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Preventing dementia

Henry Brodaty

DCRC
Dementia Collaborative Research Centres

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Healthy Brains Positive Ageing

Can we prevent dementia?

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

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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)

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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

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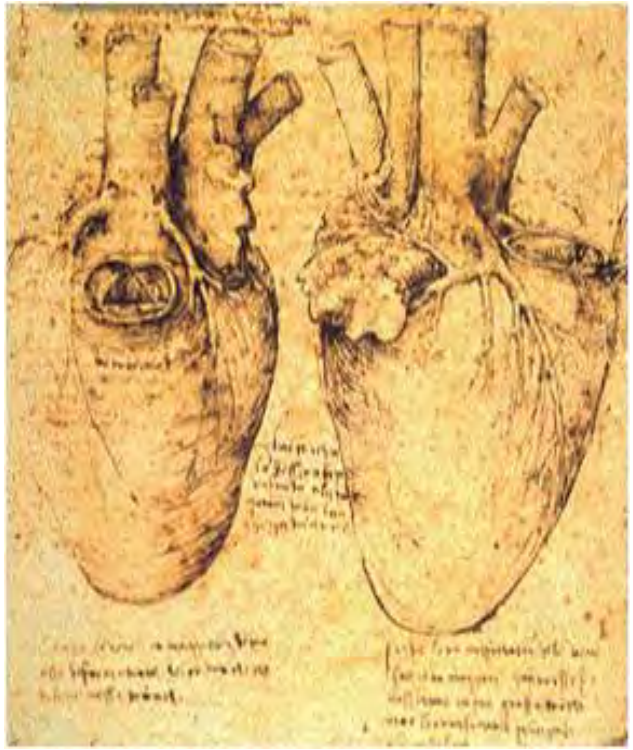
Cardiovascular Factors



The human heart
Leonardo Da Vinci

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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

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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**

Williamson JD et al, J*AMA.* 2019;321(6):553-561. doi:10.1001/jama.2018. 21442

Prabhakaran S_*JAMA*;2019;322:512-3

Sprint Mind Investigators, *JAMA.* 2019:322:524-534

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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**

Walker KA et al, JAMA, 2019:322:535-545

Sabina S et al, *BMJ*, 2019; 366:14414

Whitehall II cohort study (UK)

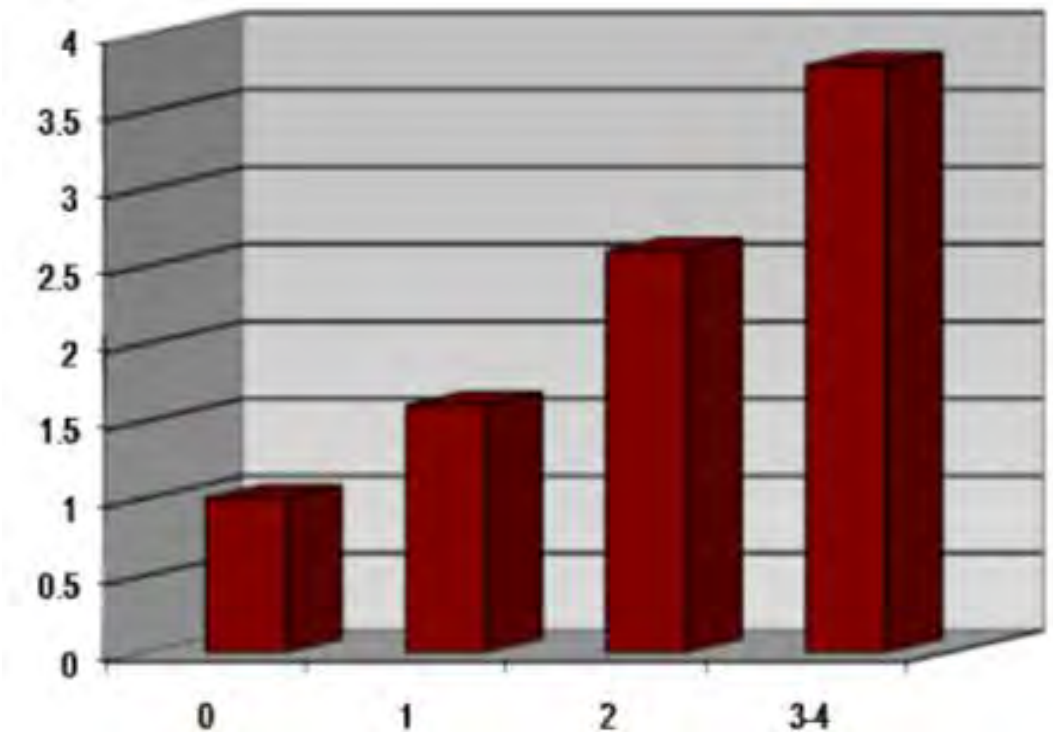
- **7899 Participants' cardiovascular (CVS) health aged 50 ± 5 yrs,**
- **CVS Health score (smoking, BMI, diet and physical activity)**
- **Better CVS health → less dementia approx. 20 years later**

Dosage Effect

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

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Statins to prevent AD

- 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

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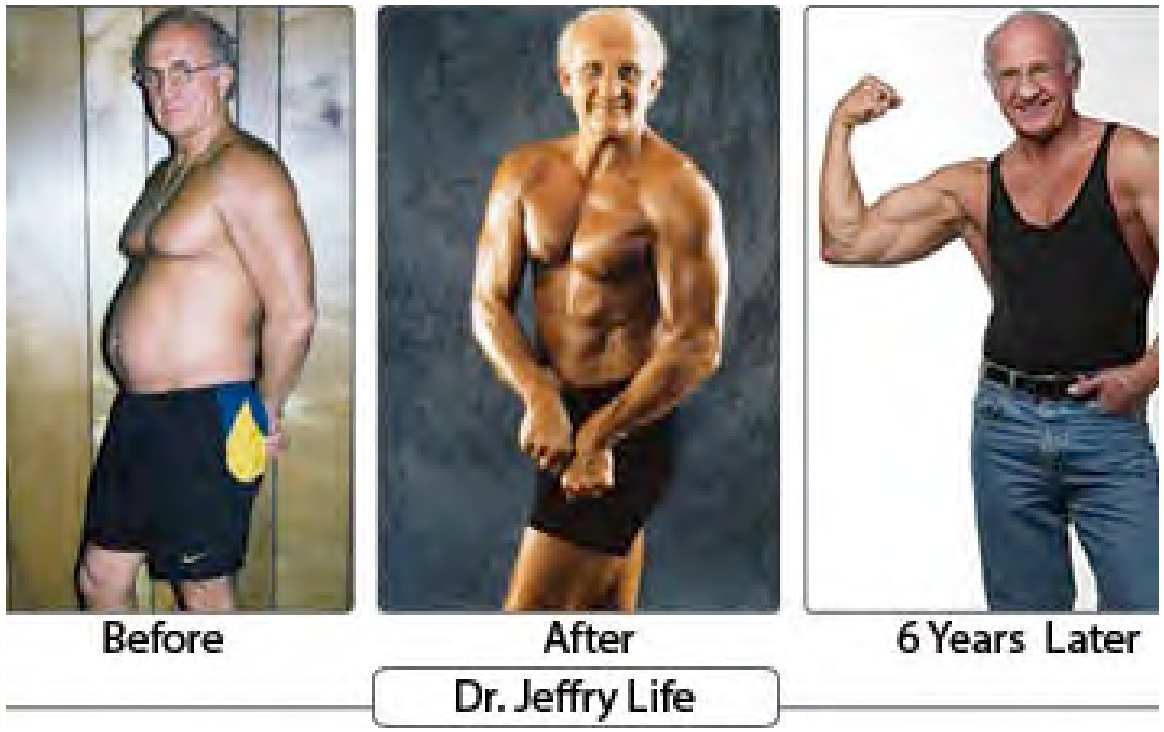
Physical activity = Protective

- 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



[1]Jedrziewski et al (2007). Alz Dem; 3:98-108; [2] Lautenschlager et al (2008) JAMA; 300(9):1027-1037;
[3]Ravaglia et al (2007) Neurology; [4]Larson et al (2006) Ann Intern Med; 144:73-81;
[5]Laurin et al, Arch Neurol 2001;58:498-504; [6]Middelton et al, PLos ONE 2008;3(9):e3124

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

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Graff-Radford NR, *Alzheimer's Research and Therapy* 2011, 3:6

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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 ≥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]

[1]Chandler MJ et al. *Neuropsychol Rev* 2016; 26: 225-51
[2]Hill NT et al. *Am J Psychiatry* 2017; 174: 329-40
[3] Butler M et al. *Ann Intern Med* 2018; 168: 63-8

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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[1]

- Combining structurally different cognitive interventions [1]
- Confidence intervals vary based on quality of meta-analysis[1]
- In healthy older adults: a meta-analysis → modest efficacy which varied across cognitive domains...
  …unsupervised training at-home & > 3x/week: ineffective [1]
- No good evidence that *any* intervention reduces MCI → dementia
- 2 low quality studies suggest +ve impact on dementia incidence [3,4]

1. Valenzuela M, personal communication, 2019
2. Lampit A et al, PLoS Med 2014; 18;11(11):e1001756. doi: 10.1371/journal.pmed.1001756
3. Buschert VC, Giegling I, Teipel SJ, et al. *J Clin Psychiatry.* 2012;73(12):e1492-1498.
4. Edwards JD, Xu H, Clark DO, Guey LT, Ross LA, Unverzagt FW. *Alzheimers Dement (N Y).* 2017;3(4):603-611.

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Obesity in Mid-Life

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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

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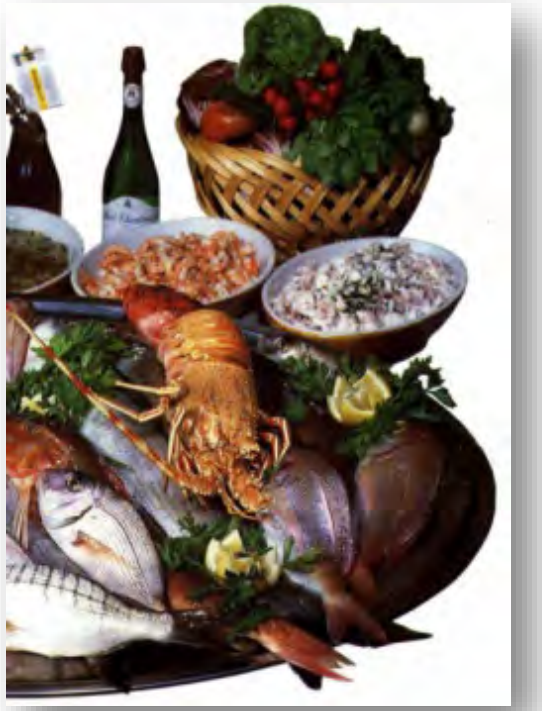
What is Mediterranean-style diet?

- 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



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Western diet v Eastern diet

Afternoon tea, Hotel Istana

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B Vits and homocysteine

- OPTIMA: Folate 0.8mg + Vit B_{12} 0.5mg + B_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

- Smith AD et al, PLoS ONE, 2010; Douaud et al. PNAS 2013;110:9523-28
- Ford AH, Almeida OP Systematic review 19 RCTs *J Alz Dis.* 2012;29:133-49 doi: 10.3233/JAD-2012-111739
- Clarke R et al Am J Clin Nutr 2014;100:657–66
- van der Zwaluw, Neurology;2014:83:1–9

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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

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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

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Natural therapies

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

Ginkgo leaves

Member of ginger family

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Unproven but popular on net

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

Promising?

- Resveratrol, activates sirtuins
- Next generation anti-ageing compounds

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Hearing loss

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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

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Do hearing aids help?

- 25-year prospective study – ↑dementia incidence if self-reported hearing problems except if use hearing aids[1]
- Cross–sectional ELSA: hearing loss assoc[d] with worse cognition if not using hearing aids; mediated by social isolation[2]
- For people aged >50, tested 2-yearly over 18 years, immediate & delayed recall deteriorated less after initiation of hearing aid use[3]
- WHO report (2019) – insufficient evidence

[1]Amieva H *J Gerontol A Biol Sci Med Sci* 2018;73:1383–1389

[2]Ray J et al *JAMA Otolaryngol Head Neck Surg* 2018;144:876-882

[3]Maharani A, *JAGS* 2018; 66(6): 1130-6

Social isolation

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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% incr^{d} 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

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Hormone Replacement Therapy

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

Sleep and dementia

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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?

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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

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Environmental factors

- 30% of population attributable risk of AD cases from 7 environmental factors [1,2]
- If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide
- Highest estimated Population Attributable Risk for AD
  - Global: low education contributes ≈20%
  - USA, Europe, UK : physical inactivity contributes ≈20%
- 10 environmental factors → 35% PAR dementia[3]

[1]Barnes & Yaffe, 2011; [2]Norton et al, 2014
[3] Livingston G et al, Lancet 2017

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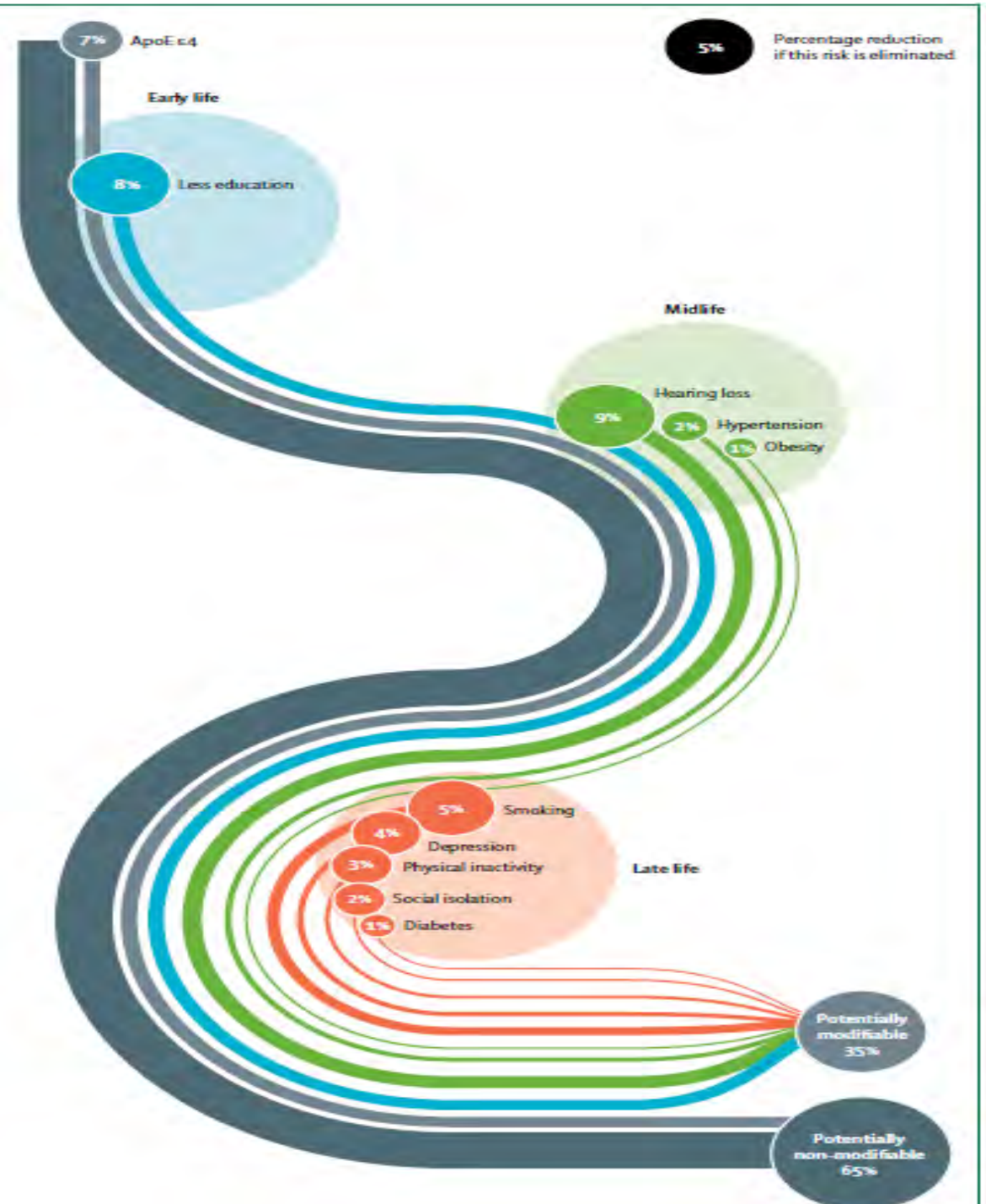

Life course model of contribution of modifiable risk factors for dementia

~~(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%

35%

Livingston G et al, Lancet 2017

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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) → 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 …..

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Wu YT et al Nature Neurology Reviews 2017

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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?

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Wu YT et al Nature Neurology Reviews 2017

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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?

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Multi-component intervention studies

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

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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

Maintain Your Brain tria

https://www.maintainyourbrain.org/

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MAINTAIN YOUR BRAIN

led by the Centre for Healthy Brain Ageing (CHeBA), is the largest clinical trial in the world targeting risk factors for Alzheimer's disease and dementia for people aged 55-77 using online tools.

I AM A MYB PARTICIPANT

ABOUT MAINTAIN YOUR BRAIN

Type here to search

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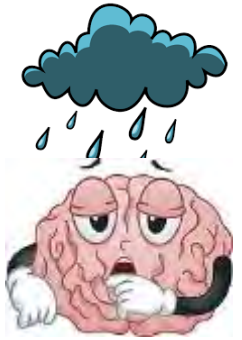
4/05/2019

RCT: Four basic modules

Physical activity

Diet & nutrition

Brain training



Depression

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www.maintainyourbrain.org.au

- 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

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Drug studies

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

RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES 2019

World Health Organization

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 [1]**

[1] **Lourida I** JAMA. 2019 Jul 14. doi: 10.1001/jama.2019.9879. **Association of Lifestyle and Genetic Risk With Incidence of Dementia**

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Policy Implications

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

Ideally delay till after ….

….

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Policy Implications

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

Ideally delay till after ….

…. we die

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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

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