

# Can Alzheimer's disease be prevented?

*Henry Brodaty*

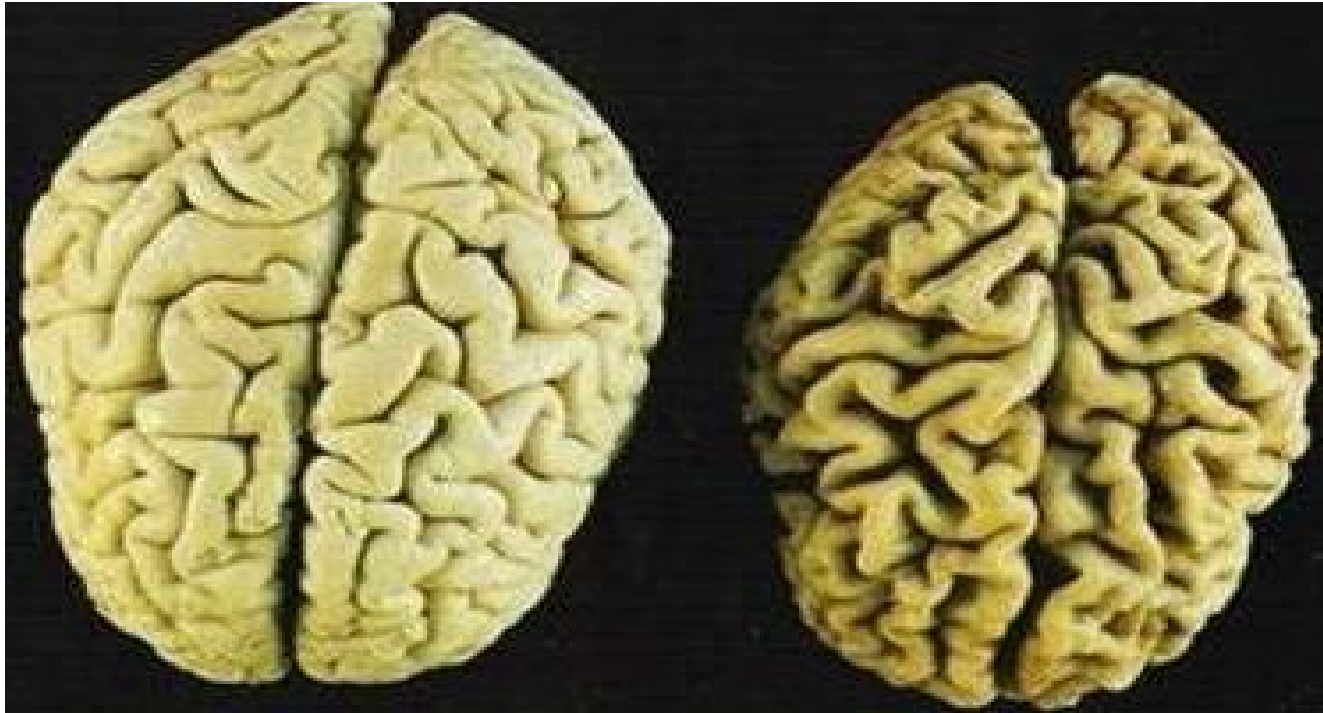
Never Stand Still

Medicine



# Can we prevent dementia?

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

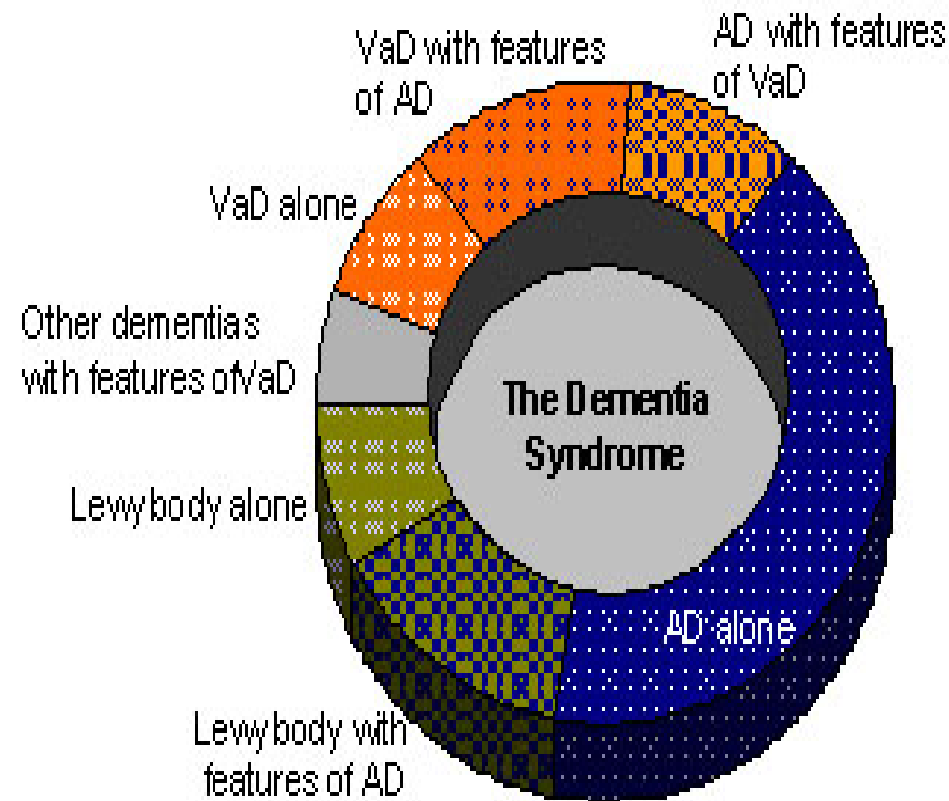


# Elimination vs Postponement

- **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)

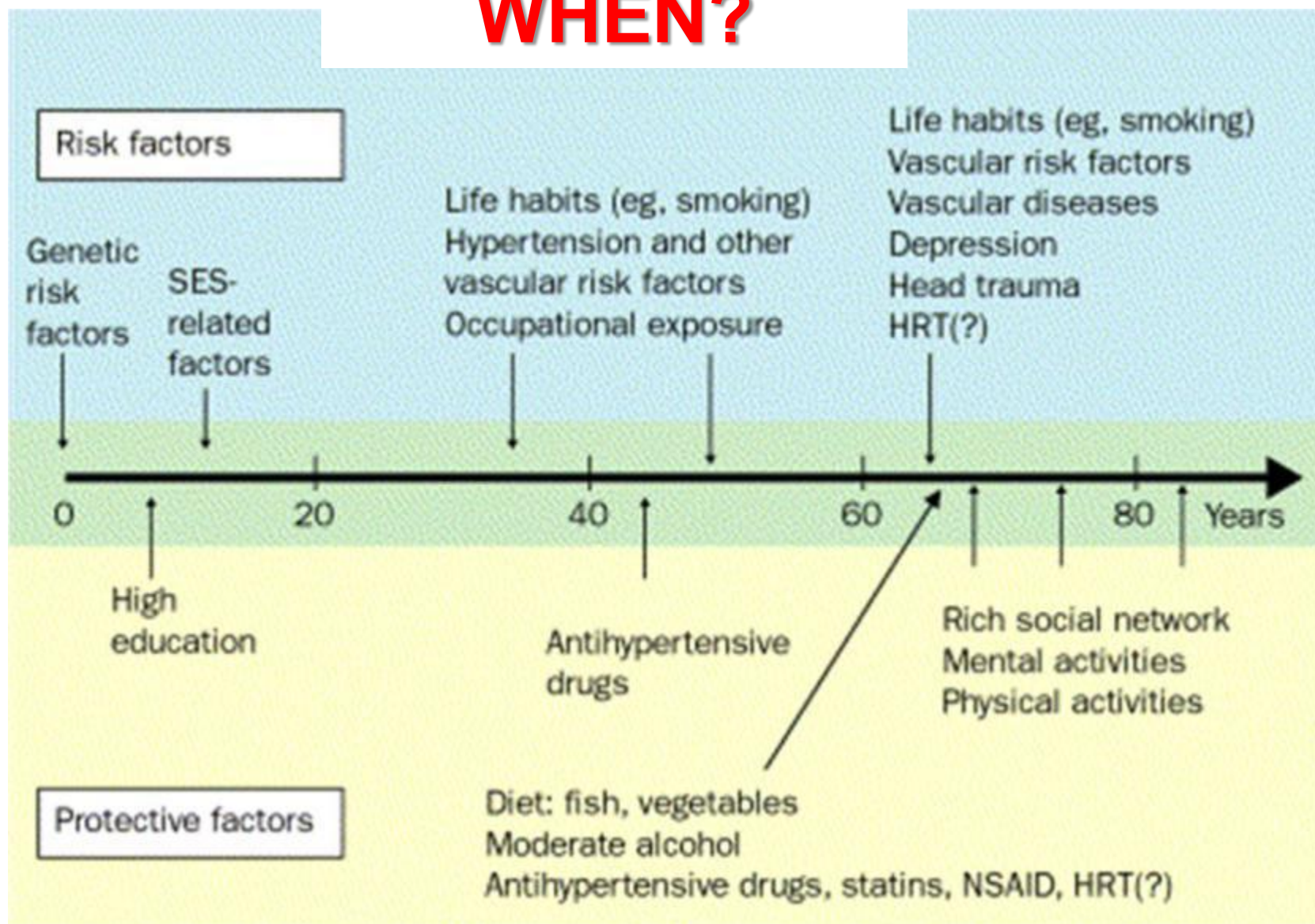
# **WHAT** are we aiming to prevent: **Dementia, AD, VaD, Mixed dementia?**



- **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)**

# WHEN?



# 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

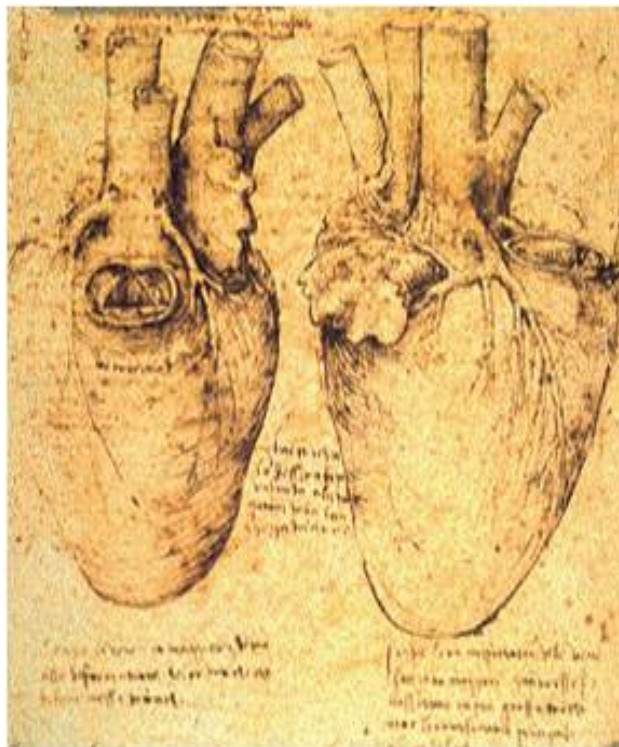


- **Look after your heart**
- **Be physically active**
- **Mentally challenge your brain**
- **Follow a healthy diet**
- **Enjoy social activity**

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



# Cardiovascular Factors



**The human heart  
Leonardo Da Vinci**

# Blood Pressure (BP) and Dementia

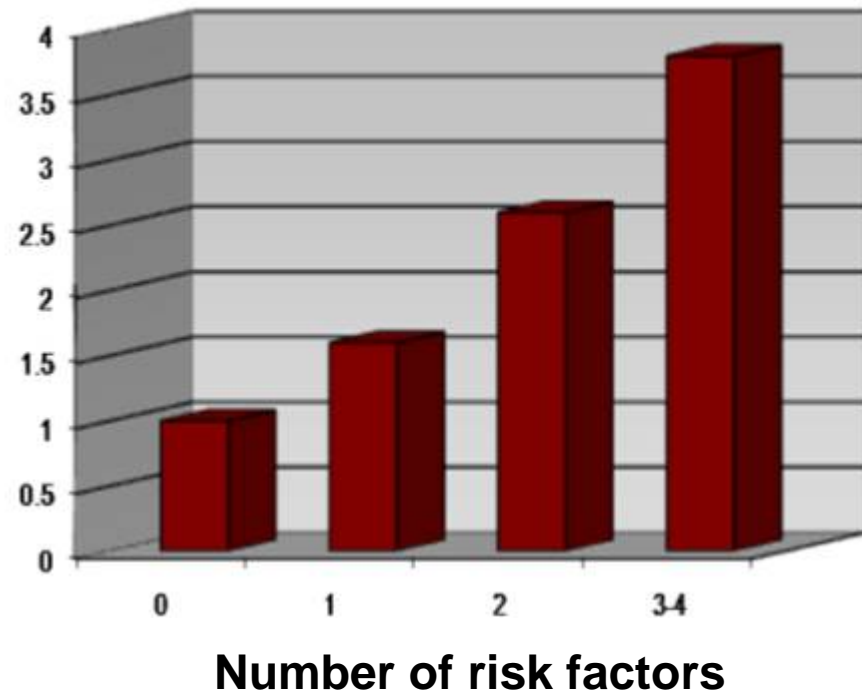
- Mid-life hypertension associated with late-life dementia
- BP ↓ before dementia onset
- Hypertension Rx → risk ↓
- Each year of Rx → dementia risk ↓
- 60% ↓ risk of all dementia and AD
- 5 RCTs conflicting results
- Can harm if lower BP too much in older old



# Dosage effect

**As CVD risk factors accumulate,  
AD dementia risk increases**

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



# Do anti-hypertensives prevent dementia

- Mixed results from studies
- HYVET study 80yo+
- Indapamide  $\pm$  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**

**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



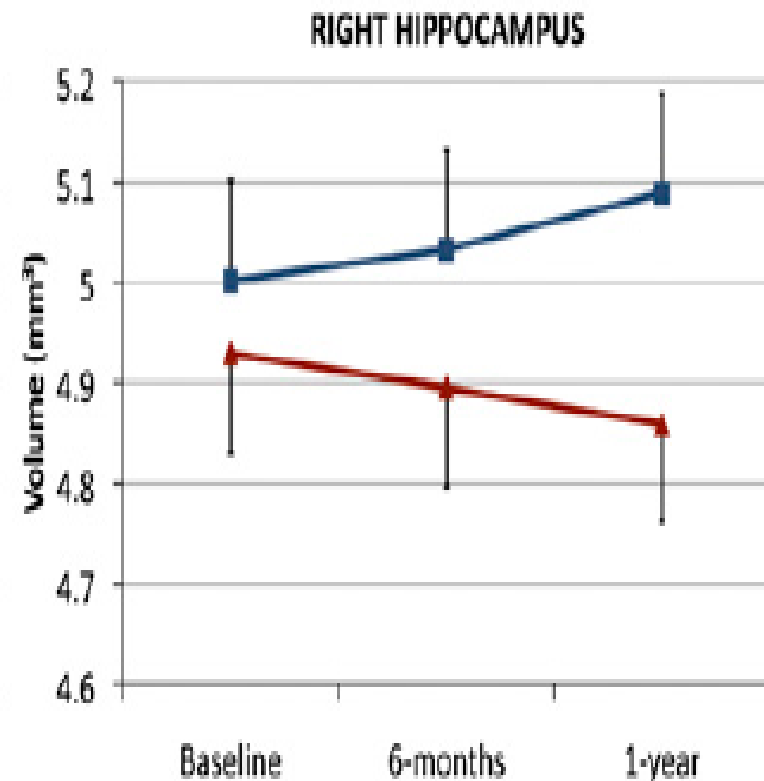
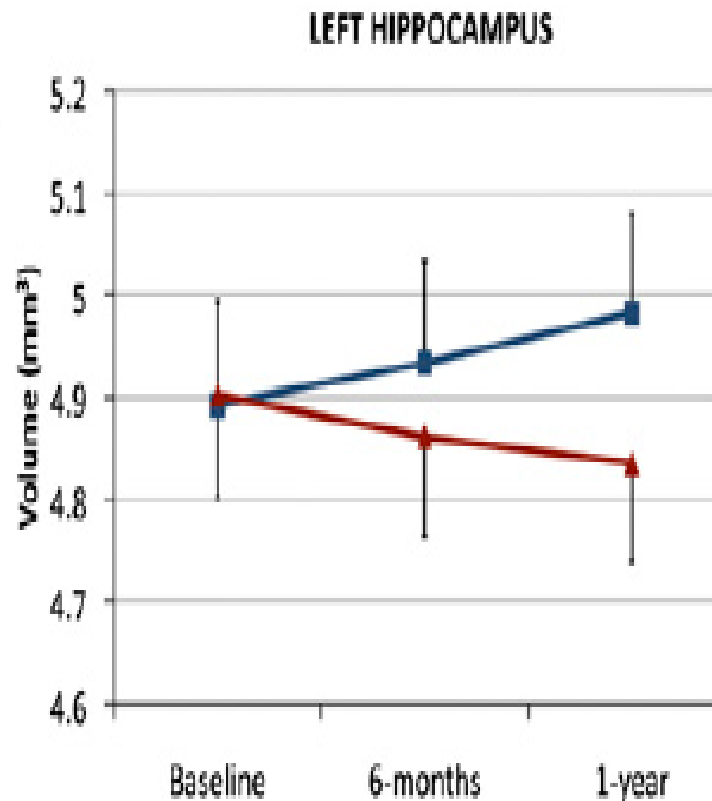
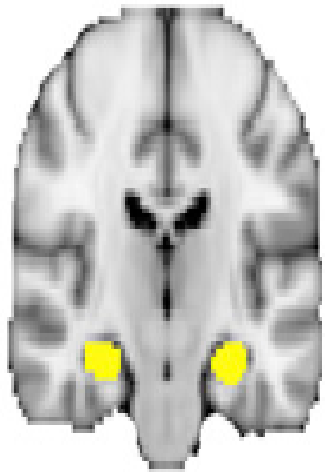
# Physical activity

- **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

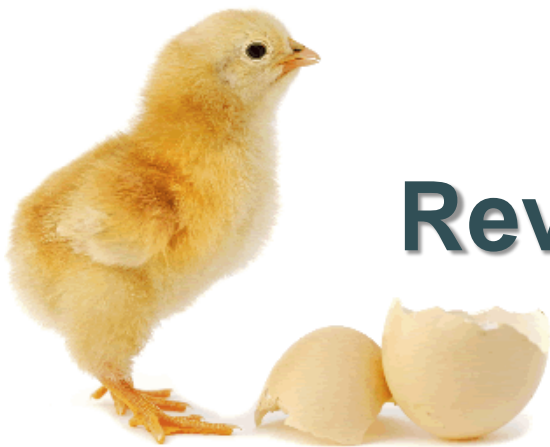
# Dose of Exercise for Brain Health

- **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

# 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 groups maintained those domains at 10y; but not the memory group
- All 3 gps maintained IADLs > controls @ 10y
- Speed group: > 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
  - 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<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**

# 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<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 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](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)

# 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 ( $\approx 50$  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% CI 1.32–1.85), < 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;**

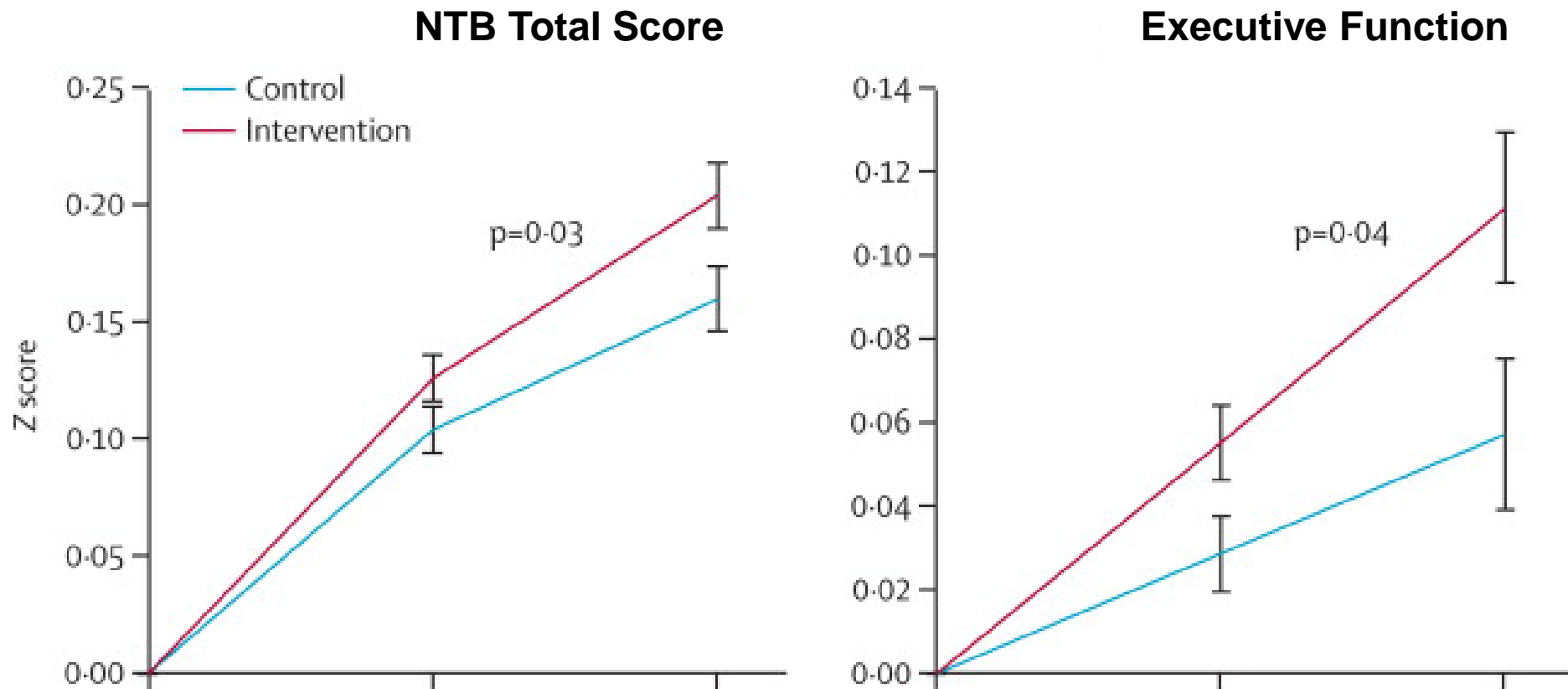
**[http://dx.doi.org/10.1016/S0140-6736\(15\)60461-5](http://dx.doi.org/10.1016/S0140-6736(15)60461-5)**



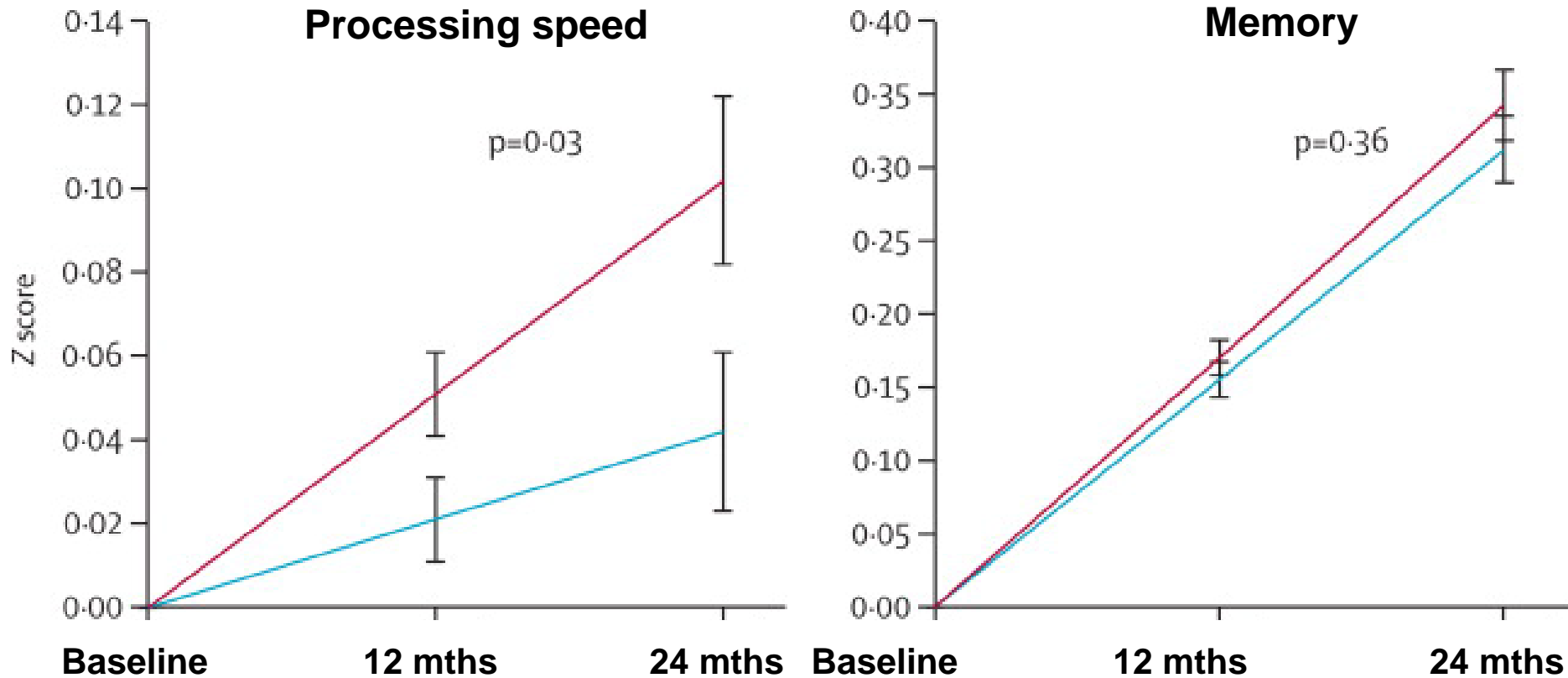
# Finger intervention

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

# Drug treatments

- Enzyme inhibitors
  - $\beta$  secretase
  - $\gamma$  secretase
- Immunotherapy
  - Active
  - Passive
    - Antibody – eg gantenerumab
    - solanezumab
  - Insulin nasal spray
  - Tau protein (Rember)



# The A4 trial

- Clinically normal, A $\beta$  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 amnesic MCI + positive biomarker – amyloid imaging or CSF
- **Methylene blue (Tau Rx)**
  - Participants with amnesic 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)**

**[www.cheba@unsw.edu.au](mailto:www.cheba@unsw.edu.au)**

**Dementia Collaborative Research Centre**

**[www.dementiaresearch.org.au](http://www.dementiaresearch.org.au)**

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