Lifestyle factors to prevent dementia
Henry Brodaty

Changing demographics: Australia

ABS: Population by Age and Sex, Australian States and Territories Jun 2010.
ABS: Population projections, Australia, 2006 to 2101.
Patterns of disease over last 100 years

Death rates Australia (1907-2003): Circulatory diseases

Patterns of disease: 85+yr olds

Death rates Australia (1968-2003): nervous system diseases

Magnus & Sadkowsky 2006. Cat. no. PHE 73. Canberra: AIHW.
Projections of a tripling of world’s dementia population by 2050

World Alzheimer Report, ADI, 2009

Tripling in Australia

Access Economics for Alzheimer’s Australia, 2009

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#

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%

¹Brookmeyer et al. (1998)
Iceberg Phenomenon

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 nutrition
  - 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 midlife BP
- High midlife cholesterol
- High homocysteine

The human heart, Leonardo Da Vinci

Treatment for hypertension

- Hypertension Rx → risk ↓ \(^1,2,3,4\)
- Each extra year of treatment →
  > reduction in risk of dementia\(^5\)
- 60% ↓ risk of all dementia and AD
- 5 RCTs\(^6\) 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)*
  - *Meta-analysis*; *Cochrane review*
- No benefit as treatment of AD 8

1. Rockwood et al, 2002 (Canadian Health & Aging)

---

**Homocysteine, B₁₂, Folate & AD**

- ↑ blood serum homocysteine = cardiovascular risk factor
- Associated with ↑ risk for AD (VaD) 3-5
- Homocysteine can be treated with Vit B₁₂, B₆ 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 homocysteine
  - No adverse effects reported

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


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

1 Stewart et al Neurology 1997:48(3):626-32;
3 Broe et al Arch Neurol 2000;57:1586-91;
4 In't Veld et al, NE J Med 2001;345:1515-21
5 ADAPT Research Group Neurology 2007:68:1800-08
Can Ginkgo biloba Prevent Dementia?\textsuperscript{1}

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

\textsuperscript{1}DeKosky et al, JAMA. 2008; 300(19):2253-2262

GuidAge trial

Over 5 years
Conversion to AD

No effect on stroke incidence


Natural therapies

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

Member of ginger family
Ginkgo leaves
Medicinal plants & dementia

- Evidence for cognitive improvement ≤ pharmacologic treatments
- Medicinal plants for BPSD appear more promising e.g. Lemon balm, lavender oil
- Prevention – not adequately tested
  - Brahmi, circumin, coconut oil

Nutriceuticals

- Souvenaid (Nutricia)* launch on 7th May
  - Flavoured 125ml drink
  - Mixture of vitamins and lipids
- Two RCTs benefit on memory tests
  - In early Alzheimer’s
  - Not on function or other cognitive domains
  - Cost $4.16 per day

Nutrition / Supplements

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

Note: HB is member of Nutricia Advisory Board
**Alcohol & Dementia**

- Many negative studies (mainly X-sectional)
- **Longitudinal studies**
  - Wine consumption ↓ dementia risk
  - Light-to-moderate alcohol (1-3 drinks/day) ↓ risk of dementia (HR = 0.58)
  - Monthly & weekly wine intake ↓ risk of dementia (OR = 0.43, 0.33)
  - XS alcohol in midlife → 3 fold ↑ in risk

1 Orgogozo et al, 1997 (PAQUID),
2 Ruitenberg et al, 2002 (Rotterdam study),
3 Truelsen et al, 2002 (Copenhagen study),

---

**Fish/Seafood & AD: PAQUID**

- 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


**Mediterranean Diet to Prevent MCI & AD**

**Study 1:**
- > adherence to Mediterranean diet → dementia risk ↓
- “Dose” dependent effect

**Study 2:**
- N= 2364 Ss, FU 4.5 yrs
- 275 incidents of MCI
- Effects on incident MCI and progression from MCI to AD

Scarmeas et al, Arch Neurol. 2006;59:912-921
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

Flavonoid-rich Wine, Tea and Chocolate \(^1\) and Coffee \(^2\)

- Some evidence of association with reduced risk of cognitive decline or reduced risk of developing AD

2 Eskelinen et al, J Alzheimer’s Disease. 16 (2009):85-91

Foods rich in anti-oxidants

- Small red beans
- Blueberries
- Red kidney beans
- Pinto beans
- Cranberries
- Artichoke hearts
- Berries: - black
- Rasp- and Straw-
Vit D

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;59:1259-63
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 ?

No definitive evidence for dietary recommendations

Use it or lose it?

Activities & AD
- Leisure
- Cognitive
- Physical
**Mental activity less risk for dementia**

- More leisure activities less dementia 5 yrs later \(^1\)
- > 6/13 leisure activities over last month self-reported eg walking, reading, hobbies, visiting, restaurants, movies or sport 2.9 yrs later → 38% less risk of dementia (RR 0.62, 95%CI 0.46-0.83) \(^2\)
- More reported cognitive activity at baseline delayed the onset of memory decline 5 yrs later, independent of education \(^3\)

---

**Individual Protective Factors**

Dichotomised high v low; median follow-up 7.1y; all give OR of about 0.5

- Education
- Occupation
- Pre-morbid IQ
- Mentally stimulating leisure activities

---

**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

---

\(^2\) Scarmeas et al, Neurology 2001;57:2236-2242
\(^3\) Hall et al. Neurology. 2005;73:356–361

---

**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?

---

**The power of physical activity**

Erickson et al., 2011

---
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?


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

Alzheimer's Australia

- [http://yourbrainmatters.org.au](http://yourbrainmatters.org.au)
Conclusion

• Cannot prevent dementia, but can we wait? 
• 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
• www.cheba.unsw.edu.au
• http://yourbrainmatters.org.au

Jeanne Calment 1875-1997