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, \(\downarrow\) prevalence by >20%
  - 5 yrs, \(\downarrow\) prevalence by 50%

\(^1\)Brookmeyer et al. (1998)

Iceberg Phenomenon

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

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

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

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

Treatment for hypertension

- Hypertension Rx → risk ↓ 1,2,3,4
- Each extra year of treatment → > reduction in risk of dementia5
- 60% ↓ risk of all dementia and AD
- 5 RCTs6 conflicting results; some benefit of antihypertensives for dementia prevention
- Can harm if lower BP too much in older old 7

Dosage effect

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

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 \: 1 x
- 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)
2 Wolozin et al, 2000, 3 Jick et al, 2000, 4 Haag MDM et al, JNNP. 2009

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<sub>12</sub>, Folate & AD**

- ↑ blood serum homocysteine = cardiovascular risk factor
- Associated with ↑ risk for AD (VaD)<sup>3-5</sup>
- Homocysteine can be treated with Vit B<sub>12</sub>, B<sub>6</sub> and folic acid (folate)<sup>1,2</sup>
- No evidence (?) yet that reducing homocysteine changes risk of AD

<sup>1</sup>Wang et al, 2001; <sup>2</sup>Luchsinger JA. 2007. Archives of Neurology; 64: 86-92;
<sup>3</sup>McCaddon et al, 1998; <sup>4</sup>Clarke et al, 1998; <sup>5</sup>Lehman et al, 1999;

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**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 homocysteine
  - No adverse effects reported


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**Medications**

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

- Lab studies & epidemiology, HRT → 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 ≥ 10 yrs) was associated with ↓ risk of AD but not current use
- ?Critical period post-menopausal 6
  - HRT in < 65yrs may → 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


Can Ginkgo biloba Prevent Dementia?1

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

1. DeKosky et al, JAMA. 2008; 300(19):2253-2262
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, circumin, 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\(^4\)


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 = 6 months +
- 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


Vit D

Mixed results from X-sectional & observational studies
Depends on measures used
  - MMSE not assoc with Vit D
  - Better exec function assoc 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.amjpharm.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
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;59:1256-63
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 0.46-0.83)
- More reported cognitive activity at baseline delayed the onset of memory decline 5 yrs later, independent of education

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 ≥ 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 –ve¹
• Diabetes – type 2
  – 30-90% higher risk of AD¹-⁵
  – ↑ incidence of 'any dementia' (including AD and VaD) in Ss with DM in 7/10 studies⁶
• Depression – Prodrome vs causal ⁷
• 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
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