Preventing dementia

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 – trials to date have failed

• Disease postponement\(^1\): delay AD onset by…
  • 2 years, \(↓\) prevalence by 20%
  • 5 years, \(↓\) prevalence by 50%

\(^1\)Brookmeyer et al. (1998)
Life course approach
Is early life the most important target?

• 70% of world dementia in developing countries where there are high rates of:
  • Low foetal birth weight for gestational age
  • Poor education
  • Poor socio-economic environment
  • Foetal maldevelopment
  • Low parental education & occupation
  • Poor dietary history
Cardiovascular Factors

The human heart
Leonardo Da Vinci
Blood Pressure & Dementia

- Mid-life hypertension associated with late-life dementia
- Treating blood pressure decreases risk in some studies
- Each year of treatment decreases risk

Caveats
- Can harm if lower BP too much in older old
SPRINT- MIND Trial

- Does treating high blood pressure to target < 120 mm Hg systolic better than < 140 mm
- 9361 hypertensive older adults with high CV risk but no diabetes, dementia or stroke
- At 1 year, mean sBP 121 vs 134
- Less mild cognitive impairment in intensive BP treated group and trend for less dementia
- Less increase over 4 years in white matter lesions


Prabhakaran S, *JAMA*;2019;322:512-3

Sprint Mind Investigators, *JAMA*. 2019;322:524-534
Blood pressure and dementia

Atherosclerosis risk in communities (US)

• BP recorded 5x/ 24 years in 4761 participants
• Midlife N, late life N → 1.31/100 Person Years
• Midlife = N, Late life Hi → 1.99/100 PY
• Midlife Hi, Late life Hi → 4.26/100 PY
• Midlife N, Late Lo → 2.07/100 PY
• Midlife Hi, Late Lo → 4.26/100 PY

Whitehall II cohort study (UK)

• 7899 Participants’ cardiovascular (CVS) health aged 50 + 5 yrs,
• CVS Health score (smoking, BMI, diet and physical activity)
• Better CVS health → less dementia approx. 20 years later
The more vascular risk factors the greater AD/ dementia risk

- Hypertension
- Smoking
- Hypercholesterolemia
- Obesity
- Diabetes
- Physical inactivity

Luchsinger et al 2005

Number of risk factors

Slide adapted from Michael Valenzuela
Statins neither prevent nor increase risk of cognitive impairment or dementia\(^1\)

Benefits of statins may vary by type of statin, sex, race\(^2\)

\(^1\) McGuiness B et al, 2016; CD003160 (1) Cochrane Database of Systematic Reviews

\(^2\) Zissimopoulos J et al, JAMA Dec 2016
Physical activity = Protective

• Several studies show physical activity protective against cognitive decline, dementia, Alzheimer’s, vascular dementia
• More is better – puffed, weights
• At least three times per week
• At least 150 minutes per week
Check with your doctor

Never too late, never too early

Can aerobic exercise protect against dementia?

• Preserves cognition and slows cognitive decline
• Decreased incident dementia
• 8/11 Randomised Control Trials in healthy older persons: cognition & fitness improved
• Biomarkers improved, e.g. brain volume
• Animal studies – growth factors improved, brain derived neurotrophic factor improved, more new nerve cells, less inflammation
• Less Alzheimer’s disease pathology

Graff-Radford NR, Alzheimer’s Research and Therapy 2011, 3:6
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
Cognitive interventions healthy older adults

- Not yet possible to say if CCT can help older people to maintain good cognitive function
- Trials (all $\geq 3$ m) still quite short for examining long-term effects as people age
- Future research
  - Do longer periods of training work better?
  - Can training produce lasting effects?

Gates N et al, Cochrane Systematic Review, 2019
Meta-analyses of CCT for MCI

• 30 trials computerised, therapy-based and multimodal interventions vs control for MCI: effects on ADL (d 0.23) & metacognitive outcomes (d 0.30) ¹

• 17 trials of ≥ 4 hours of CCT (N=351; control N=335) for MCI → moderate effect post-training on general cognition (Hedges' g=0.35; 0.20-0.51); no long-term evidence about prevention of dementia; but uncertain or high risk of bias in 14/17 trials ²

• 5 high quality trials insufficient evidence ³

Cognitive interventions people with dementia

• Relative to control intervention, but not to various alternative treatments, CT probably associated w small to moderate positive effects on global cognition and verbal semantic fluency at end of treatment

• Benefits appear to be maintained in the medium term

• Certainty of findings is low or very low

• Future studies should:
  • stronger measures to mitigate risks of bias
  • provide long-term follow-up
  • focus on direct comparison of CT versus alternative treatments rather than passive or active control

Bahar-Fuchs A et al, Cochrane Systematic Review 2019
Caveats about meta-analyses

• Combining structurally different cognitive interventions
• Confidence intervals vary based on quality of meta-analysis
• In healthy older adults: a meta-analysis → modest efficacy which varied across cognitive domains...
  …unsupervised training at-home & > 3x/week: ineffective
• No good evidence that any intervention reduces MCI → dementia
• 2 low quality studies suggest +ve impact on dementia incidence
  1. Valenzuela M, personal communication, 2019
Obesity in Mid-Life
Mid-Life Obesity

• Compared to normal weight, midlife obesity increases risk of dementia later in life
  • BMI 25-30: 34% increased risk
  • BMI > 30: 91% increased risk
• Obesity paradox: In late life being overweight is not a risk factor, may be protective
Mind your diet

- Mediterranean diet
- Antioxidants
What is Mediterranean-style diet?

- Abundant plant foods
- Fresh fruit as typical daily dessert
- Olive oil as principal source of fat
- Dairy products (cheese, 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
Western diet v Eastern diet
Afternoon tea, Hotel Istana
B Vits and homocysteine

• OPTIMA: Folate 0.8mg + Vit B\textsubscript{12} 0.5mg + B\textsubscript{6} 20mg
  • Reduce brain atrophy and improve cognition
  • Mainly in people with high homocysteine

• Two systematic reviews and one trial no benefit from homocysteine lowering Rx

- van der Zwaluw, 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 epidem. evidence
• Fish oil – some evidence, natural source ie fish better
• Curcumin – some evidence (laboratory)
• WHO: Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should NOT be recommended to reduce the risk of cognitive decline and/or dementia
  • evidence: moderate; recommendation: strong
Smoking and AD

• Current smoking
  • increase risk for AD

• Previous smoking
  • Risk not significantly increased

Anstey K. Am J Epidem 2008
Alcohol

• Weak evidence benefit of moderate alcohol
  • i.e. abstinent → higher risk, j-shaped curve

• What is moderate?

• Not all studies confirm

• Heavy alcohol is risk factor

• Which alcohol – (red) wine?
  • Evidence not strong

• Alcohol linked to higher rates of cancer
Natural therapies

- Ginkgo biloba X
- Turmeric, curcumin ?
- DHA, omega 3 ??
- Fo-ti root
- Soy isoflavone
- Vitamin E, Selenium X
- Saffron
- Brahmi
- Huperzine A
Unproven but popular on net

- Coconut oil
- Grain Brain
- Ketogenic diet
- Many others??

Promising?

- Resveratrol, activates sirtuins
- Next generation anti-ageing compounds
Hearing loss
Hearing loss and incident dementia

- Lin 2011 RR 2.32 (1.32-4.07)
- Gallacher 2012 RR 2.67 (1.38-5.17)
- Deal 2016 RR 1.55 (1.10-2.19)
- Peripheral hearing loss associated with significant risk for dementia
- Follow-ups 9, 12 and 17 years
Do hearing aids help?

- 25-year prospective study – ↑dementia incidence if self-reported hearing problems except if use hearing aids¹
- Cross-sectional ELSA: hearing loss associated with worse cognition if not using hearing aids; mediated by social isolation²
- For people aged >50, tested 2-yearly over 18 years, immediate & delayed recall deteriorated less after initiation of hearing aid use³

³Maharani A, JAGS 2018; 66(6): 1130-6
Social isolation
Socialisation and dementia

- Less frequent social contact, less social participation, and more feelings of loneliness associated with increased risk of dementia
- 57% increase risk = comparable to late-life depression 85% and physical 82% increased risk
- Good social engagement, pooled reduction in risk 22%, (but significant publication bias)
- WHO: Insufficient evidence but … social participation and support strongly connected to good health & wellbeing throughout life

Penninkilampi R, Casey A-N, Fiatarone-Singh M, Brodaty H. 2018
WHO Report on Risk reduction 2019
Hormone Replacement Therapy

- HRT – neither harmful or beneficial close to menopause
- Increased risk in women taking HRT from age 65yr?
Sleep and dementia
Sleep and dementia

- About 1-in-2 older adults have regular insomnia
- About 1-in-2 older adults have sleep-disordered breathing
- Slow wave sleep associated with amyloid-β protein clearance from brain in animal and human studies
- Sleep-disordered breathing associated with poor sleep
- Poor sleep associated with worse cognition
- Can correcting insomnia and sleep-disordered breathing prevent or delay?
- Does incipient dementia cause sleep disorders?
Air Pollution

• Perhaps small contribution
• Insufficient evidence

“Air Pollution Robs Us of Our Smarts and Our Lungs”
GIBBENS S, National Geographic, 2018
9/10 people breathe in polluted air
Environmental factors

• 30% of population attributable risk of AD cases from 7 environmental factors $^1,^2$

• If 25% lower prevalence of these risk factors $\rightarrow$ 3 million fewer AD cases worldwide

• Highest estimated Population Attributable Risk for AD
  • Global: low education contributes $\approx$20%
  • USA, Europe, UK: physical inactivity contributes $\approx$20%

• 10 environmental factors $\rightarrow$ 35% PAR dementia$^3$

$^1$Barnes & Yaffe, 2011; $^2$Norton et al, 2014
$^3$Livingston G et al, Lancet 2017
Life course model of contribution of modifiable risk factors for dementia

(ApoE ε4 7%)
- Low education 8%
- Hearing loss 9%
- Hypertension 2%
- Obesity 1%
- Smoking 5%
- Depression 4%
- Physical inactivity 3%
- Social isolation 2%
- Diabetes 1%

Livingston G et al, Lancet 2017
Is incidence of dementia/ cognitive impairment declining?

• Review 14 studies … trends in dementia prevalence (9 studies) and incidence (5)
• Sweden, Spain, UK, Netherlands, France, USA, Japan and Nigeria.
• All (except Japan) \(\rightarrow\) stable or declining prevalence and incidence of dementia
• Some effects in males; others females only
• No single risk or protective factor fully explains observed trends, but …..

Wu YT et al Nature Neurology Reviews 2017
Is incidence of dementia/ cognitive impairment declining?

- ...major societal changes and improvements in
  - living conditions, early childhood
  - education
  - healthcare, cardiovascular
- might have favourably influenced physical, mental and cognitive health throughout life, and...
- ... be responsible for ↓ risk of dementia in later life
- BUT ... effect of epidemics of obesity & diabetes?

Wu YT et al Nature Neurology Reviews 2017
But…. How reliable are these findings?

- Most studies are observational or single interventions
- Reverse causality?
  - Alzheimer’s disease builds up in brain over 20+ years before it becomes clinically evident
  - Could incipient dementia lead to less cognitive activity, exercise, socialisation, etc
- Can intervention studies prove that adopting these recommendations decrease cognitive decline?
Multi-component intervention studies

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

• Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

• Interventions
  • Diet
  • Cognitive training
  • Exercise – PMR and aerobic
  • Manage metabolic & vascular risk factors
  • Social activities

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

- At 2 years improvement on
  - Composite Neuropsychological battery
  - Speed of information processing
  - Executive functioning
  - Complex memory (but not memory overall)
- At 5 years other benefits on health

Ngandu et al. The Lancet. 2015;
http://dx.doi.org/10.1016/S0140-6736(15)60461-5
RCT: Four basic modules

- Physical activity
- Diet & nutrition
- Brain training
- Depression
Almost 100,000 participants 55-77yo from 45 and Up study contacted → about 12,000 responded
6236 participants randomised to coaching or information
Eligible for up to four modules depending on risk factors
First year finished October 2019
Boosters monthly for years 2 & 3
If successful → less cognitive decline by Year 3
If more funding → less dementia by Year 8
… interaction with genetic markers
Drug studies

- Vaccines or enzyme inhibitors against Aβ
  - A4 Study
  - DIAN – TU
  - Alzheimer Prevention Initiative (Colombia)
Policy Implications

• The world is ageing
• >30 years of drug trials have failed to find a cure for Alzheimer’s disease
• How will world cope with 50m people with dementia, 82 million in 2030 and 152m in 2050?
• Prevention or delay onset is critical
• Even if genetic predisposition, lifestyle reduces risk

Policy Implications

- Can we prevent Alzheimer’s and other dementias
- Not yet, but delay onset is possible
- 2-year delay $\rightarrow$ 20% reduction in prevalence
- 5-year delay $\rightarrow$ 50% reduction

Ideally delay till after ....

....
Policy Implications

• Can we prevent Alzheimer’s and other dementias
• Not yet, but delay onset is possible
• 2-year delay $\rightarrow$ 20% reduction in prevalence
• 5-year delay $\rightarrow$ 50% reduction

Ideally delay till after …. 

…. we die
Our challenge in ADI

• Influence government and bureaucracy to instigate prevention programs
  • Population – education, exercise, engagement
  • Lifecourse approach
  • Primary care
  • With colleagues
    • cardiac, diabetes, Hpt, exercise physiology
  • Develop scalable programs

• All of us need to BE THE CHANGE
  • Lead by example