



Dementia: great expectations

Hope and realism

Henry Brodaty

Never Stand Still

Medicine



FIGHT ALZHEIMER'S
SAVE AUSTRALIA
FIGHTDEMENTIA.ORG.AU



Australian Government

**National Health and
Medical Research Council**

N H M R C

**NHMRC National
Institute for Dementia
Research (NNIDR)**

Today's topics

- **Terminology**
- **Cause of AD**
- **Why this is important**
- **Diagnosis**
- **Prevention**
- **Drug treatment of AD – the silver bullet**
- **Behavioural and Psychological Symptoms**
- **Conclusions**

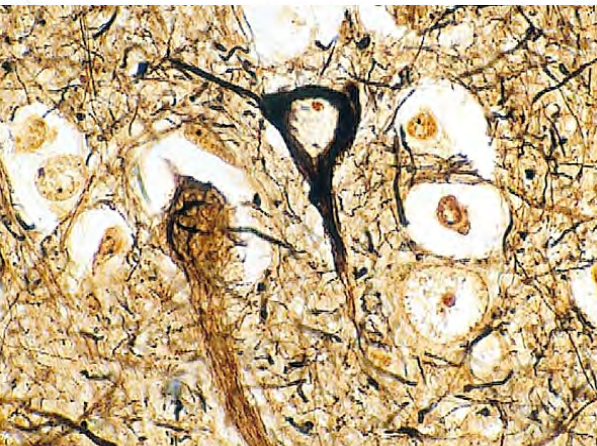
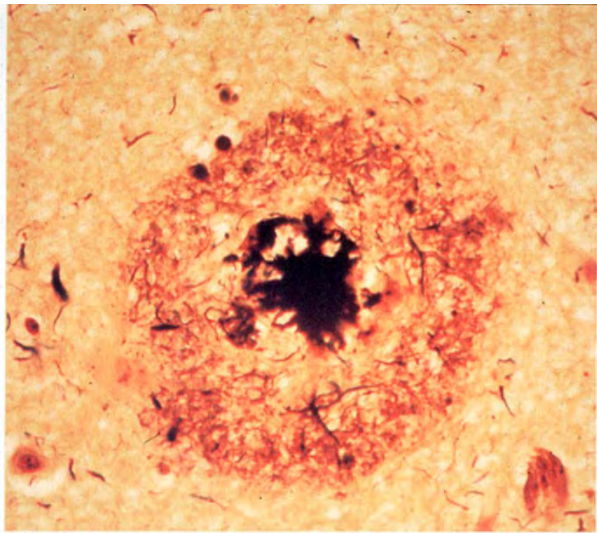
Let's get our terms straight

- **Dementia/s = umbrella term**
 - **Alzheimer's disease (AD)**
 - **The other (non-Alzheimer's) dementias**
 - **Vascular dementia**
 - **Lewy body dementia**
 - **Fronto-temporal dementia**
 - **100 others**
- **Mild Cognitive Impairment**
- **Cognition**



Cause: Brain in AD

- Brain atrophy, loss of nerve synapses and branches
- Breakdown of APP releasing $A\beta$ protein $\rightarrow$ clumps $\rightarrow$ toxic to brain $\rightarrow$ plaques
- Phosphorylated tau $\rightarrow$ paired helical filaments $\rightarrow$ NFTs
- Chemicals in brain $\downarrow$ esp ACh



The cause of AD??

- **Make excess A β protein**
 - **Familial AD, mutations in APP, PSEN1 or 2**
 - **Onset in 40s, 50s.**
- **Decreased clearance of β - amyloid**
 - **Late onset AD, ApoE4**
- **Role of tau**
- **Many other pathways involved, eg...**

Many other factors ...

- **Insulin resistance in brain**
- **Inflammation**
- **Support cells (astrocytes, glial cells) in brain**
- **Progranulin**
- **Repressor Element 1-Silencing Transcription factor (REST) protects neurons from oxidative stress and amyloid β -protein toxicity**
 - **decreased in AD and other dementias**

Cause: realism

- **For young onset autosomal dominant AD cause seems clear**
- **For late onset sporadic AD, we know risk factors and pathological paths but not cause**

Why dementia is important ... globally?

- 47 million people → 131 m by 2050
 - 2/3 in developing countries
- ≈10m new cases per year, every 3.2 seconds
- Cost US\$818 billion, 1.09% of global GDP

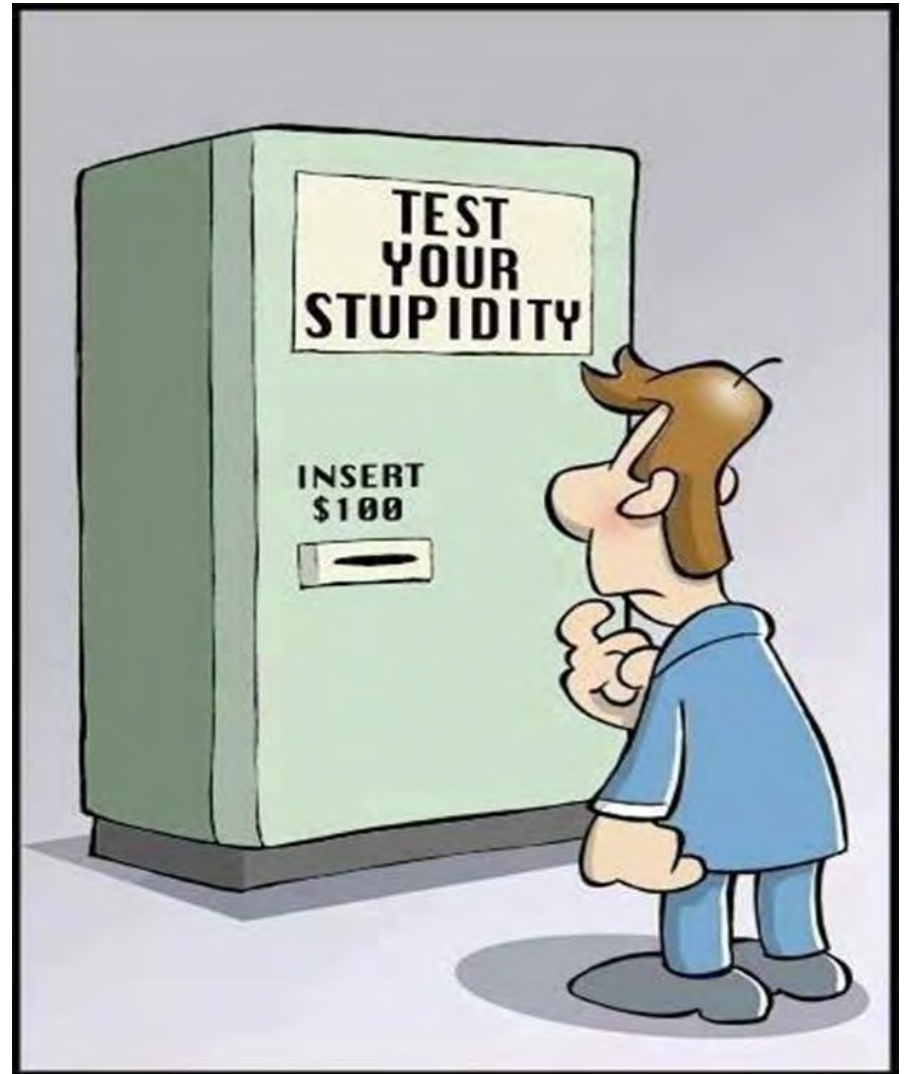
Why dementia is important in Australia?

- 413,000 in 2017 → 1.1 million by 2056 ¹
- 244 new cases of dementia each day in 2017
- Cost to community \$14 billion in 2017
 - 61% direct costs, 38% opportunity costs
 - → \$28b by 2056
- If 5% ↓ n^o of people ≥ 65 developing dementia
→ save \$5.7b from 2016-25 & \$120.4b by 2056
- 28,000 under 65 years of age ²
- Aboriginal people have higher rate

¹ *The Economic Cost of Dementia in Australia 2016-2056, NATSEM 2017*; ² *Dementia in Australia, AIHW, 2012*

Why dementia is important?

- Because we fear it



Why dementia is important?

- Because we fear it
- Because we are getting older as a population
- Because we are living longer as individuals
- Because age is the major risk factor for dementia
- Because we have it OR we know someone who has it
- Because we see what dementia does

The hope

- **Are numbers decreasing?**
- **Studies from Sweden, Denmark, Spain, Netherlands, USA show that the number of *new cases* per each age group has declined in the last 20 years**
- **Better education, health care, diet, lifestyle may be responsible**

The realism

- **Prevalence, number of existing cases, is ↑**
 - **Ageing of population outweighs decline in new cases**
 - **People with dementia are living longer**
- **Obesity & diabetes epidemics may ↑ incidence**
- **Developing countries are ageing rapidly**

Diagnosing Dementia: the gap



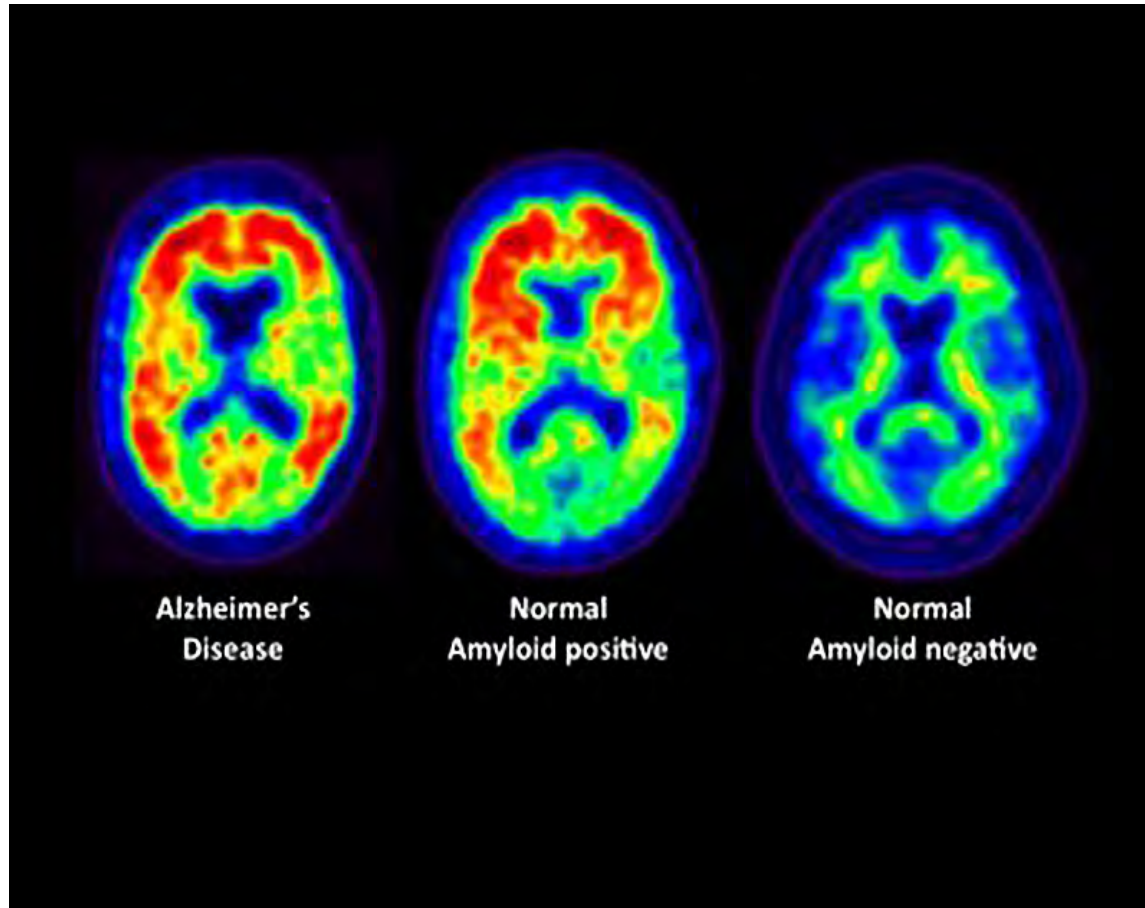
- **2-3 year gap from Sx to Dx**
- **50% of (mild) dementia undiagnosed in GP**
- **DTA, AA, LaTrobe and DCRC ‘Timely Diagnosis’**
 - **Aim to reach 5000 GPs**
 - **Face-face or online**

Diagnosis: the revolution

Tradition: History + Examination + Tests → Dx

- **Neuroimaging**
 - MRI scans
 - PET imaging, now of amyloid & tau protein
- **Cerebro-Spinal Fluid (Lumbar puncture)**
- **Genetics** - advances but not yet for most
- **Blood test** - advances but not yet

PET amyloid imaging: normal vs AD



- 35% persons 60+ amyloid+
- ↑ risk clinical progression
- Will all amyloid +ve develop AD?

Lumbar puncture = Spinal tap

- **Change in proteins in CSF**
 - **Decrease in amyloid beta protein and increase in tau and phospho-tau proteins**
 - **If all measures are normal in pt with mild memory disturbances almost excludes AD**

Diagnosis of AD - realism

- **Biggest challenge is in primary care**
- **No test 100% accurate yet**
- **No blood test sufficiently accurate to use yet**
- **The older the patient, the more likely brain will have multiple pathologies AD, α -synuclein, TDP43, vascular changes**
- **Predictive testing not accurate enough and not recommended**
- **Would you be tested today to see if you would develop AD in 2, 5 or 20 years?**

Can we prevent dementia?

- Disease **elimination**
 - eg smallpox vaccination
 - best prospect is AD vaccine for those at risk
- Disease **postponement**¹: delay AD onset by...
 - 2 years, ↓ prevalence by 20%
 - 5 years, ↓ prevalence by 50%

¹Brookmeyer et al. (1998)

Is early life the most important target?

- **60-70% 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-indigenous¹**

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



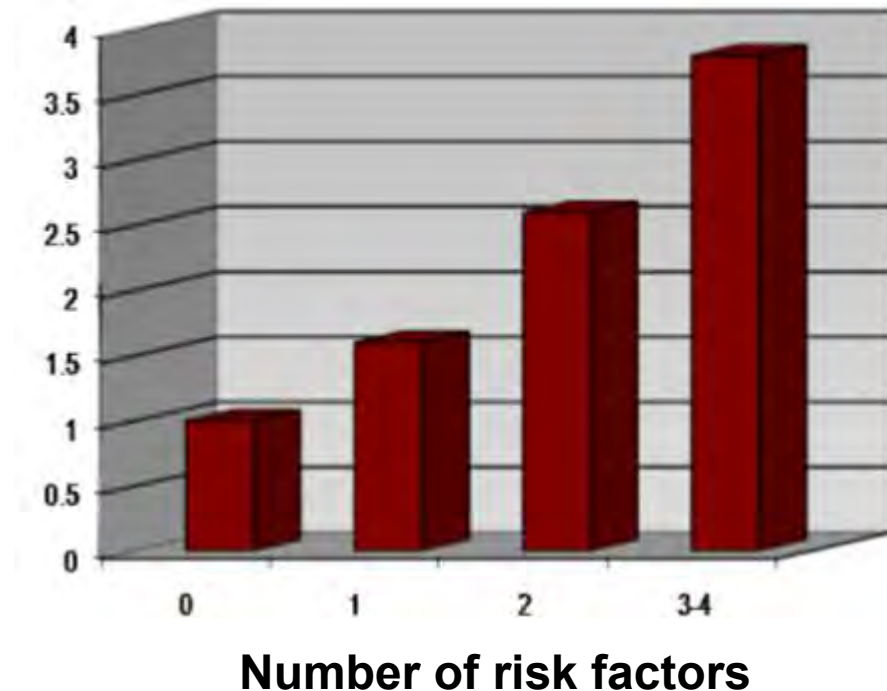
- **Look after your heart**
- **Be physically active**
- **Mentally challenge your brain**
- **Follow a healthy diet**
- **Enjoy social activity**

yourbrainmatters.org.au

Dosage effect

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

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



Statins to prevent AD

Two reviews in 2016 conflict:

- Good evidence that statins neither prevent nor increase risk of cognitive impairment or dementia¹
- Statins linked to reduced AD risk – differences by sex, race & statin ²



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

²Zissimopoulos JM et al, 2016, JAMA Neurology

Physical activity



Can exercise protect against dementia?

- **Preserve cognition and slow cognitive decline**
- **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 Trial²**
- **More is better – puffed, weights**
- **≥ 3 x per week; >150 min/wk, e.g. Perth Study³**
- **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; Lautenschlager N, *JAMA* 2008

The hope: physical activity ...

- Improves fitness
- Improves physical health - ↓ heart disease, Hi BP, diabetes, some types of cancer, osteoporosis, sarcopenia
- Reduces morbidity & mortality
- Improves mental health
- Improves confidence, quality of life

http://www.mednwh.unimelb.edu.au/research/health_promotion.htm

Physical activity: the realism

- **Reverse causality**
- **Effect size of physical activity**
- **Interaction of genetics and lifestyle**
- **Side effects possible if not done correctly**

Mental Activity



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 evident¹**
- **Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence¹**
- **Results held when covariates in source studies were controlled for²**

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

²Valenzuela MJ. Sachdev P. (2006) Psychol Med. 36(8): 1065-1073

Cognitive training

- **Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly¹**
 - 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 dementia²**
 - 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.



Realism mental training

- **Reverse causality**
- **Which mental activity**
 - **Crosswords?? Sudoku??**
 - **Musical instrument? New language?**
 - **Computer cognitive training, are benefits:**
 - **Sustained?**
 - **Generalise beyond computer?**

Diet



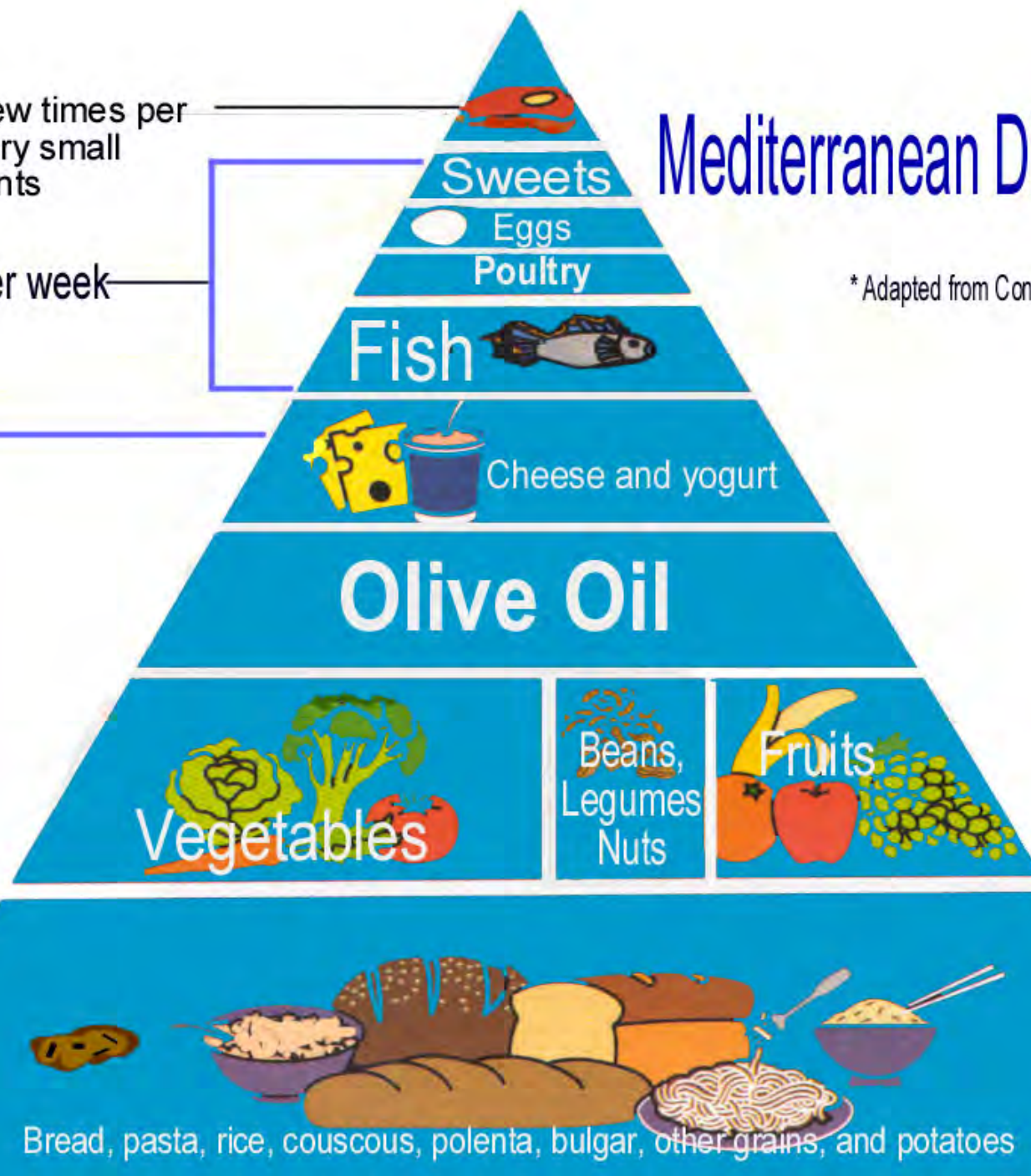
Red meat - a few times per month in very small amounts

A few times per week

Daily

Mediterranean Diet Pyramid*

* Adapted from Consumer Reports, Nov'94



Bread, pasta, rice, couscous, polenta, bulgar, other grains, and potatoes

Nutrition / Supplements



- Alcohol ? moderate
- Fish/Seafood/ $\omega 3$?
- Vitamin D ?
- Caffeine ?
- Vitamin E ?
- Vitamin C x

Food sources better than supplements

Smoking and AD

- **Current smoking**
 - increase risk for AD
- **Previous smoking**
 - Risk not significantly increased

Anstey K. Am J Epidemiol 2008

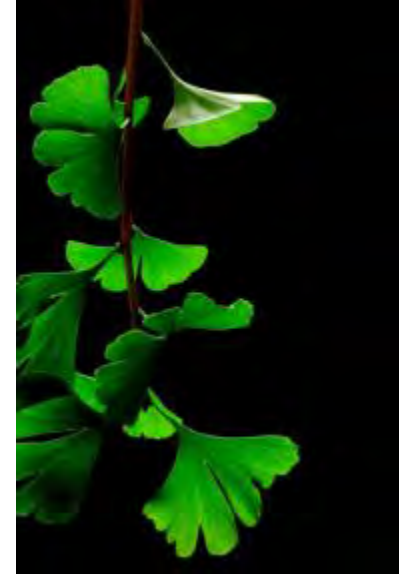
Alcohol

- **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**

Diet: realism

- **Diet, exercise, vascular health, diabetes, obesity – all linked**
- **Obesity in mid-life is a risk factor; late life not**
- **RCTs for long periods impossible**

Other factors

- HRT – neither harmful or beneficial close to menopause
- Hearing loss ↑ risk 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^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)**

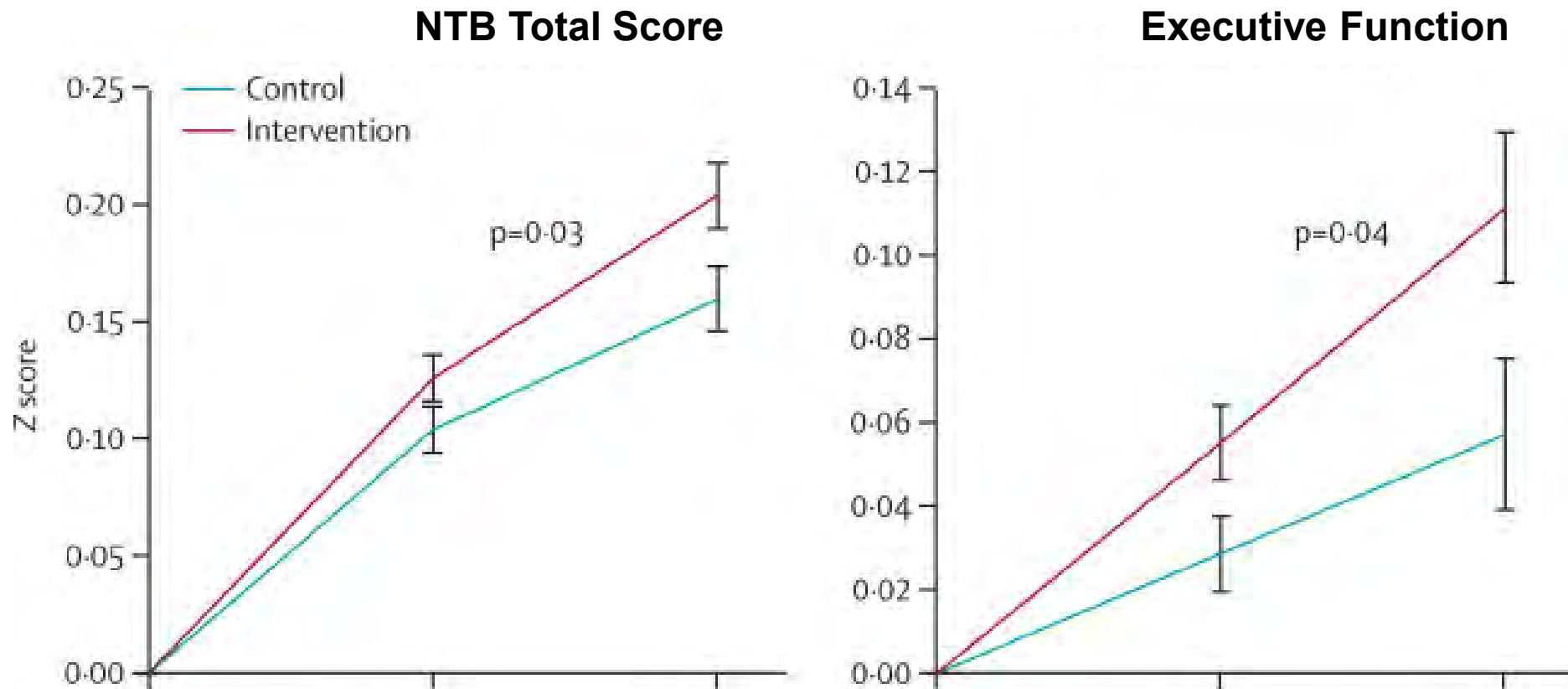
Barnes & Yaffe, 2011; Norton et al, 2014



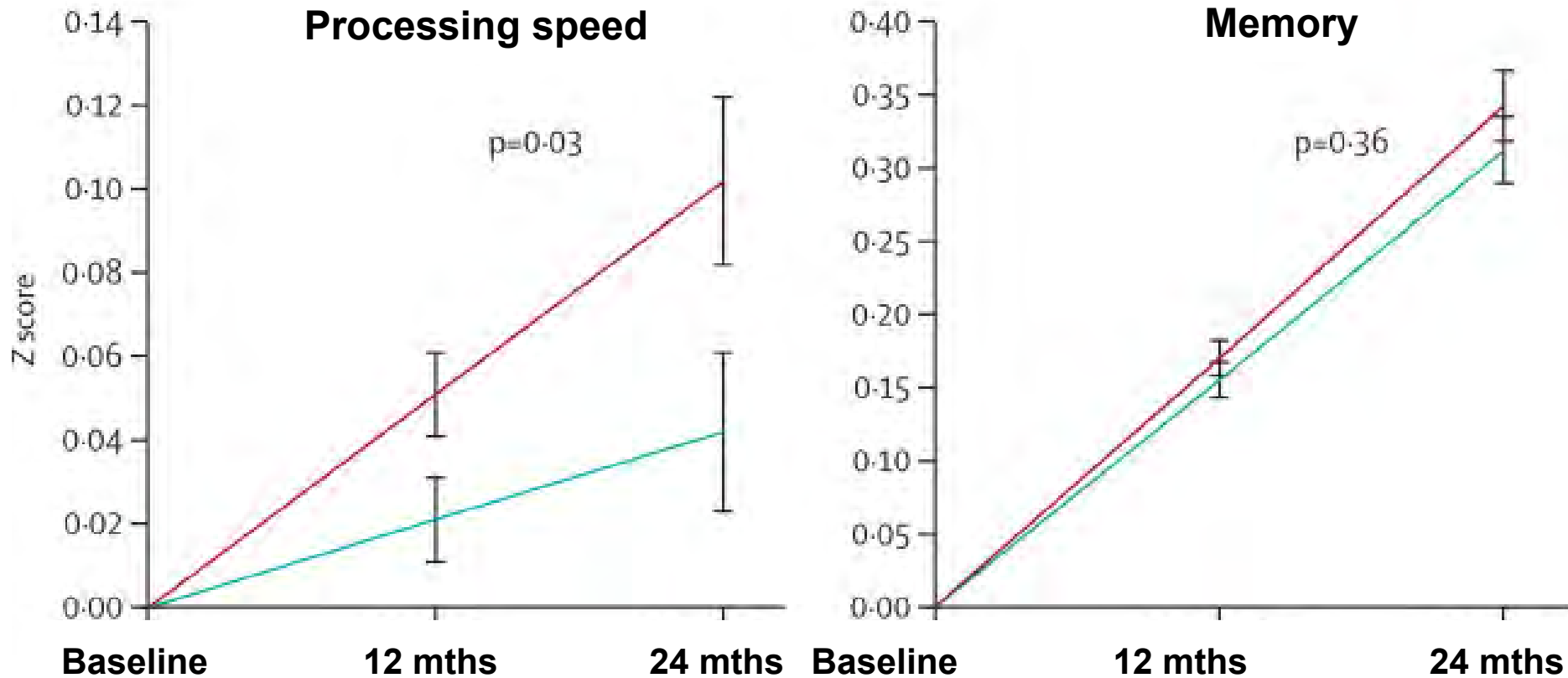
Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- **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**
- **New cases of all-cause dementia and AD did not significantly differ between groups.**
- **Signif. less non-AD dementia in intervention (1%) vs control group (2%) (HR 0.37; p=0.007)**
- **Subgroup with untreated hypertension adherent to intervention, significantly fewer new dementia cases (4% vs 7%; HR 0.54; p .02)**

Internet based prevention trials

- **Healthy Aging Through Internet Counselling in the Elderly (HATICE)** <http://www.hatice.eu/>
- ***Maintain Your Brain***
 - NHMRC funded, 5 years, 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 prevention trials

- **A4 Study - Clinically normal, A β positive**
- **DIAN – TU – Dominantly inherited AD**
- **Alzheimer Prevention Initiative (Colombia)**

- **Prevent MCI → AD**
 - **Tau therapeutics**
 - **β -secretase inhibitor**

Drug trials = the hope



Strategies

- **Anti-amyloid**
 - Enzyme inhibitors
 - Immunotherapies – active, passive
- **Anti- tau**
- **Neurotransmitter enhancers**
 - Cholinesterase inhibitors
 - Memantine
 - Serotonin receptor antagonists
- **Others: intranasal insulin, RAGE, NGF**

Anti-amyloid therapies - 1

- **Reduce production of A β protein**
 - **α -secretase upregulation**
 - Etazolate (EHT-0202)
 - **β -secretase inhibition**
 - Rosiglitazone (stimulate PPAR γ) - failed
 - Verubecestat (Merck) – failed
 - **γ -secretase inhibition**
 - Semagecestat –worse than control

Anti-amyloid therapies - 2

- Immunisation to promote A β clearance
 - Active immunisation
 - AN-1792 → sterile meningoencephalitis
 - Shorter peptides to avoid T-cell activation
 - Passive immunisation with antibodies
 - Bapineuzumab – ceased, negative result
 - Solanezumab – primary outcome negative (Nov 2016)
 - Gantenerumab - trial stopped; but ↓PET plaque (ns) and ↓ tau in CSF (signif)
 - Aducanumab – Phase 1b positive
 - IV immunisation with immunoglobulin - failed

Anti-amyloid therapies - 3

- **Prevent A β aggregation**
 - **Tramiprosate (3APS) – ceased**
 - **PBT1 (clioquinol) – ? eye toxicity**
 - **PBT2 – disrupts Zn, Cu required for aggregation**

Anti-tau

- **Modulation of phosphorylation**
 - Glycogen synthase kinase 3 β (GSK3 β) & Cyclin dependent kinase 5 (CDK5) inhibitors
 - Activate phosphatase
- **Tau-directed immunotherapy**
 - Active or Passive
- **Small molecule inhibitors of protein aggregation**
 - Methylthioninium (methylene blue, Rember)
- **Microtubule stabilisation Epothilone D (EpoD)**
- **Antisense oligonucleotides**

Himmelstein DS et al Pharmacology & Therapeutics 2012

DeVos et al. Science Translational Medicine 2017

Promote neuronal function

- **Mitochondrial dysfunction**
 - Latrepirdine (Dimebon) - failed
- **Nerve growth factors: Delivery to brain is barrier**
 - Viral vectors
 - Nanotechnology
- **Inhibit RAGE (receptor for advance glycation end-products)**
- **Anti-inflammatory treatments – TNF- α blocker**

Other treatments

- **5-HT₆ Receptor antagonist, idalopirdine**
 - Encouraging results in 2014 (with donepezil)
 - higher doses no benefit; lower doses ??
- **Long acting intra nasal insulin**
- **Deep brain stimulation targeting limbic memory circuit in pts with mild AD**
- **Nerve growth factor**
- **Nutraceuticals – Axona, Souvenaid**

AD Cures – graveyard

- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Semagacestat (γ -secretase inhibitor)
- Bapineuzemab
- Verubecestat (β -secretase inhibitor)
- Celecoxib
- Dimebon
- Intravenous Immunoglobulin

Why failures despite Phase 1/2 trial success?

- **Wrong time? Too late in disease process?**
- **Wrong target? Amyloid may not be the one**
- **Wrong patient? 30% of trial participants did not have AD as per amyloid PET Scans**
- **Wrong model? May need multiple drugs simultaneously eg TB, H. bacter, leukaemia**

Realism – drug treatments



- No silver bullets
- Billions invested with no return
- Pharma still interested but some not
- Most trials for AD
- World Dementia Council aim for cure by 2025 unlikely¹

‘The mainstay of treatments for AD is supportive care from family ..’²

¹ Cummings J et al, 2016 Alz Research & Therapy

²Scheltens P et al, Lancet, 2016:388:505-17

Behavioural and Psychological Symptoms of Dementia BPSD



What are BPSD?

- **Agitation**
- **Aggression**
- **Calling out/ screaming**
- **Disinhibition (sexual)**
- **Night time disturbance**
- **Shadowing**
- **Swearing**
- **Wandering**
- **Depression**
- **Anxiety**
- **Apathy**
- **Delusions**
- **Hallucinations**
- **Irritability**
- **Elation/euphoria**

The bio-psycho-social framework

**Socio-
environmental**

Interpersonal

Biological

Psychological

How to intervene: *Environment*

- Secure grounds
- Personalised space
- Non-institutionalised environment
- Home-like
- Colour, furnishings, architecture, lighting
- Resident mix
- Size of facility
- Aroma therapy
- Pets
- Robots
- Toys, dolls

Interpersonal

- **Family carers can be effective therapists for people living in the community (ES 0.34) ¹**
- **Person centred care training reduced agitation in NHs – sustained 4 months later & cost-effective ²**

¹Brodaty H & Arasaratnam C, Am J Psychiatry, 2012

²Chenoweth L et al, Lancet Neurology, 2009

Psychological

- **Humour therapy ↓agitation, ↓depressⁿ, ↑QoL^{1,2}**
- **Tailored Activity Program^{3,4} – OT led**
- **Others – Volunteers, music, singing, dance therapy, Integrating kindergarten/ babies**

¹Low LF et al BMJ Open 2013; ² Brodaty et al Am J Ger Psych 2014

³ Gitlin L et al, Am J Ger Psych 2008 & ⁴Gerontologist, 2009



Key elements

- Engagement
- Understanding
- Time

Barriers

- Time
- Money
- Staff
- Attitudes
- Training



Pharmacological interventions

Rx for BPSD - summary

- **Antipsychotics** – effect on aggression, psychosis, ?agitation, but ↑risk of AEs, stroke, death
- **Antidepressants** – negative trials for depression
 - Citalopram effect on agitation, AEs - QTc↑, cog↓
- **Analgesics** – effect on agitation (paracetamol 3g/d)
- **Anticonvulsants** – no or little effect
- **Benzodiazepines** – risk of confusion, falls
- **Cholinesterase inhibitors** – effect on apathy
- **Memantine** ?benefit for agitation/aggression/delusions/ hallucinations

HALT study: Deprescribing antipsychotics in NHs

- **Identify residents on antipsychotics ≥ 3 m**
- **Permission from NHs, families & GPs**
- **Train nurse champions in nursing homes to teach other nurses how to manage BPSD**
- **Academic detailing of GPs**
- **$\approx 75\%$ cease antipsychotics; remain off for 12m**
- **No re-emergence of behaviours**
- **No significant drug substitution**

Conclusions

- Research on dementias - challenging & vibrant
- The more we know, the more we don't know!
- Research focus on AD but strong groups working in Vascular dementia, LBD, FTD
- Research can drive drug Rx *and* improvements in diagnosis and care
- Australia has leading researchers in basic, diagnostic, translational, carer, residential areas
- Funding for research is major issue
- Australian Dementia Registry would boost care & research

Thank you

Centre for Healthy Brain Ageing (CHeBA) UNSW

www.cheba@unsw.edu.au

Dementia Collaborative Research Centre

www.dementiaresearch.org.au

h.brodaty@unsw.edu.au