Can Alzheimer's disease be prevented?

Henry Brodaty

Never Stand Still | Medicine

DCRC Dementia Collaborative Research Centres

CHeBA Healthy Brains Positive Ageing

Can we prevent dementia?

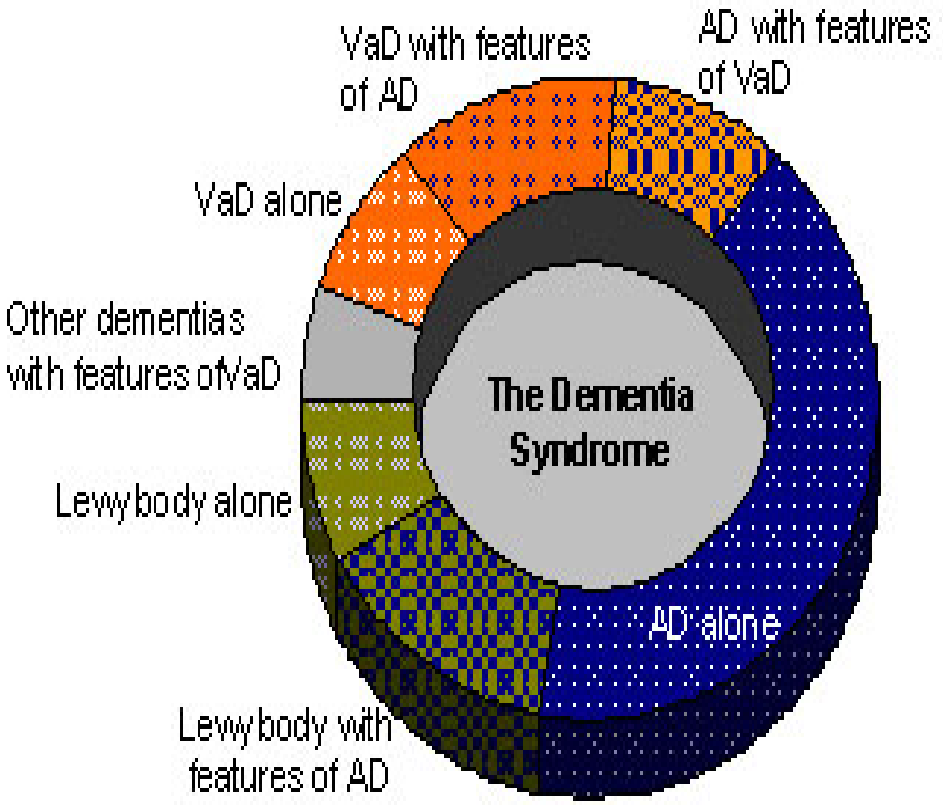
- **The adult brain weighs about 1.3 kg**
- **Dementia shrinks it to 1/2 its usual size**

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)

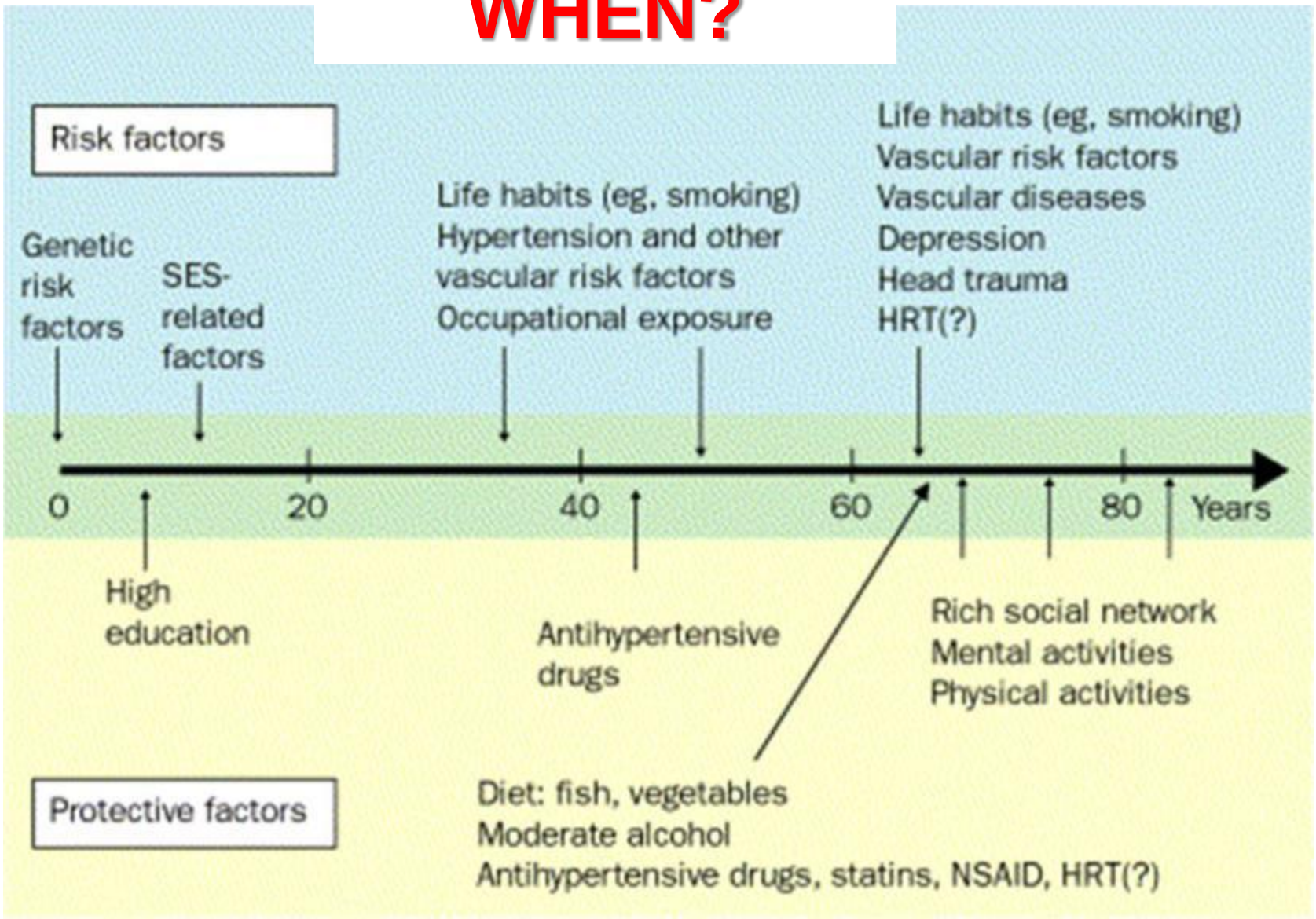
WHAT are we aiming to prevent: Dementia, AD, VaD, Mixed dementia?



- **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)

WHEN?


Risk factors
Genetic risk factors
SES-related factors
Life habits (eg, smoking)
Hypertension and other vascular risk factors
Occupational exposure
Life habits (eg, smoking)
Vascular risk factors
Vascular diseases
Depression
Head trauma
HRT(?)
0
20
40
60
80
Years
High education
Antihypertensive drugs
Rich social network
Mental activities
Physical activities
Protective factors
Diet: fish, vegetables
Moderate alcohol
Antihypertensive drugs, statins, NSAID, HRT(?)

Life Course Approach: childhood

- **Genetic determinants**
- **Environmental determinants**
  - **Foetal maldevelopment**
  - **Low birth weight *for gestational age***
  - **Low education**
  - **Parental educat^{n} & occupat^{n}**
  - **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?

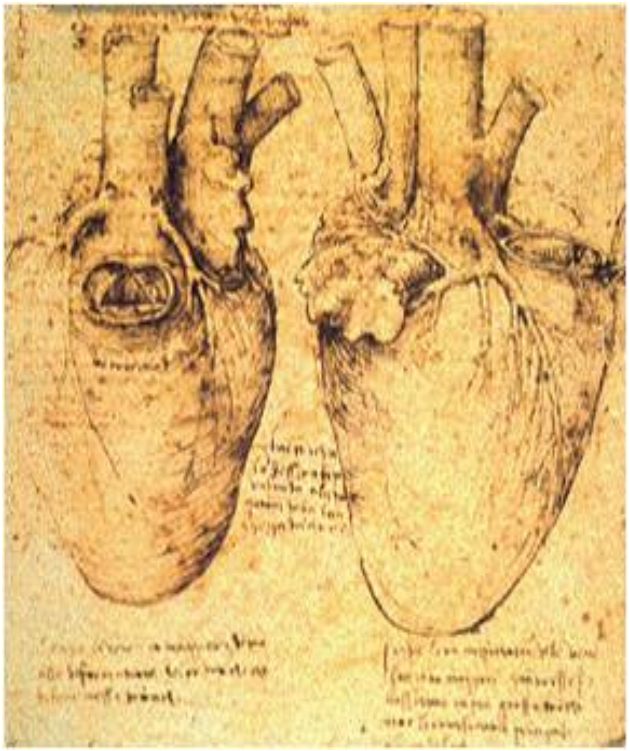
- **70% of world dementia in developing countries**
  - **Low foetal birth weight**
  - **Poor or no education**
  - **Poor socio-economic environment**
- **12.4% West Australia's Kimberley Aboriginal people have dementia = 5.2x non-indigenous[1]**

Smith K et al, Neurology, 2008;71: 1470-1473

- **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

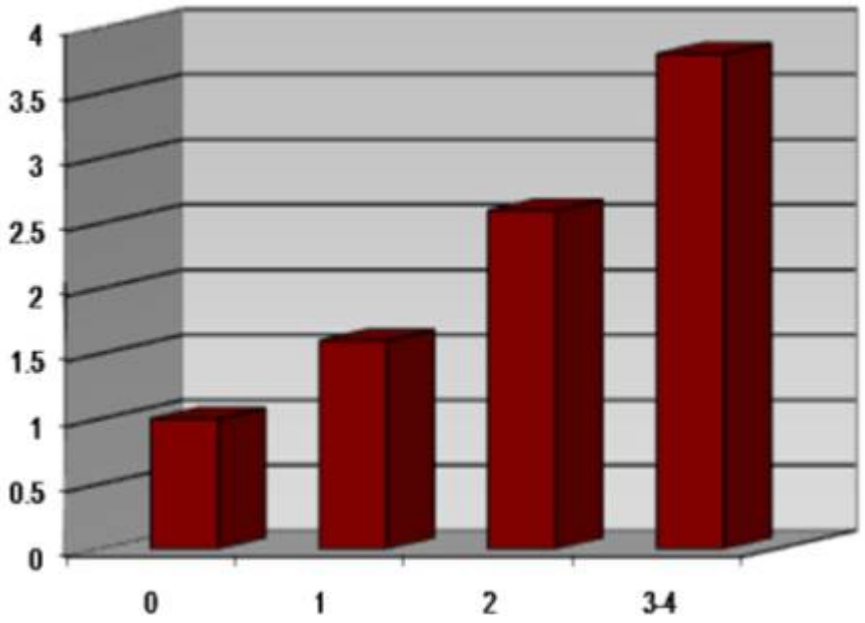
Blood Pressure (BP) and Dementia

- **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**

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

Slide adapted from Michael Valenzuela

Do anti-hypertensives prevent dementia

- **Mixed results from studies**
- **HYVET study 80yo+**
- **Indapamide ± perindopril vs placebo**
- **Terminated early, > CVAs and deaths in controls**
- **No significant difference in dementia betw Rx & placebo (hazard ratio 0·86, 95%CI, 0·67–1·09)**
- **Combined meta-analysis favoured treatment (HR 0·87, 0·76–1·00, p 0·045)**

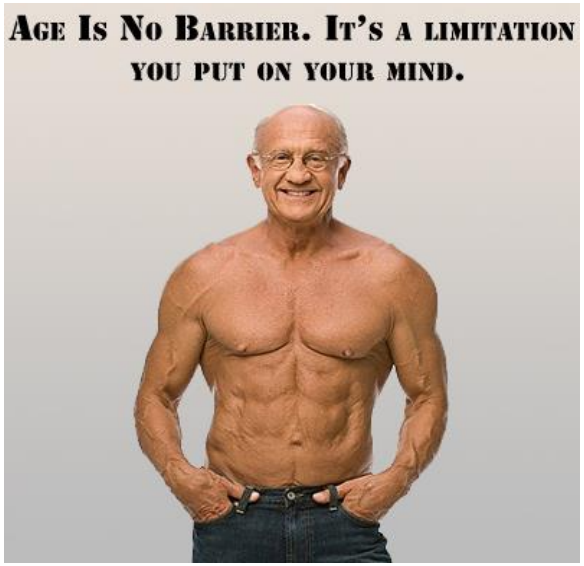
Peters R et al *Lancet Neurol* 2008; 7: 683–89

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**

[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?

- **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

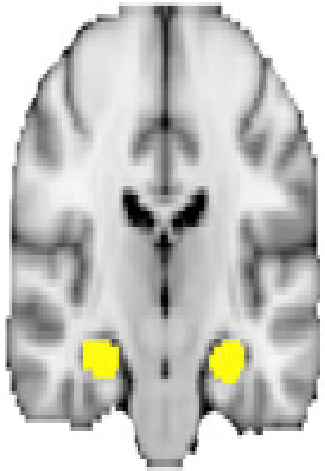
Physical activity

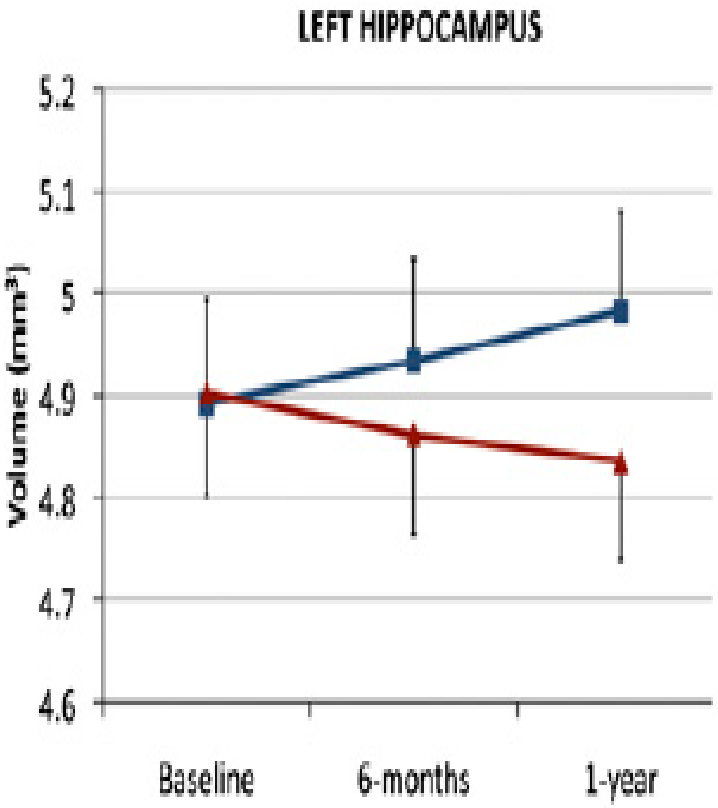
- **Physical activity benefits older adults to prevent dementia: Never too late to start**
- **Moderate intensity (brisk walking) 30 min 5d/wk**
- **Evidence for specific exercise not clear; more than one type and more exercise may be better**
- **Resistance training better in SMART Trial[2]**
- **Combine with social and mental activity better?**

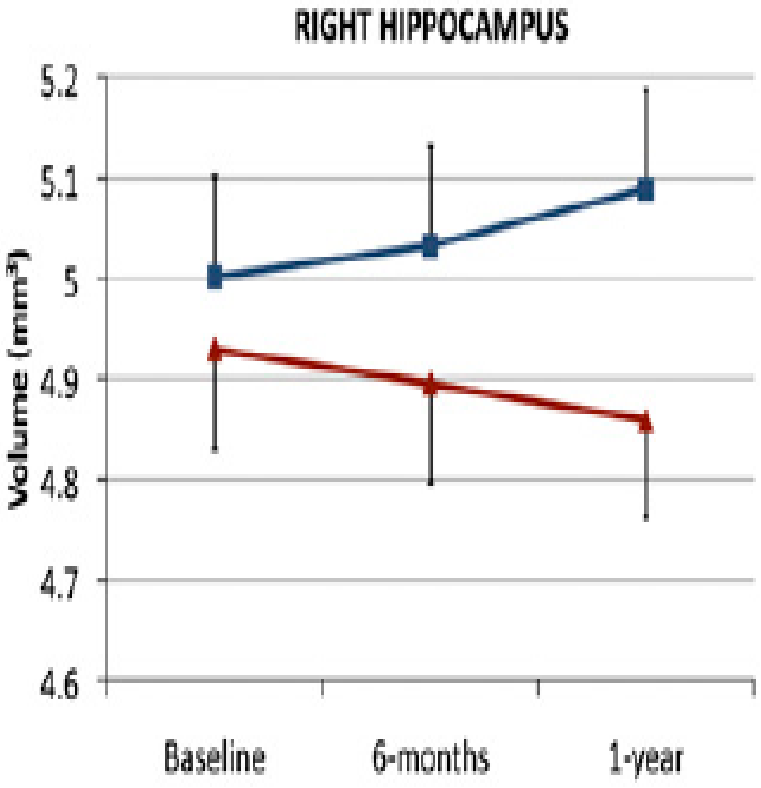
Denkinger et al. *Z Gerontol Geriat 2012*; 45:11–16 DOI 10.1007/s00391-011-0262-6
Fiatarone Singh MA et al *JAMDA* 2014;15:873-80

The power of physical activity

Hippocampus







Erickson et al., 2011

Dose of Exercise for Brain Health

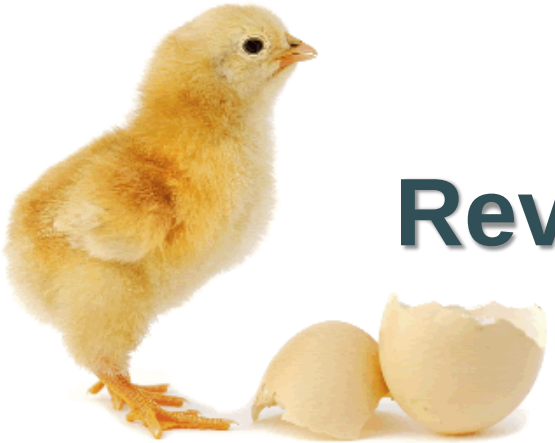
- **Frequency**
  - 3-7 days/wk aerobic
  - 2-3 d/week resistance training
- **Volume**
  - 45-60 min/session
  - Sufficient to reduce body fat/metabolic health if that is a goal
- **Intensity**
  - Fitness outcomes proportional to intensity
  - Fitness outcomes proportional to brain/cognitive changes
  - → highest intensity feasible in given cohort

Slide courtesy of Prof Maria Fiatarone Singh

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 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]**

[1]Valenzuela MJ. Sachdev P. (2006). Psychol Med. 36(4): 441-454;
[2]Valenzuela MJ. Sachdev P. (2006) Psychol Med. 36(8): 1065-1073

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**

Reijnders, J., et al., Ageing Res. Rev. (2012), doi 10.1016/j.arr.2012.07.003

Cognitive training

- **Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly[1]**
  - **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[2]**
  - **11 RCTs, no benefit**

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Bahar-Fuchs, Clare, Woods – Cochrane Database Syst Rev. 2013 Jun 5;6:CD003260. doi: 10.1002/14651858.CD003260.pub2.

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 groups maintained those domains at 10y; but not the memory group**
- **Al 3 gps maintained IADLs > controls @ 10y**
- **Speed group: > still driving, < dementia [2]**

[1]Rebok GW, JAGS 2014; [2] AAIC Conf July 2016

Obesity in mid-life

Mid-Life Obesity

- **Compared to normal weight, midlife obesity increases risk of dementia later in life**
  - **34% if BMI 25-30 RR 1.34 [95% CI 1.08, 1.66]**
  - **91% if 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 change[1]**
- **Obesity paradox – late life overweight ≠ risk factor, ? protective**

[1]Loef 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 Δ
- 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**
  - **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 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 epidem. 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

Ginkgo leaves

Member of ginger family

Unproven but popular on net

- **Coconut oil**
- **Grain Brain**
- **Many others??**

Promising?

- **Resveratrol**
- **Next generation anti-ageing compounds**

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^{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 incidence of dementia/ cognitive impairment declining?

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**

Matthews et al. *The Lancet*, 2013. http://dx.doi.org/10.1016/S0140-6736(13)61570-6.
Qiu et al . Neurology 2013;80:1888–1894
Christensen et al. *The Lancet* 2013. http://dx.doi.org/10.1016/S0140-6736(13)60777-1

Implications of reduced prevalence

- **Environmental factors**
  - **Better education?**
  - **Better attention to lifestyle factors?**
    - **Cardiovascular?**
    - **Diet?**
    - **Perinatal and early childhood?**

HRT for prevention

- **Lab studies & epidemiology → protective**
- **WHIMS – HRT doubles risk of AD/ cog. decline**
- **Later studies of HRT indicate window of positive effects after menopause (≈ 50 yo)**
  - **signif. ↓ risk of mortality, heart failure, or myocardial infarction, without increase in risk of cancer, DVT or CVA (Schierbeck LL et al *BMJ 2012; 345 doi: http://dx.doi.org/10.1136/bmj.e6409*)**
- **Women who had ovaries removed pre-menopause had better cognition if HRT Rx**

HRT & cognition

- **2 recent RCTs (WHIMS-Y and KEEP-Cog) → neither harm nor benefit of HT interventions closer to menopause**

McCarrey AC, Resnick SM.
Horm Behav 2015;74:167-72

Social isolation

Socialisation and dementia

- **Meta-analysis of 19 studies**
- **Socialisation = < frequent social contact (esp) RR: 1.57 (95% CI1.32–1.85), < social participation, and > feelings of loneliness associated with increased risk of dementia**
- **Size large, cf late-life depression & dementia (OR: 1.85); physical activity & AD (1.82)**
- **Why - use it or lose it, ↓stress, ↑better health behaviours, ↑access to health services?**

Kuiper JS + (2015) _Ageing Research Reviews;22:39–57

Socialisation and cognition

- **Carlson et al 2015, RCT, 2 yrs social activities - teaching young public school children to read**
- **Men in intervention group ↑brain volume (hippocampus) vs controls ↓ brain volume**
- **Same, but smaller, effect in women**

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**

Multi-component studies

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

FINGER study

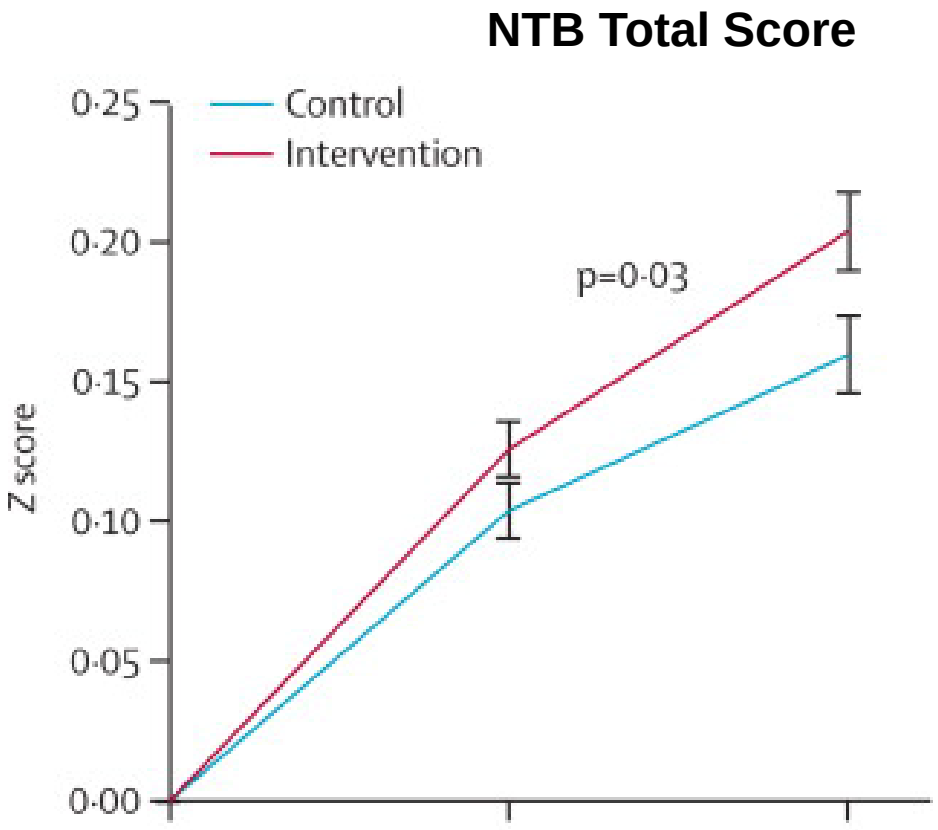
- **Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)**

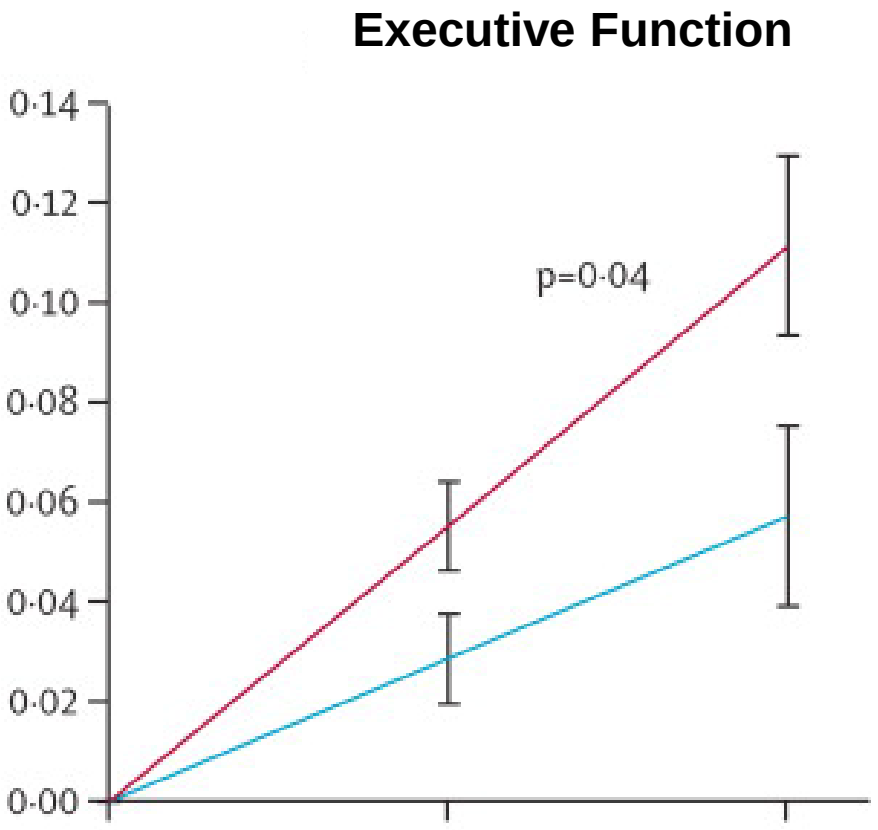
Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

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

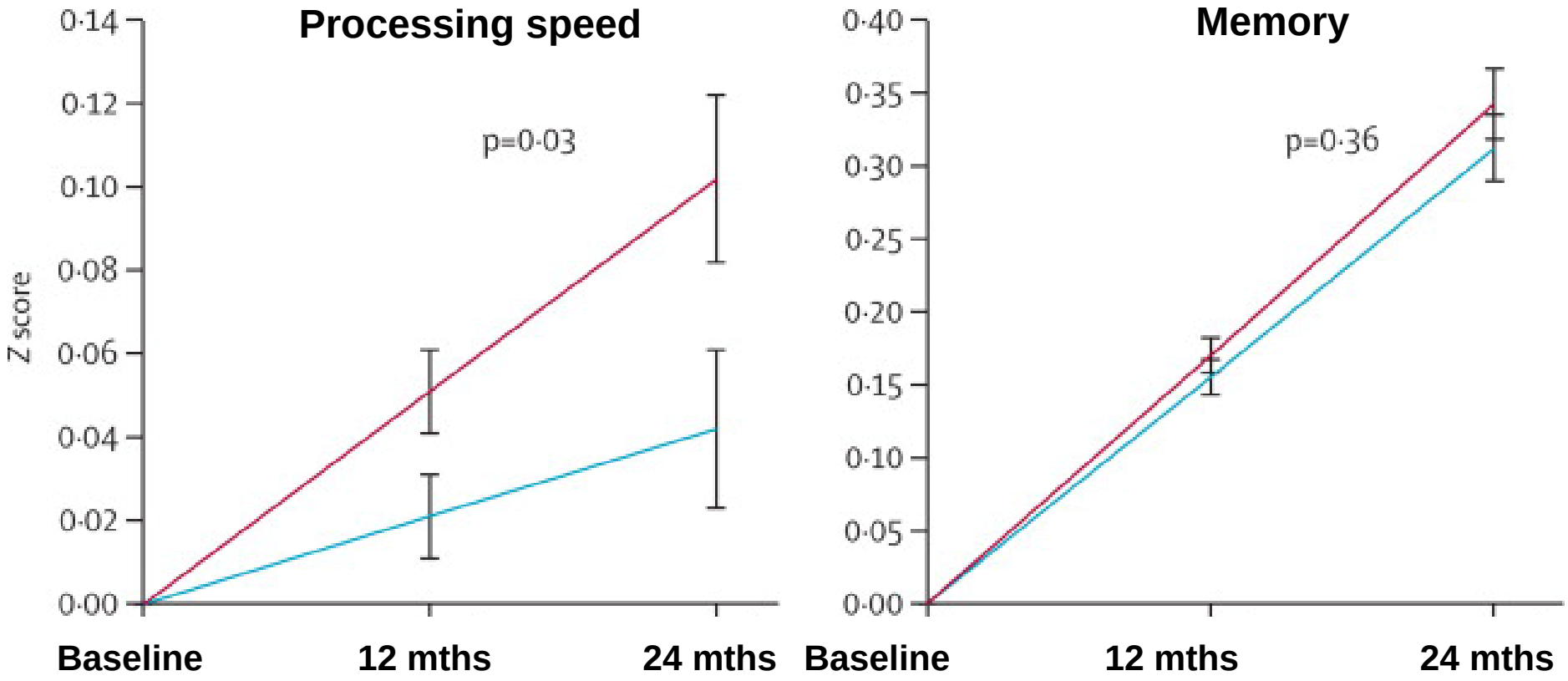




Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

UNSW AUSTRALIA

Mean change in cognition over 2 years



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

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Prevention of Dementia By Intensive Vascular Care (preDIVA) trial

- **Multicomponent intervention targeting vascular risk factors**
- **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**

Moll van Charante EP, Lancet 2016

Prevention of Dementia By Intensive Vascular Care (preDIVA) trial

- **New cases of all-cause dementia and AD did not significantly differ between groups.**
- **Two important signals**
  - **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, signific. fewer new dementia cases (4% vs 7%; HR 0.54; p = 0.02)**

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

Drug treatments

- Enzyme inhibitors
  - β secretase
  - γ secretase
- Immunotherapy
  - Active
  - Passive
    - Antibody – eg gantenerumab
    - solanezumab
  - Insulin nasal spray
  - Tau protein (Rember)

The A4 trial

- **Clinically normal, Aβ positive**
- **Solanezumab; N = 1000, 70yrs+**
- **Cognitive tests over three years**
- **Imaging tests will track structural and functional brain changes**
- **Outcomes: provide important information about the effectiveness of clearing amyloid from the brain in the early stages of the disease and inform future prevention studies**

Principal investigator: Reisa Sperling, M.D., Harvard Medical School, Boston.

Dominantly Inherited Alzheimer Network (DIAN-TU)

- **Aimed at AD caused by gene mutation**
- **Sample: adult children of people with a mutated gene known to cause AD**
- **Gantenerumab & solanezumab**
- **Testing: Clinical interviews, Mental status testing, Brain scans (MRI, PET), Blood assays (genetic, CSF)**

Moulder et al. Alzheimer's Research & Therapy. 2013; 5:48
http://www.dian-info.org/default.htm

Alzheimer's Prevention Initiative

- **Treatment trials, biomarker studies & registries**
- **One trial (NCT01998841): Using Crenezumab (vs placebo) for those at risk of early onset AD (genetic mutation)**
  - **Large extended family in Colombia who share rare genetic mutation (PSEN1 E280A)**
  - **Likely to develop dementia around 45 yrs old**

http://banneralz.org/research-plus-discovery/alzheimers-prevention-initiative.aspx

Prevent MCI → AD

- **Beta-secretase inhibitor (Merck)**
  - **Participants with amnestic MCI + positive biomarker – amyloid imaging or CSF**
- **Methylene blue (Tau Rx)**
  - **Participants with amnestic MCI or mild to prevent p-tau accumulating**

Can AD be prevented?
Not yet but …
… may be delayed
Two approaches broadly…

Drugs

&/or

Lifestyle

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

Thank you for listening

CHeBA (Centre for Healthy Brain Ageing)

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Dementia Collaborative Research Centre

www.dementiaresearch.org.au

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