Can lifestyle prevent Alzheimer’s disease?

Henry Brodaty
Can we prevent dementia?

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

• Disease elimination
  – eg smallpox vaccination
  – best prospect is AD vaccine

• Disease postponement\(^1\): delay AD onset by …
  – 2 years, ↓ prevalence by 20%
  – 5 years, ↓ 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 ¹
• In older people, mixed dementia > common than AD

¹ MRC CFAS Study (2003)
Life Course Approach: childhood

- Genetic determinants
- Environmental determinants
  - Foetal maldevelopment
  - Low birth weight *for gestational age*
  - Low education
  - Parental education & occupation
  - 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
Your Brain Matters
A Guide to Healthy Hearts & Minds

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

yourbrainmatters.org.au
Cardiovascular Factors

The human heart
Leonardo Da Vinci
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
As CVD risk factors accumulate, AD dementia risk increases

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

Dosage effect

Luchsinger et al 2005

Slide adapted from Michael Valenzuela
Statins to prevent AD

Good evidence that statins do not prevent or increase risk of cognitive impairment or dementia

McGuiness B et al, 2016; CD003160 (1)
Cochrane Database of Systematic Reviews,
Physical activity = protective

- Several studies show physical activity protective against cognitive decline, dementia, Alzheimer’s, vascular dementia
- More is better – puffed, weights
- ≥ 3x per week; >150 min/wk, e.g. Perth Study
- Check with your doctor

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
Physical activity

- Physical activity benefits older adults to prevent dementia: Never too late to start
- Moderate intensity (brisk walking) 30 min 5d/wk
- Evidence for specific exercise not clear; more than one type and more exercise may be better
- Resistance training better in SMART Trial
- Combine with social and mental activity better?

Fiatarone Singh MA et al JAMDA 2014;15:873-80
The power of physical activity

Erickson et al., 2011
Physical activity benefits

- Improved fitness
- Improved physical health - ↓ heart disease, Hi BP, diabetes, some types of cancer, osteoporosis, sarcopenia
- Reduced morbidity & mortality
- Improved mental health
- Improved confidence, quality of life

http://www.mednwh.unimelb.edu.au/research/health_promotion.htm
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?

Or

Could prodromal dementia (pathology build-up before symptoms apparent) influence activities?
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 evident¹
- Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence¹
- Results held when covariates in source studies were controlled for²

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
  - 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
  - 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
ACTIVE study\(^1\)

- 10yr f-up of RCT single-blind trial, Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE); 3 interventions (memory, reasoning and speed) + no-contact control gp
- 10 training sessions; 4 boosters @ 11 & 35 m
- Speed & reasoning gps maintained those domains at 10y; not memory gp
- AI 3 gps maintained IADLs > controls @ 10y
- Speed gp: > still driving, < dementia \(^2\)

\(^1\)Rebok GW, JAGS 2014; \(^2\) AAIC Conf Conf July 2016
Obesity in mid-life
Mid-Life Obesity

• Compared to normal weight, midlife obesity increases risk of dementia later in life
  – BMI 25-30: RR 1.34 [95% CI 1.08, 1.66],
  – BMI > 30: RR 1.91 [1.4, 2.62]).

• If obesity is included, there will be 9% higher forecast for US and 19% for China, in 2030 (and 2050) than forecasts that rely solely on the demographic change¹

• Obesity paradox – late life overweight ≠ risk factor, ? protective

¹Loef M, Walach H. Obesity (2013) 21, E51-E55
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
Mediterranean diet: PREDIMED

- 447 healthy, mean age 67, hi CV risk no CV ∆
- RCT: Medi + 30g/d nuts* v Medi + EVOO (1 litre/week) v Control (↓fat diet)
- Median f-up 4 yrs
- Both interventions better on RAVLT and colour trails 2 tests
- All intervention groups stable on composite cognitions; controls declined
- Medi + supplement with nuts or EEVO assoc with improved cognition

* 15g walnuts, 7.5g hazelnuts, 7.5g almonds per day

Cinta Valls-Pedret, JAMA Intern Med. 2015;175(7):1094-1103.
Nutrition / Supplements

- Alcohol ? moderate
- Fish/Seafood/ω3 ?
- Vitamin D ?
- Caffeine ?
- Vitamin E ?
- Vitamin C x

*Food sources better than supplements*
B Vits and homocysteine

- OPTIMA: Folic acid 0.8mg + Vit B12 0.5mg + B6 20mg
  - Reduce brain atrophy and improve cognition
  - Principally in people with high homocysteine
    - Smith AD et al, PLoS ONE, 2010;
    - Douaud et al. PNAS 2013;110:9523-9528

- Two systematic reviews and one trial did not find homocysteine lowering treatments beneficial
  - Clarke R et al Am J Clin Nutr 2014;100:657–66 Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials. – 11 large trials, 22,000 individuals
  - van der Zwaluw 2yr RCT,B vits in 2919 Ps w HCy↑ Neurology;2014:83:1–9
Vit D, NSAIDs, fish, curcumin

- Vit D – low levels of Vit D are common and associated with development of dementia
  - No evidence that taking Vit D lowers risk
- Anti-inflammatories – mixed epidemi. evidence
- Fish oil – some evidence, natural source ie fish (epidemiological)
- Curcumin – some evidence (laboratory)
Smoking and AD

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

Anstey K. Am J Epidem 2008
Alcohol

- Some evidence benefit with moderate alcohol
  - i.e. abstinent → higher risk, j-shaped curve
- Not all studies confirm
- Interaction with ApoE4 – contradictory results?
- Heavy alcohol is risk factor
- Which alcohol – (red) wine?
  - Evidence not strong
- What is moderate?
Natural therapies

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

- HRT – neither harmful or beneficial close to menopause
- Hearing loss RR 1.55-2.32
- Less ‘socialisation’
  - increases risk of cognitive decline/ dementia
  - moderates effect of Alzheimer pathology on cognitive function
Environmental factors

- 30% 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
- Highest estimated Pop\textsuperscript{u} Attributable Risk for AD
  - 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)

Barnes & Yaffe, 2011; Norton et al, 2014
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
Is 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

Christensen et al. *The Lancet* 2013. [http://dx.doi.org/10.1016/S0140-6736(13)60777-1](http://dx.doi.org/10.1016/S0140-6736(13)60777-1)
US dementia 1997-2008 and 2000-12

- Framingham Heart Study¹: dementia incidence in elderly declined by $\approx 20\%$ per decade between 1977 and 2008
  - only those with $\geq$ high school education
- Health and Retirement Study² $\approx 10,000+$ at each wave, all 65yo +, mean $\approx 75$yo
- Prevalence 11.6% $\rightarrow$ 8.8%
- More education accounted for some of 2.8%↓

¹ Satizabal CL, NEJM 2016
² Langa KM JAMA Int Med 21/11/2016
Implications of reduced prevalence

- Environmental factors
  - Better education?
  - Better attention to lifestyle factors?
    - Cardiovascular?
    - Diet?
    - Perinatal and early childhood?
Multi-component studies

- FINGER
- Pre-DIVA
- HATICE
- Maintain Your Brain
FINGER study

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)
- First large, long term RCT of multi-domain interventions aimed at improving cognition
- Eligibility: 60-77 yrs, CAIDE dementia risk score ≥6; cognition at or slightly below mean for Finnish norms (eg, ≤ 26 MMSE)

Ngandu et al. The Lancet. 2015; http://dx.doi.org/10.1016/S0140-6736(15)60461-5
Finger intervention

- Intervention
  - Diet
  - Cognitive training
  - Exercise – PMR and aerobic
  - Manage metabolic and vascular risk factors
  - Social activities
Mean change in cognition over 2 years

NTB Total Score

Executive Function

http://dx.doi.org/10.1016/S0140-6736(15)60461-5
Mean change in cognition over 2 years

Processing speed

Memory

Baseline               12 mths               24 mths
Baseline               12 mths                  24 mths

Prevention of Dementia By Intensive Vascular Care (preDIVA) trial

- Multicomponent intervention targeting vascular care
- 6-yr, open cluster-RCT in primary care
- 3,526 cognitively healthy persons age 70-78
- usual care or usual care + 3 additional visits/yr led by nurse, focused on vascular care
- $1^0$ outcomes dementia incidence & disability
- median follow-up of 6.7 years

Prevention of Dementia By Intensive Vascular Care (preDIVA) trial

- New cases of all-cause dementia and AD did not significantly differ between groups.
- Non-AD dementia signif. less in intervention (1%) vs control group (2%) (HR 0.37; p=0.007)
- Subgroup with untreated hypertension adherent to intervention, signif. fewer new dementia cases (4% vs 7%; HR 0.54; p 0.02)
Conclusion preDIVA trial

• Long-term, nurse-led vascular care in an unselected population of community dwelling older people is safe and may reduce incidence of non-Alzheimer's dementia

• Potentially clinically meaningful effects in lowering incident dementia in people with untreated hypertension adherent to intervention

• Control treatment was good

Healthy Aging Through Internet Counselling in the Elderly (HATICE)

• Develop an innovative, interactive internet intervention platform to optimise treatment of cardiovascular disease in the elderly
• Test this new intervention in a RCT to investigate whether new cardiovascular disease and cognitive decline can be prevented

• Richard E, http://www.hatice.eu/
Prevention trial, NHMRC funded, 5 years
- Internet based, largest trial in world
- 18,000 Australians 55-75 years old
- Exercise, cognitive training, diet, depression
- Blood pressure, cholesterol, glucose
- Tailored to individual risk factors

www.cheba.unsw.edu.au
Large studies underway

- A4 Study
- DIAN – TU
- Alzheimer Prevention Initiative (Colombia)

- Prevent MCI → AD
  - Tau therapeutics
  - β-secretase inhibitor
Can AD be prevented? Not yet but … ..may be delayed

yourbrainmatters.org.au

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

www.cheba@unsw.edu.au

Dementia Collaborative Research Centre

www.dementiaresearch.org.au

h.brodaty@unsw.edu.au