



# Can lifestyle prevent Alzheimer's disease?

*Henry Brodaty*

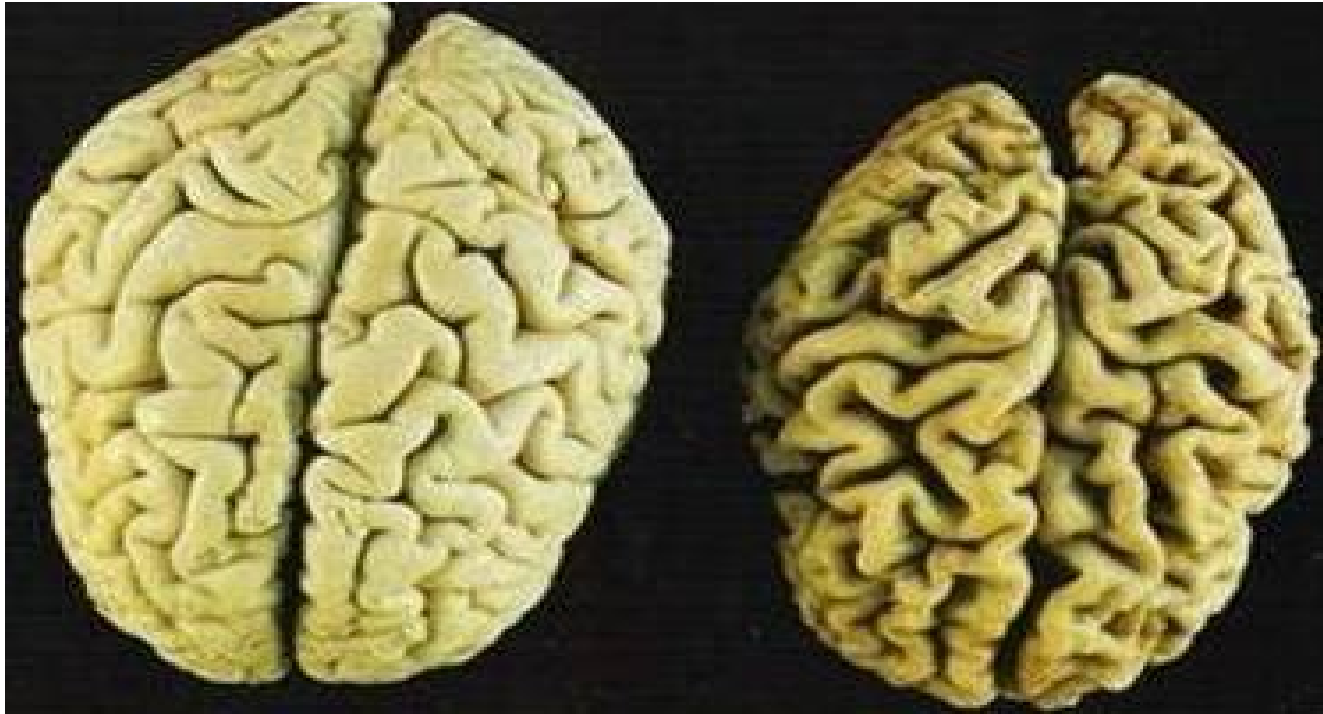
Never Stand Still

Medicine



# Can we prevent dementia?

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

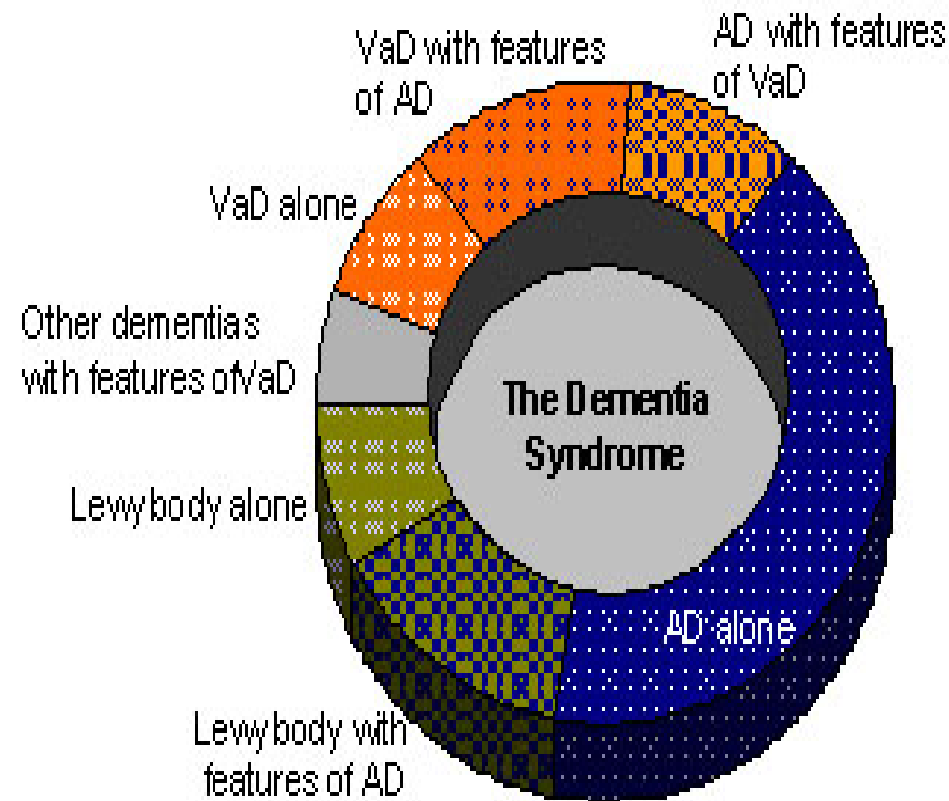


# Elimination vs Postponement

- **Disease elimination**
  - eg smallpox vaccination
  - best prospect is AD vaccine
- **Disease postponement<sup>1</sup>: delay AD onset by...**
  - 2 years, ↓ prevalence by 20%
  - 5 years, ↓ prevalence by 50%

<sup>1</sup>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 <sup>1</sup>**
- **In older people, mixed dementia > common than AD**

**<sup>1</sup> MRC CFAS Study (2003)**



# Life Course Approach: childhood

- Genetic determinants
- Environmental determinants
  - Foetal maldevelopment
  - Low birth weight *for gestational age*
  - Low education
  - Parental educat<sup>n</sup> & occupat<sup>n</sup>
  - Low socio-economic status
  - Dietary history
  - Loss of parent before 11yo

**Reduced  
cognitive  
reserve**

# 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<sup>1</sup>**

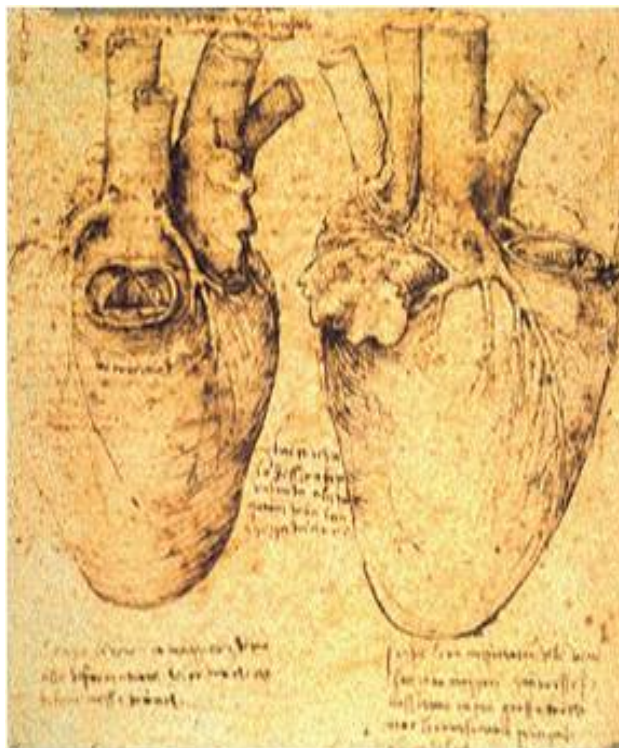
Smith K et al, Neurology, 2008;71: 1470-1473



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

**[yourbrainmatters.org.au](http://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

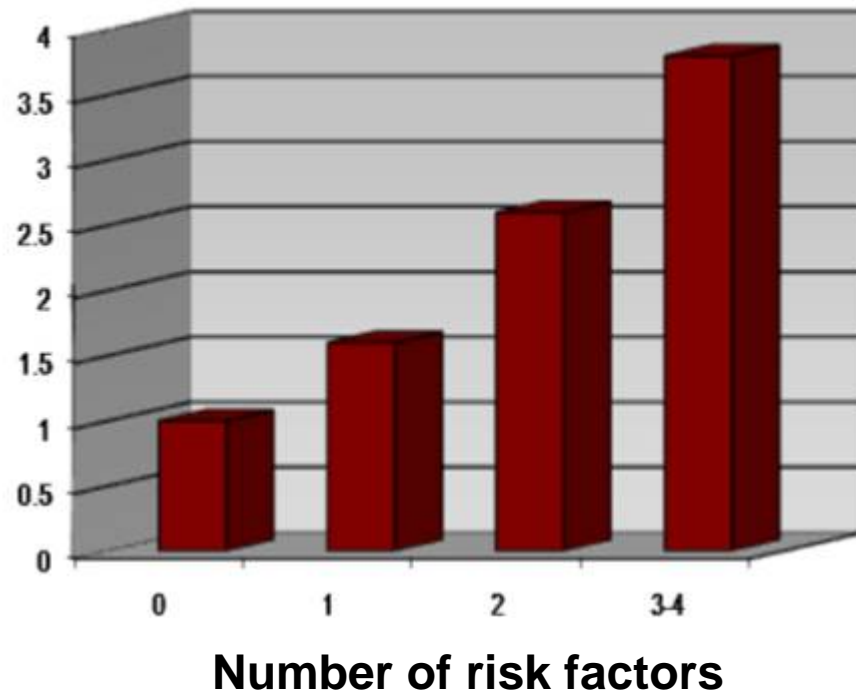


# Dosage effect

As CVD risk factors accumulate,  
AD dementia risk increases

- If we count risk factors...

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



# Statins to prevent AD



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

**McGuinness B et al, 2016; CD003160 (1)  
Cochrane Database of Systematic Reviews,**

# Physical activity = protective

**AGE IS NO BARRIER. IT'S A LIMITATION  
YOU PUT ON YOUR MIND.**



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

<sup>1</sup>Jedrziwski et al (2007). Alz Dem; 3:98-108; <sup>2</sup> Lautenschlager et al (2008) JAMA; 300(9):1027-1037; <sup>3</sup>Ravaglia et al (2007) Neurology; <sup>4</sup>Larson et al (2006) Ann Intern Med; 144:73-81; <sup>5</sup>Laurin et al, Arch Neurol 2001;58:498-504; <sup>6</sup>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

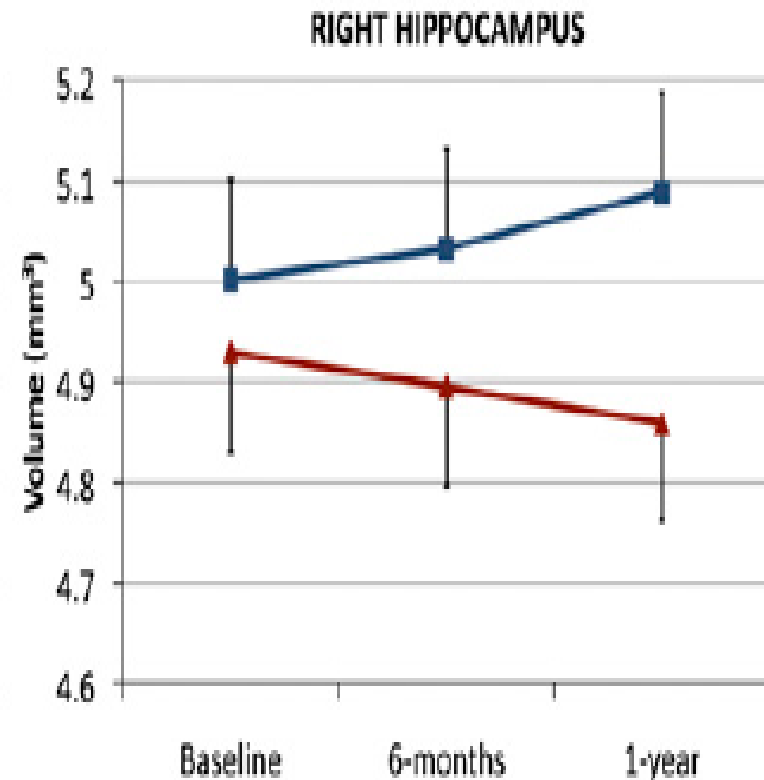
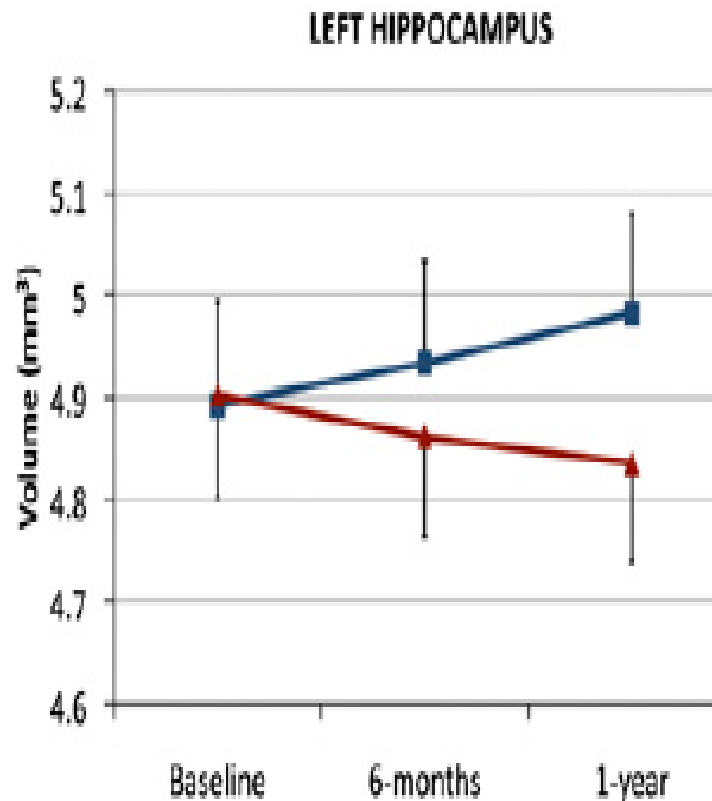
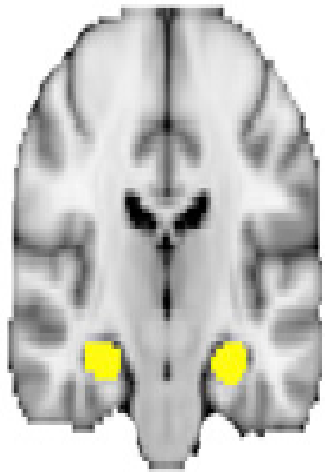
# Physical activity

- **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<sup>2</sup>**
- **Combine with social and mental activity better?**

Denkinger et al. *Z Gerontol Geriatr* 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



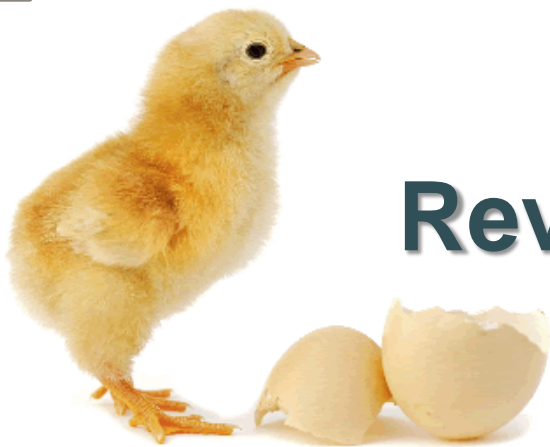
Erickson et al., 2011

# 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](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)<sup>1</sup>**
- **Dose - response relationship evident<sup>1</sup>**
- **Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence<sup>1</sup>**
- **Results held when covariates in source studies were controlled for<sup>2</sup>**

<sup>1</sup>Valenzuela MJ. Sachdev P. (2006). Psychol Med. 36(4): 441-454;

<sup>2</sup>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<sup>1</sup>**
  - 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<sup>2</sup>**
  - 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<sup>1</sup>

- 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
- All 3 gps maintained IADLs > controls @ 10y
- Speed gp: > still driving, < dementia <sup>2</sup>

<sup>1</sup>Rebok GW, JAGS 2014; <sup>2</sup>AAIC 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 change<sup>1</sup>
- Obesity paradox – late life overweight ≠ risk factor, ? protective

<sup>1</sup>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  $\leq$  8% of calories



# **Mediterranean diet: PREDIMED**

- **447 healthy, mean age 67, hi CV risk no CV  $\Delta$**
- **RCT: Medi + 30g/d nuts\* v Medi + EVOO (1 litre/week) v Control ( $\downarrow$ 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/ $\omega$ 3 ?
- 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 Epidemiol 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, curcumin**
- **DHA, omega 3**
- **Fo-ti root**
- **Soy isoflavone**
- **Vitamin E, Selenium**
- **Folate, B6, B12**
- **Saffron**
- **Brahmi**
- **Huperzine A**

**Ginkgo  
leaves**



**Member of  
ginger  
family**



# 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<sup>u</sup> 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

Matthews et al. *The Lancet*, 2013. [http://dx.doi.org/10.1016/S0140-6736\(13\)61570-6](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](http://dx.doi.org/10.1016/S0140-6736(13)60777-1)



# US dementia 1997-2008 and 2000-12

- Framingham Heart Study<sup>1</sup>: dementia incidence in elderly declined by  $\approx 20\%$  per decade between 1977 and 2008
  - only those with  $\geq$  high school education
- Health and Retirement Study<sup>2</sup>  $\approx 10,000+$  at each wave, all 65yo +, mean  $\approx 75$ yo
- Prevalence 11.6%  $\rightarrow$  8.8%
- More education accounted for some of 2.8% $\downarrow$

<sup>1</sup> Satizabal CL, NEJM 2016

<sup>2</sup> 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  $\geq 6$ ; cognition at or slightly below mean for Finnish norms (eg,  $\leq 26$  MMSE)**

Ngandu et al. *The Lancet*. 2015;

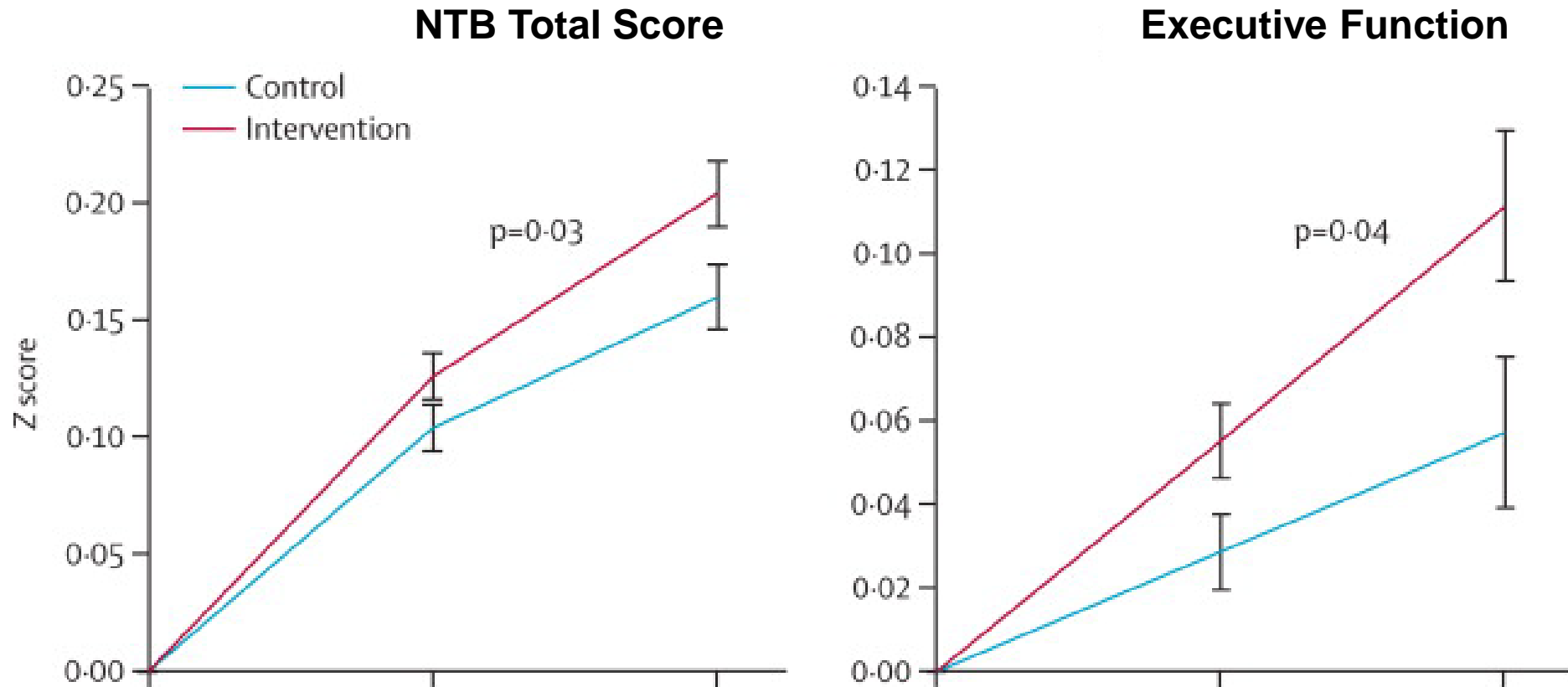
[http://dx.doi.org/10.1016/S0140-6736\(15\)60461-5](http://dx.doi.org/10.1016/S0140-6736(15)60461-5)



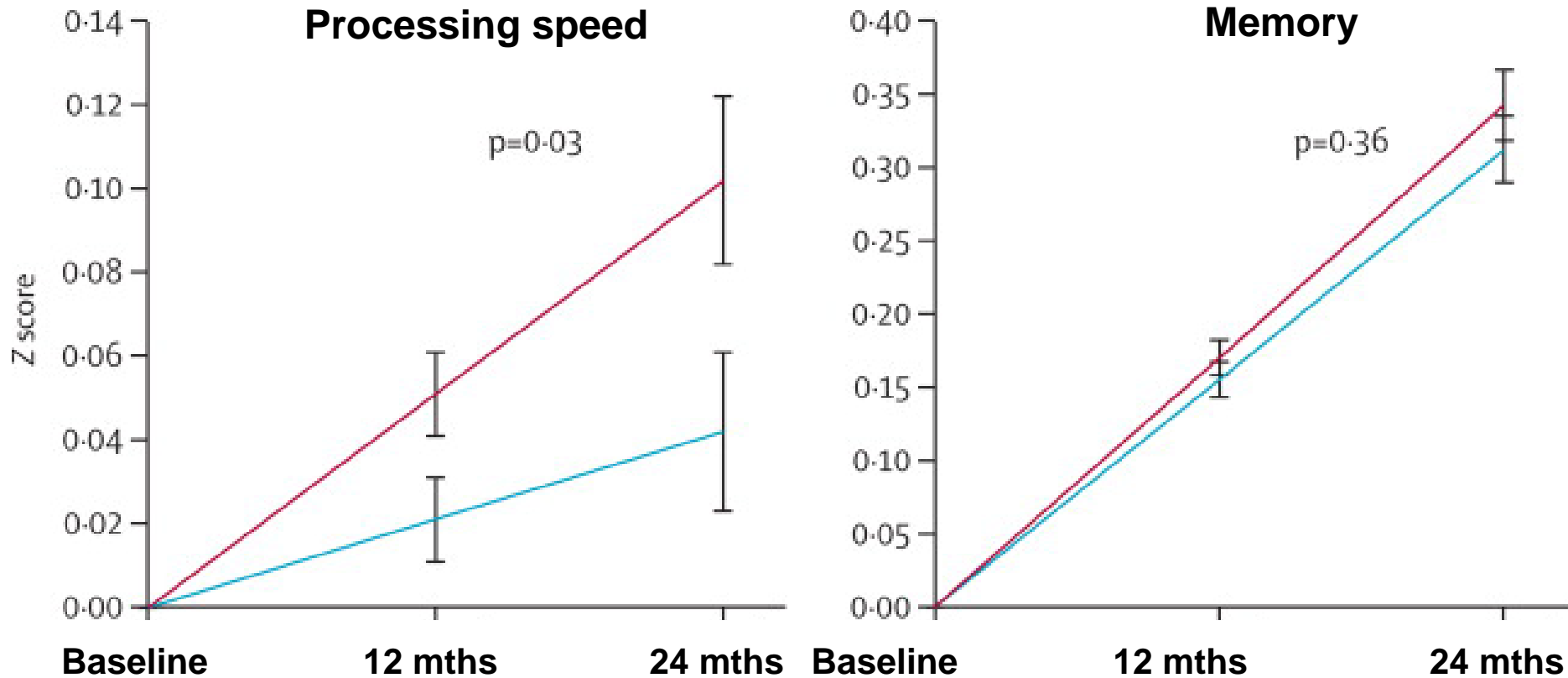
# Finger intervention

- **Intervention**
  - **Diet**
  - **Cognitive training**
  - **Exercise – PMR and aerobic**
  - **Manage metabolic and vascular risk factors**
  - **Social activities**

# Mean change in cognition over 2 years



# Mean change in cognition over 2 years



# **Prevention of Dementia By Intensive Vascular Care (preDIVA) trial**

- **Multicomponent intervention targeting vascular**
- **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<sup>o</sup> 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.**
- **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

**Moll van Charante EP, Lancet 2016**

# 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](http://www.cheba.unsw.edu.au)**



# Large studies underway

- **A4 Study**
- **DIAN – TU**
- **Alzheimer Prevention Initiative (Colombia)**
  
- **Prevent MCI → AD**
  - **Tau therapeutics**
  - **$\beta$ -secretase inhibitor**



**Can AD be prevented?  
Not yet but ...  
..may be delayed**

**[yourbrainmatters.org.au](http://yourbrainmatters.org.au)**

- **Look after your heart**
- **Be physically active**
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# Thank you

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