2001;58:1640-6)
Treatment for hypertension

- Hypertension Rx → risk ↓\textsuperscript{1,2,3,4}
- Each extra year of treatment → reduction in risk of dementia\textsuperscript{5}
- 60% ↓ risk of all dementia and AD
- 5 RCTs\textsuperscript{6} conflicting results; some benefit of antihypertensives for dementia prevention
- Can harm if lower BP too much in older old \textsuperscript{7}

As CVD risk factors accumulate, AD dementia risk increases

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

Luchsinger et al 2005

Number of risk factors

Slide adapted from Michael Valenzuela
Statins to prevent AD

- Epidemiological studies → statins associated with lower rates of AD \(^1\)\(^-\)\(^3\)
- Probably any statin but not other Lipid Lowering Agents \(^2\),\(^3\),\(^4\) \(\sqrt{\,}\); \(^1\) \(\times\)
- No benefit in larger studies or reviews
  - *Heart Protection Study (N 20,536)*\(^5\)
  - *Meta-analysis*\(^6\); *Cochrane review* \(^7\)
- No benefit as treatment of AD \(^8\)

1. Rockwood et al, 2002 (Canadian Health & Aging)
Natural History: Blood Pressure, Cholesterol & AD

- ApoE ε4, high midlife total cholesterol and midlife BP are independent AD risk factors\(^1\)
- BP & cholesterol of AD pts no higher than controls
- Cholesterol levels gradually ↓ with age\(^2\)
- More rapid ↓ in those who develop dementia
  - Up to 15 yrs prior to diagnosis\(^3\)
  - Indicator for early preclinical stage?\(^3\)

\(^1\)Kivipelto et al, *Neurology* 2001;56:1683-1689
\(^2\)Kivipelto et al, *CNS Drugs* 2002; 16(7):435-44
Homocysteine, B$_{12}$, Folate & AD

- ↑ blood serum homocysteine = cardiovascular risk factor
- Associated with ↑ risk for AD (VaD)$^{3-5}$
- Homocysteine can be treated with Vit B$_{12}$, B$_6$ and folic acid (folate)$^{1,2}$
- No evidence (?)yet) that reducing homocysteine changes risk of AD

VITACOG trial: homocysteine & MCI

- N = 271, 70+, MCI, time = 24 months
- RCT, double blind; B vitamins vs. placebo
- Outcome: rate of brain atrophy (MRI)
- Results: ≈ 30% less atrophy in Rx vs placebo (0.7% pa vs 1.0% p.a.)
  - Effect was greatest for those with highest baseline homocysteine
  - No benefit for those with lowest homocyst\textsuperscript{n}
  - No adverse effects reported

Medications

- HRT
- NSAIDs
- Ginkgo biloba
- Medicinal plants
- Anti-AD drugs
HRT & AD: Mixed Evidence

- Lab studies & epidemiology, HRT $\rightarrow$ protective
- Two prospective studies indicated benefit $^{1,2}$
- ..... but UK GP research base no benefit $^{3}$ ...
- ..... WHI found increased risk of dementia $^{4}$
- Cache County study $^{5}$ concluded that
  - prior HRT (for $\geq$ 10 yrs) was associated with $\downarrow$ risk of AD but not current use
- ?critical period post-menopausal $^{6}$
  - HRT in < 65yrs may $\rightarrow$ cognitive benefit$^{7}$ $^{8}$
- KEEPS – HRT protective/beneficial cardiovascular; no effect on memory$^{9}$

NSAIDs & AD

• Epidemiological studies → longer and higher dose use of NSAIDs (eg Voltaren, Naproxen, Indocid) associated with less AD ¹-⁴

• RCTs do not confirm preventative or treatment effects

• NSAIDs can cause significant side effects

¹Stewart et al Neurology 1997;48(3):626-32;
³Broe et al Arch Neurol 2000;57:1586-91;
⁴In’t Veld et al, NE J Med 2001;345:1515-21
⁵ADAPT Research Group Neurology 2007;68:1800-08
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
GuidAge trial

Over 5 years
Conversion to AD

No effect on stroke incidence

Medicinal plants & dementia

- Evidence for cognitive improvement <=> pharmacologic treatments
- Medicinal plants for BPSD appear more promising eg Lemon balm, lavender oil
- Prevention – not adequately tested
  – Brahmi, curcumin, coconut oil

Drugs to prevent AD

- Move to earlier and even pre-symptomatic diagnosis
- Biomarkers – CSF, PET-PiB
- Potential to treat people at risk
  - Immunotherapy
  - secretase inhibitors
Nutrition / Supplements

- Alcohol
- Fish/Seafood
- Caffeine
- Vitamin E
- Vitamin C
- Fats
Alcohol & Dementia

• Many negative studies (mainly X-sectional)

• **Longitudinal studies**
  – Wine consumption ↓ dementia risk$^1$
  – Light-to-moderate alcohol (1-3 drinks/day) ↓ risk of dementia (HR = 0.58)$^2$
  – Monthly & weekly wine intake ↓ risk of dementia (OR = 0.43, 0.33)$^3$
  – XS alcohol in midlife → 3 fold ↑ in risk$^4$

$^1$Orgogozo et al, 1997 (PAQUID),
$^2$Ruitenbergen et al, 2002 (Rotterdam study),
$^3$Truelsen et al, 2002 (Copenhagen study),
Fish/Seafood & AD: PAQUID$^1$

- N = 1674 aged 68+, 7 yr f/u
- 170 developed dementia (135 AD)
- Fish & seafood consumption ↑ in higher educated
- Controlling for education, age, sex: eating fish/seafood ≥ 1 X week
  OR (dementia)= 0.73, 95% CI 0.52-1.03
  OR (AD) = 0.69, 95% CI 0.47-1.01

$^1$Barberger-Gateau et al *BMJ* 2002;325:932-3
Omega 3 fatty acids

- No RCT with incident dementia as the outcome
- Evidence from 3 RCTs on cognitive function
  - N = 3536 (3 studies); 6, 24 & 40 months
  - No benefit for cognitive function
- Various tests (MMSE, memory, executive function)

Fruit & vegetables

• 9 Cohort studies, N = 44,004
• Follow-up = 6months +
• Increased vegetable intake associated with lower dementia risk & slower cognitive decline
• Evidence for fruit intake lacking

Folate & B vitamins

- Homocysteine – 4/5 cohort studies reported relationship with incident dementia/AD
- Fish & fatty acids – 6/8 cohort studies found no reduction in incident dementia/AD based on fish or fatty acids intake
  - No evidence in RCT for fatty acid supplements
- Insufficient evidence to draw conclusions about dietary factors & AD/dementia
  - Need larger RCTs

Diet and cognition

• Some evidence for protection against cognitive decline
  – Fruits and vegetables – limited evidence, but suggests protective effect
  – Mediterranean diet – evidence for slower cognitive decline, reduced risk of progression from MCI to AD, reduced AD risk

• Based on current evidence there are no definitive dietary recommendations for preventing dementia

Mixed results from X-sectional & observational studies
Depends on measures used
– MMSE not assoc with Vit D
– Better exec function assoc$^d$ with higher Vit D

• 7 yr longitudinal study: higher Vit D intake protective against AD (control for sun)

• Barnard & Colon-Emeric. Amer J Ger Pharmacotherapy. doi:10.1016/j.amjopharm.2010.02.004
Vitamin E

- Early epidemiological studies demonstrated benefit from high dietary Vit E but mixed evidence for taking supplements
- Later studies have not shown benefit
- One meta-analysis found slightly but significantly *higher* mortality rates in heart patients on Vitamin E
Does Fat Matter?
Do Calories or Fats Matter?

• Fats - mixed evidence
  – Fats may be harmful or even beneficial
• Calories appear to be harmful
  – Obesity linked to AD (independent of risk of diabetes)
• Midlife (not late life) obesity is risk factor
• Loss of weight linked to AD but only within 3 years of diagnosis ... maybe not eating well

Engelhart et al *Neurology* 2002;59:1915-1921
Luchsinger et al *Arch Neurol* 2002;59:1258-63
Gustafson et al *Arch Intern Med* 2003;163:1524-1528
Nourhashemi et al *Neurology* 2003;60:117-119
Summary of evidence for protection

Suggestive √, Possible?
- Fish/ fish oil?
- Mediterranean diet?
- Vegetables?
- Alcohol??
- Flavenoids?
- Vitamin D?
- Tea?

Evidence against x
- Omega 3 supplement x
- Fruit x
- Ginkgo x

Evidence for harm
- Polyunsaturated fat x
- Mono ?
Use it or lose it?

Activities & AD
- Leisure
- Cognitive
- Physical
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

  $\rightarrow$ 38% less risk of dementia (RR 0.62, 95%CI 0.46-.83)

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

References:

2. Scarmeas et al, Neurology 2001;57:2236-2242
Late life leisure activities

- Chinese sample, 2.4yrs f/up; N = 1463, 65yrs+
- High level **mental** activity related to less decline
  - Global cognition \( (\beta = -0.23, p < .01) \)
  - Language \( (\beta = -0.11, p < .05) \)
  - Executive function \( (\beta = -0.13, p < .05) \)
- Hi level **physical** activity related to less decline
  - Episodic memory \( (\beta = -0.08, p < .05) \)
  - Language \( (\beta = -0.15, p < .01) \)

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) \(^1\)
- Dose - response relationship evident\(^1\)
- Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence\(^1\)
- Results held when covariates in source studies were controlled for\(^2\)

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 rehabilitation

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

Physical activity = protective

- Literature review\(^1\): trend for ↓ risk
- Lautenschlager: 24 wk RCT\(^2\) less cognitive ↓
- Ravaglia et al (only for VaD) \(^3\)
- Larson et al\(^4\): physical activity ≥ 3 times/wk
- Canadian Study of Health and Aging
  - 50% ↓ for AD\(^5\)
  - Effect more pronounced for those with worse baseline cognition\(^6\)

Causality? Reverse causality?

Do leisure, mental or physical activity lower risk of dementia?

Or

Are those with better cognitive function and lower risk of dementia more likely to participate?
Physical activity

• Evidence from observational & control studies

• Conclusions
  – Physical activity is beneficial for older adults in prevention of dementia
    • Never too late to start
  – moderate intensity (brisk walking) 30 min 5 days/wk
  – No evidence for a specific exercise, but > 1
  – More exercise may be better; aerobic + resistance?
  – Combine with social and mental activity better?

Fitness

- Association betw. objectively measured midlife cardiorespiratory fitness and all-cause dementia in advanced age over 25 yrs (19-30yrs)
- 125 700 person-years of Medicare follow-up
- Highest quintile 36% ↓ hazard of all-cause dementia vs those in the lowest quintile (HR = 0.64 [95% CI, 0.54-0.77])

Fitness

- 150 mins per week of moderate intensity could improve fitness by 1 to 2 maximal Mets.
- But in active population may need $\geq 5$ hrs/week.
- US trends in physical activity are poor: $< 10\%$ of population achieves 150 minutes/wk (measured).
- Self-reported estimates of physical activity exceed the objective measures 6-fold.

Other Risk Factors

- Smoking
  - Current smoking if ApoE ε4 –ve
- Diabetes – type 2
  - 30-90% higher risk of AD
  - ↑ incidence of 'any dementia' (including AD and VaD) in Ss with DM in 7/10 studies
- Depression – Prodrome vs causal
- Head injury with loss of consciousness
- Aluminium x

Summary – Risk, ?, Protect

- Age
- Family history
- ApoE ε4
- Down’s syndrome
- Midlife ↑BP
- Midlife ↑cholesterol
- Homocysteine ↑
- Depression
- Diabetes (DM2)
- Head injury
- Fats
- FH of Downs
- Statins
- HRT
- NSAIDS
- B12 & folate
- Ginkgo biloba
- Education
- Leisure activity
- Cognitive activity
- Physical activity
- Alcohol
- Seafood
- Caffeine, tea
Implementation of lifestyle changes
How to implement?

- Public campaigns
- Telephone reminders
- Use of apps
- Internet based programs
- Primary care driven
- Initiation vs sustainability
- Financial incentives eg health insurance
Being brain healthy is important for everyone - at any age, whether you’re young, old or in between. To live a brain healthy life, you need to look after your brain, your body AND your heart. They are all important.

These are the three key areas of Alzheimer’s Australia’s Your Brain Matters program to help you live a brain healthy life:

- Keep your brain challenged and be socially active
- Be fit and healthy by eating healthily and participating in regular physical activity
- What’s good for the heart is good for the brain. Manage your blood pressure, cholesterol, blood sugar, body weight and avoid smoking

Following the Your Brain Matters program is particularly important once you reach middle age, as this is when changes in the brain might start to occur. These changes can lead to memory and thinking problems.
How to implement?

- Telephone delivered interventions for physical activity & diet change
  - 20/27 comparisons (25 studies) showed evidence for behaviour change
  - 10 studies with follow-up
    - 3 showed maintenance for at least 50% outcomes
- Limited evidence on if/how these interventions can be implemented in ‘real-world settings’

Conclusion

• Cannot prevent dementia but can we wait?¹
• May be able to delay onset of dementia
• Lifestyle changes - we all can/should make
  – Multiple benefits, minimal adverse effects
• Challenge is implementation
  – Population
  – Primary care
  – Health care professionals lead the way

NIH State of Science on Prevention of AD and Cognitive Decline 2010
Thank you

• [www.dementiaresearch.org.au](http://www.dementiaresearch.org.au)
• [www.cheba.unsw.edu.au](http://www.cheba.unsw.edu.au)
• [http://yourbrainmatters.org.au](http://yourbrainmatters.org.au)

Jeanne Calment 1875-1997