

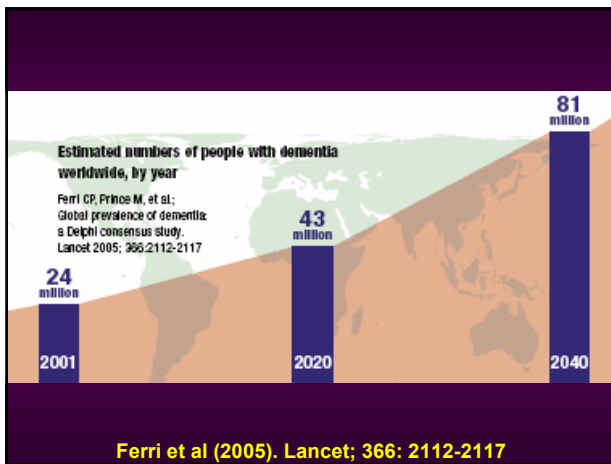
Prevention of Alzheimer's Disease

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www.med.unsw.edu.au/adfoap

International Epidemiology

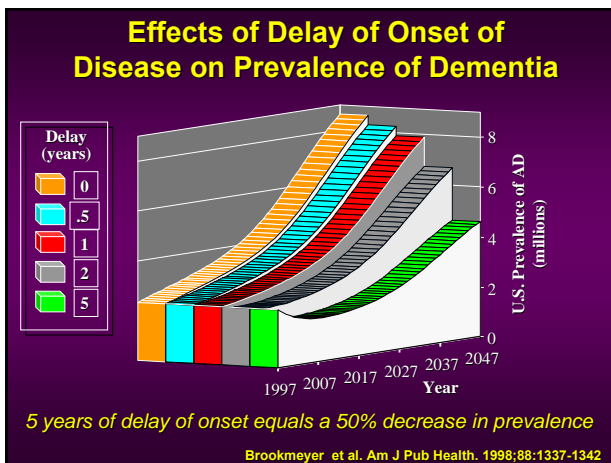
- > 24 million people worldwide with dementia
 - 60% in developing countries
- Set to double every 20 years to 81 million in 2040
 - 71% in developing countries
 - Rate of increase 3 – 4 times higher in developing countries

Ferri et al (2005). Lancet; 366: 2112-2117



Elimination vs Postponement

- Disease elimination
 - eg smallpox vaccination
 - best prospect is AD vaccine
- Disease postponement (Brookmeyer R, 1998)
 - delay AD onset by
 - 2 yrs → ↓ prevalence by 20%
 - 5 yrs → ↓ prevalence by 50%



Delay onset + delay progression

- Estimate 26.6m people with AD
- By 2050 → x4 = 1 in 85 world population
- About 43% @ high level = NH care
- Delay onset by 2 yrs, reduce by 22.8m
 - 12.3m in early & 10.5m late stage
- Delay progression by 1 yr, extra 2.8m
- Delay onset by 1 yr and progression by 1 yr → 9.2m fewer: (8.7m in late stage)

Brookmeyer R 10.06.07

Cost Implications

- World wide cost US\$315b ¹
- Life-time health savings by *eliminating* dementia ²
 - 3% in men
 - 8% in women
- But delay in progression may cost more in total

¹Wimo, Winblad et al, 2005

²Bonneux et al, *BMJ*, 1998;316(7124):26-29

Primary Prevention of AD



Need to understand risk and protective factors in order to target prevention



Strong risk factors for AD

- Age
- Family history
- Down's syndrome
- Genes
 - Familial AD
 - C14, C1, C21
 - Sporadic AD
 - ApoE4, multiple other genes

Genetic contribution

Population attributable risk

- APP 0.02%
 - PS1 0.24%
 - PS2 0.04%
- } 0.3%



Susceptibility genes (some of many ...)

- | | | |
|-------|---------------|-----------|
| ApoE* | VLDL receptor | α2MG |
| AACT | LRP | NACP, etc |
- Apo ε4 ≅ 10% of AD cases

Hofman A 11.06.07

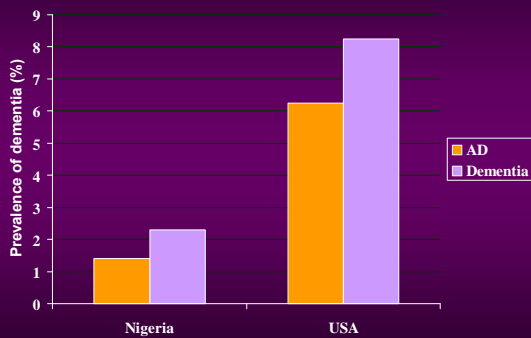
Environment and AD



- Prevalence study of dementia in Africans in:
 - Ibadan, Nigeria
 - Indiannapolis, USA¹

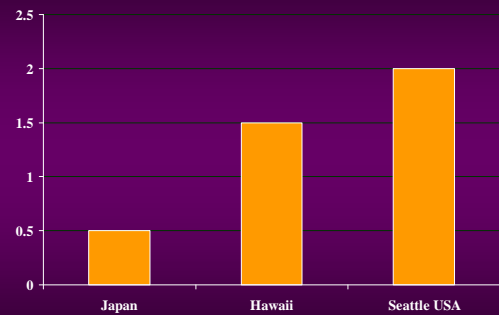
¹Hendrie H, *Am J Psychiat* 1995;152: 1485-92

Ibidan-Indiannapolis study¹



¹Hendrie H, *Am J Psychiat* 1995;152: 1485-92

AD : VaD ratio in Japanese Men



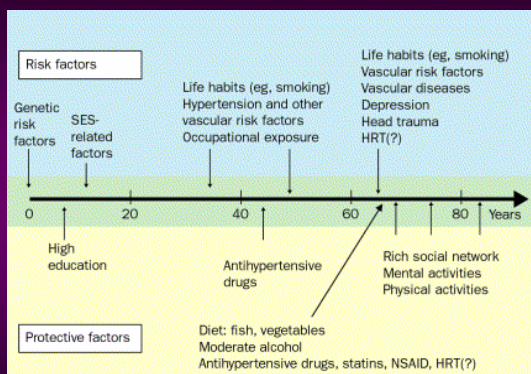
Yoshitake et al. (Hisayama) *Neurology*, 1995
White et al. (Honolulu) *JAMA*, 1996
Graves et al. (Kame study) *Amer. J. Enid.*, 1996

Less Strong Risk Factors

- Low education
- *Head injury (with loss of consciousness)*
- Cardiovascular factors
 - High BP, atherosclerosis, AF, DM
 - Cerebrovascular disease
- Diabetes mellitus
- Depression
- Loneliness
- Other illnesses eg hypothyroidism

Possible protective factors

- Lifestyle
- Physical exercise
- Intellectual activity
- Social engagement
- Medications
- Diet/ Supplements



Foetal Origin of Adult Disease

- Low birthweight for date assoc^d with later:
 - IHD
 - Obesity
 - Insulin resistance
 - impaired GTT
 - NIDDM

Whalley L et al, *Lancet Neurology*, 2006;5:87-96

FOAD & Dementia

- FOAD acts directly on brain during embryogenesis
- FOAD acts indirectly through adult cardiac disease & hyperglycaemia
- FOAD accelerates ageing → premature age dependent disorders

Whalley L et al, Lancet Neurology, 2006;5:87-96

Socioeconomic status in childhood

- Father's low SES linked to sons' cognitive ability even adjusting for education ¹
- Effect of disadvantaged upbringing stronger if ApoE4+ ²
- Detection artefact – easier to diagnose

Turrell G et al *J Gerontol B* 2002
Moceri VM et al, *Neurology*, 2001

Childhood Intelligence

- Linked to Late Onset (but not Early Onset) dementia
- Effect on lower performance in late life vs cognitive decline
- May be linked to factors which make dementia more easily detected

Whalley et al *Neurology* 2000; *ibid BMJ* 2001

Education



Ron Filtch, awarded PhD in engineering, aged 92

- Higher education associated with lower prevalence of AD
- Intelligence vs education?
- Critical time for education?
- Nun Study < AD in brain if at 20 yo > idea density and > complex grammar

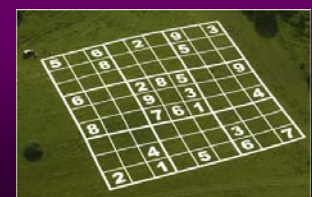
Life Course Approach

- Foetal maldevelopment → *antenatal care and > support for young unwed mothers*
- Low educational attainment → *> education*
– In US 83% completed high school in 2001 vs 12% in 1910; Av. schooling Eritrea 4.5y
- Occupation - *education*
- Low socio-economic status → *policy, economy*
- Dietary history → *Nutrition*

Whalley L et al, Lancet Neurology, 2006;5:87-96



Mental Activity and Dementia: A Case of Use it or Lose it?



Use it or lose it

Having fun to avoid Alzheimer's

HAVING fun and enjoying life can reduce a person's risk of developing Alzheimer's disease, scientists said yesterday.

Researchers found that leisure activity—whether seeing a film, visiting friends, walking or reading—may prevent or delay the symptoms of Alzheimer's.

The scientists from Columbia University in New York studied 1722 people aged 65 or older over seven years.

The subjects reported their participation in 13 leisure activities, covering intellectual, physical and social pursuits.

Dr Yaakov Stern, who led the research, said:

"Even when controlling for factors like ethnic group, education and occupation, subjects with high leisure activity had 38 per cent less risk of developing dementia."

The study, in the journal *Neurology*, showed participation in more than one activity might have a cumulative effect.

Mental Activity & Dementia

• Overview

- Is mental activity really important?
- How can mental activity change the biology of Alzheimer's Disease?
- What kind of mental activity is effective?

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 also 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). *Psychological Medicine*. 36(4): 441-454;

²Valenzuela MJ, Sachdev P. (2006) *Psychological Medicine*. 36(8): 1065-1073

Individual protective factors

Dichotomised high v low; median follow-up 7.1y; all give OR of about 0.5

- Education
- Occupation
- Pre-morbid IQ
- Mentally stimulating leisure activities
- Overall effect

¹Valenzuela MJ, Sachdev P. (2006). *Psychological Medicine*. 36(4): 441-454;

²Valenzuela MJ, Sachdev P. (2006) *Psychological Medicine*. 36(8): 1065-1073

Leisure & AD in Manhattan¹

- N = 1,772 non-demented, >65 yrs
- Mean f/u = 2.9 yrs (range 0 - 7.2)
- Baseline self-report of 13 leisure activities over last month (1 point each)
- e.g. walking, reading, hobbies, visiting, going to restaurants, movies or sport
- Low activity i.e. ≤6, high activity >6
- High leisure RR 0.62, 95% CI 0.46 to 0.83

¹Scarmeas et al, *Neurology* 2001;57:2236-2242

Cognitive activity & AD in US: Religious Order Study¹

- N = 801, mean f/u = 4.5 yrs, 111 → AD
- Baseline self-report of 7 common information processing activities eg watching TV, reading newspapers, playing games, museums
- Ratings: 5 (daily) to 1 (once a year or less)
- Composite score = mean of frequencies
- 1-point ↑ in score ↓ AD risk by 33%
- RR 0.67, 95% CI 0.49-0.92

¹Wilson et al, *JAMA*, 2002;287:742-748

Physical activity & AD: Canadian Study of Health & Aging¹

- N = 6434, 5 yr f/u, 283 ⇒ dementia (194 AD)
- Self reported freq^u & intensity rated:
 - High = ≥ 3 X week & > vigorous than walking
 - Moderate = ≥ 3 X week & equal to walking
 - Low = < 3 X week or < vigorous than walking
 - None used as reference category
- High activity: AD OR = 0.50, 95% CI 0.28-0.29
- Trend for ↑ protection with ↑ physical activity

¹Laurin et al, *Arch Neurol* 2001;58:498-504

Physical activity & AD: Sydney Older Persons Study¹

- N = 327 non-demented, 47 ⇒ dementia
- Mean age 83.4 yrs (range 78-99), 3 yr f/u
- Mean self-reported baseline freq (per month): gardening = 9.7 (±11.4), active exercise = 3.6 (±8.1), walking = 15.4 (±12.0)
- No consistent association with neuropsychological domains
- No association with AD or dementia

¹Broe et al *Aust NZ J Pub Health* 1998;22:621-3

Physical Activity

- Beneficial on cognitive function – many studies
- May stimulate BDNF, neurogenesis
- Neurogenesis in Hippocampus & olfactory bulb in young *and old* rats



Brain reserve

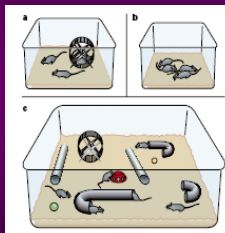
- 10-40% of persons who satisfy post mortem criteria for AD show no signs of cognitive impairment antemortem^{1,2}
- Does brain reserve protect against amyloid load?
- Brain Reserve can be hard wired eg brain size, neural density, or
- Behavioural brain reserve: flexible cognitive repertoires to compensate for neural dysfunction

¹ Mortimer JA *Geriatrics* 1997; 52 (Suppl 2): S50-53

² Neuropathology Group MRC CFAS *Lancet* 2001;375:169-171

How Could This Work?

- Mental Activity in Mice
 - Effects of mental activity on the brain have been studied using 'environmental enrichment'
 - Mice reared in enriched environments perform better on tests of memory, problem solving, reaction time etc
 - Enrichment also has a number of effects on the mouse brain



Courtesy of M. Valenzuela

Neurogenesis

- Process of producing new brain cells
- Common in adult mammals, even older mammals!
- Increased mental activity (via environmental enrichment) increases number and survival of newly created neurons *in hippocampus*
- More neurons in hippocampus may counteract expression of AD

Neuroplasticity & Environment¹

- 10-month-old mice raised for 10 months in enriched environment (toys, running wheel)
- Hippocampal neurogenesis 5X than controls
- Also ↑ learning, exploratory behaviour & locomotor activity
- ↓ lipofuscin indicating ↓ nonspecific age-dependent regeneration
→ activity has acute & sustained effect on brain plasticity

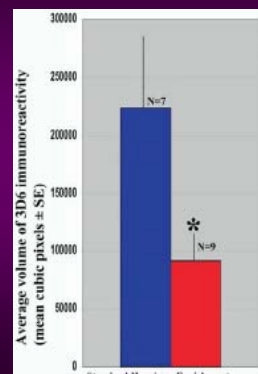
¹Kempermann et al *Ann Neurol* 2002;52:135-43

How Could This Work?

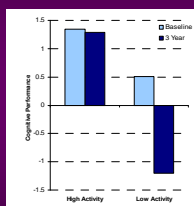
- 5 months study of environmental enrichment vs development of AD plaques in genetically modified mice
- 50% ↓ in number & size of plaques

Lazarov et al (2005)

Courtesy of M. Valenzuela



How Could This Work?



Courtesy of M Valenzuela

Hippocampus Shrinkage

- Sydney Stroke Study (Sachdev & Brodaty)
- 81 healthy elderly f/u > 3 years
- Baseline LEQ assessed complex mental activity across lifespan
- ↑ LEQ Ss = ↓ cognitive decline over 3 yrs
- ↑ LEQ Ss = 50% ↓ shrinkage of hippocampus over 3 yrs

What Kind of Mental Activity?

Lessons from Mice Studies

- Analysis of enrichment environment shows that it involves many cognitive processes and uses different parts of the brain
- Comparative mice studies have shown that no one component of environmental enrichment is sufficient to produce protective effects
- Mice studies require social, cognitive and physical activity to produce beneficial brain effects

What Kind of Mental Activity?

Three Key Ingredients

Human studies in general support mice findings. Ideal mental activity will therefore have three key ingredients:

1. Cognitive: learning something new, problem solving, remembering or strategy
2. Other people
3. Physical activity: should involve some type of physical exercise or skill

Marilyn Albert's formula

Marilyn Albert's formula

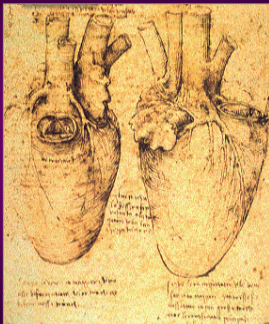
- Carrying heavy loads
- Walking
- Socialising
- Making complex decisions

Marilyn Albert's formula

- Carrying heavy loads
- Walking
- Socialising
- Making complex decisions

..... shopping!!

Cardiovascular factors



The human heart, Leonardo Da Vinci

- High blood pressure
- Stroke
- Atherosclerosis
- High cholesterol
- High homocysteine
- Smoking
- Diabetes

BP and dementia¹

- Goteborg Longitudinal Population Study
- n = 382, 15 year follow up
- Subjects who developed any dementia age 79-85 had \uparrow diastolic & systolic BP age 70
- Those who developed AD had higher diastolic blood pressure at age 70 & 75
- Blood pressure \downarrow before dementia onset
- at onset to level similar or lower to non-demented

¹Skoog et al *Lancet* 1996;347:1141-45

Hypertension & AD: Prospective population studies

- Swedish study, high diastolic BP at age 70 \uparrow AD risk 15 yrs later¹
- Honolulu-Asia Aging Study, high midlife diastolic BP \uparrow AD risk 25 yrs later²
- Finnish study, high midlife systolic BP \uparrow AD risk 21+ yrs later³
- BUT East Boston study, little association during 15 yr f/u⁴
- No evidence that late life BP increases risk⁵

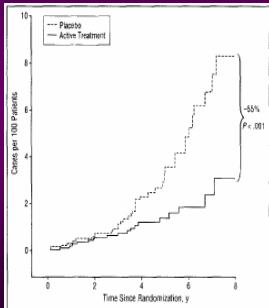
¹Notkola et al, *Neuroepidemiol*, 1998;17:14-20; ²Launer et al, *Neurol Aging* 2002;21:49-55; ³Kivipelto et al, *BMJ* 2001;322:1447-51; ⁴Morris et al, *Arch Neurol* 2001;58:1640-6; ⁵McGuinness et al, 2006 Cochrane

Antihypertensives & dementia Prospective Rx trial: Syst-Eur¹

- 2 yr DB RCT + 1.9 yr open label
- Rx: nitrendipine (10-40 mg/d) \pm enalapril maleate (5-20 mg/day) \pm hydrochlorothiazide (12.5-25 mg/d)
- At entry, systolic BP 160-219 mm Hg, diastolic BP <95 mm Hg

¹Forette et al *Arch Intern Med* 2002;162:2046-2052

Antihypertensives & dementia Prospective Rx trial: Syst-Eur¹



- Antihypertensive Rx ↓dementia risk by 55%
- controlling for sex, age, education, entry BP: RR of nitrendipine = 0.35 (95% CI 0.23-0.64)
- Rx of 1000 patients for 5 yrs can prevent 20 cases of dementia (95% CI 7-33)

¹Forette et al *Arch Intern Med* 2002;162:2046-2052

Does BP lowering prevent AD?

For persons with no previous CV Δ

- 3 trials, 12 000 Ss with Hpt; av age 72.8
- OR = 0.89 (0.69-1.16)
- 11% ↓RR of dementia (p = 0.38)
- Is effect of anti-hpt Rx only on CVD?

McGuinness et al, 2006 *Cochrane Database of Systematic Reviews Issue 2*

Rotterdam study

- Atherosclerosis – brachial–ankle gap or direct imaging of carotid artery
 - RR >2.5 x higher
- Silent infarcts 2.3x higher risk

van Oijen et al *Ann Neurol* 2007
Breteler M et al

Atrial Fibrillation & AD: Rotterdam study¹

- N = 6584, 7 yr f/u
- 176 developed dementia
- 195 diagnosed with atrial fibrillation
- AD no CVD: OR 1.8, 95% CI 0.9-3.5
- AD with CVD: OR 2.9, 95% CI 1.1-7.5
- VaD: OR 1.5, 95% CI 0.4-4.9

¹Ott et al *Stroke* 1997;28:316-321

Hypercholesterolaemia & AD: Prospective population studies

- Finnish study, midlife high cholesterol → ↑ risk for AD 21+ yrs later¹
- Finnish cohort from 7 Countries Study, men aged 70-79 had high cholesterol 15-25 yrs before AD onset²
- 3 prospective studies with short follow up → negative/contrary results³
- No evidence that late life cholesterol → risk↑

¹Morris et al, *Arch Neurol* 2001;58:1640-6;

²Notkola et al, *Neuroepidemiol*, 1998;17:14-20;

³Kivipelto et al, *CNS Drugs* 2002; 16(7):435-44

Natural history of BP, cholesterol and AD

- ApoE E4, high midlife total cholesterol and midlife BP are independent AD risk factors¹ BUT.....
- BP and cholesterol of AD patients not higher than controls
- Cholesterol levels gradually ↓ with age²
- More rapid ↓ in those who develop dementia²

¹Kivipelto et al, *Neurology* 2001;56:1683-1689

²Kivipelto et al, *CNS Drugs* 2002; 16(7):435-44

Do statins prevent AD? Do they help in treatment of AD?

Actions of statins

- ↓Cholesterol
- ↓LDL
- Anti-oxidant
- Anti-inflammatory
- Endothelial actoins
- ↓A β in plasma and CSF in dose dependent

Gandy S, 09.06.2007

Statins - Laboratory Models

- Hippocampal neurons - statins act to inhibit formation of A β ¹
- Guinea pigs - statin ↓A β in CSF and brain tissue²
- Statins that cross the blood-brain barrier efficiently, may reduce neuronal cholesterol below levels critical for A β ³

¹Simons et al, 1998; ²Fassbender et al, 2001; ³Simons et al, 2001

Statins protective?

- Epidemiological studies → significantly reduced risk of AD/dementia
 - Rockwood 2002
 - Any LLAs ↓risk of AD (OR 0.25, 0.10-0.62)
 - Protective effect only in <80 years age
 - Jick et al 2000
 - Wolozin et al 2000: effect for lovastatin, pravastatin but not simvastatin
 - Yaffe et al 2002 – trend to protect against cognitive decline

Lipid ↓ or Statins in Particular?

- *Rockwood et al, 2002* (Canadian Health & Aging)
 - Statin users ↓ risk of AD (OR = 0.26, 95% CI 0.08-0.88)
 - Any LLAs ↓ risk of AD (OR = 0.25, 95% CI 0.10-0.62)
 - protective effect only in <80 years age
- *Jick et al, 2000*
 - statin users 71% dementia ↓ risk compared to matched controls
 - non-statin LLA users no ↓ risk

Statins & AD

- *Wolozin et al, 2000*
 - statin users 60-73% AD ↓ risk
 - effect for lovastatin, pravastatin but not simvastatin
- *Yaffe et al, 2002*
 - statin users had higher MMSE
 - statin users - trend towards ↓ risk of cognitive impairment independent of lipid levels

Statins as prevention of AD?

- PROSPER trial, pravastatin/PBO for 5804 Ss with h/o vascular risk factors - - no difference in rate of cognitive ↓ @ 3y¹
- Heart Protection Study, simvastatin/PBO – no difference in cognitive ↓ @ 5y²
- Note heterogeneity – not all statins cross brain blood barrier

Shepherd et al, 2002
Heart Protection Study Collaborative Group, 2004

Statins & AD: MRC/BHF Heart Protection Study¹

- N = 20,536 with coronary disease, other occlusive arterial disease or diabetes
- 5 yr RCT: 40 mg/day simvastatin vs placebo additional to normal care
- Rx ↓ coronary death rate by 18% & non-fatal vascular events (MI, stroke, revascularisation) by 25%
- No difference between groups on incidence of dementia or cognitive impairment

¹Heart Protection Study Collaborative Group. *Lancet* 2002;360:7-22

Statins: A Meta-Analysis

- Meta-analysis of the preventive and treatment effects of statins on dementia & AD (7 studies included)
- Pooled crude OR in statin vs nonusers = 0.67 (CI: 0.54-0.82) in dementia group & 0.81 (CI: 0.64-1.02) in AD group
- Pooled adjusted RR = 0.77 (CI: 0.45-1.30) in dementia group & 0.81 (CI: 0.56-1.16) in AD group
- Statin use did not show a beneficial effect on the risk of dementia/AD

Zhou, B et al. (2007). Prevention and Treatment of Dementia or Alzheimer's Disease by Statins: A Meta-Analysis. *Dementia and Geriatric Cognitive Disorders*; 23:194-201

Homocysteine, B₁₂, Folate & AD



Sydney Morning Herald 10/03/03

Homocysteine, B₁₂, Folate & AD

- Homocysteine (HCy) - assoc^d with ↑ CAD risk
- B₁₂ & folate involved in homocysteine metabolism ie reduce levels of HCy
- Low serum B₁₂ and folate assoc with AD¹, but only in some studies
- ↑ folate intake related to ↓ risk of AD²
- ↑ HCy assoc with AD (and VaD)³⁻⁵
- HCy effect is independent of ApoE⁶
- HCy may promote atherogenesis and thrombogenesis + other neurotoxic effects

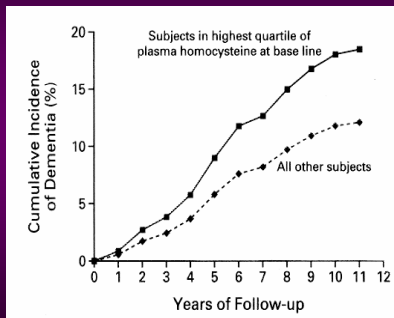
¹Wang et al, 2001; ²Luchsinger JA. 2007 *Archives of Neurology*; 64: 86-92;
³McCaddon et al, 1998; ⁴Clarke et al, 1998; ⁵Lehman et al, 1999; ⁶McIlroy et al, 2002

Other Actions of Homocysteine

- HCy may have direct neurotoxic effect by activating NMDA receptors¹
- HCy may → ↑ vulnerability of hippocampal neurons to excitotoxic and oxidative injury²
- HCy assoc^d with ↑ lipid peroxidation³
- HCy potentiates effects of Aβ on Ca⁺ influx and apoptosis⁴

¹Lipton et al, 1997; ²Kruman et al, 2000; ³Selly et al, 2002;
⁴Neuropath Group... *Lancet* 2001;357:169-175

Homocysteine & Dementia



Seshadri et al, N Engl J Med 2002;346:476-483

Folate for prevention of AD?

- Higher total folate intake but not B6 or B12 was independently related to lower AD risk ¹
- ..in predominantly Hispanic and Afro-American pop^u with high prevalence of vascular risk factors ¹
- *BUT...* Higher folate intake assoc^d w. cog ↓ ²
- No evidence for B6 or B12 protective effect

¹ Luchsinger JA *Arch Neurol* 2007;64:86-92

² Morris MC et al *Arch Neurol* 2005;62:641-645

Folate for prevention

- Benefits for transgenic mice if folate deficient
- 2 yr B vitamins in cognitively normal – no effect (McMahon et al, NEJM 2006)
- 3 yr folic acid if high HCy → cognitive benefit (Durga et al, Lancet 2007)

Folic acid for treatment

- 18 month folic acid 5mg + Vits B6 & B12
- 409 randomised 240 Vits and 169 PBO
- Mean baseline HCy 9 (ie not v high)
- No effect on ADAS-cog, CDR, ADL, NPI

Aisen P et al, 12.06.07

C-Reactive Protein & AD: Honolulu-Asia Aging Study¹

- Cohort of 1050 Japanese American men
- 25 yr f/u, 214 developed dementia (95 AD)
- CRP measured at 2nd Assessment
- OR & 95% CI for AD:
 - 2nd Quartile: 2.6 (1.2-5.5)
 - 3rd Quartile: 3.9 (1.9-8.0)
 - 4th Quartile: 1.6 (0.7-3.6)

¹Schmidt et al *Ann Neurol* 2002;52:168-174

Medications



- Statins
- HRT
- NSAIDs

HRT & AD

- Mixed evidence - Two prospective studies indicated benefit^{1,2} but UK GP research base did not³ ... AND...WHI found *increased* risk of dementia and of cognitive decline^{4,5,6}
- Cache County study concluded that
 - prior HRT (for ≥ 10 yrs) was associated with ↓risk of AD but not current use
 - ?critical period post-menopausal⁷
- Critical period:
 - HRT in < 65 yrs may provide cognitive benefit^{8,9}

¹ Tang et al, *Lancet* 1996; ² Kawaas et al, *Neurology* 1997; ³ Seshadri et al, *Arch Neurol* 2001; ⁴ Shumaker SA. et al (2003). *JAMA*; 289: 2651-2662; ⁵ Zandi et al. *JAMA* 2002; ⁶ Rapp et al *JAMA* 2003;289:2663-72, ⁷ Resnick & Henderson *JAMA* 2002; ⁸ Maki PM. (2005) *Ann NY Acad Sci*; 1052: 182-197; ⁹ Maki PM. (2006) *Neuroscience*;138: 1027-1030

Women's Health Initiative Memory Study

- Double blind RCT of 4532 women
- 0.625mg estrogen + 2.5mg progestin compared to placebo
- Mean f/u = 4.2 years
- Significantly greater % in estrogen + progestin group ↓ on modified MMSE by ≥ 2 SD (6.7%) compared to placebo (4.8%)
- Risk of dementia 45/10,000 v 22/10,000

¹Rapp et al *JAMA* 2003;289:2663-72

NSAIDs & AD

- Baltimore Longitudinal Study of Aging¹
- N = 1686, 15 yr f/u
 - ≥ 2 yrs NSAID use: AD RR 0.40, 95% CI 0.19-1.84
 - < 2 yrs NSAID use: AD RR 0.65, 95% CI 0.33-1.29
- Rochester case-controlled study, use for 7+ days 2 yrs B4 diagnosis, OR 0.79 (95% CI 0.45 - 1.38)²

¹Stewart et al *Neurology* 1997;48(3):626-32; ²Beard et al, *Mayo Clin Proc* 1998;73:951-5;

NSAIDs & AD

- Sydney Older Persons Study
 - X-sectional, inverse association between NSAIDs and AD, no dosage effect¹
- Rotterdam prospective cohort study (7yr f/u)²
 - ≤ 1 month use: OR 0.95, 95% CI 0.70-1.29
 - $1 < \text{use} < 24$ m:OR 0.83, 95% CI 0.62-1.11
 - ≥ 24 months use: OR 0.20, 95% CI 0.05-0.83

¹Broe et al *Arch Neurol* 2000;57:1586-91;
²In't Veld et al, *NE J Med* 2001;345:1515-21;

NSAIDs: Naproxen & Celecoxib

- RCT Double blind trial of naproxen and celecoxib for primary prevention of AD
- 70+ yrs with family history of AD, randomly assigned to celecoxib 200 mg BID, naproxen sodium 220 mg BID, or placebo (2001-2004)
- Celecoxib vs placebo HR = 1.99 (CI: 0.80-4.97); Naproxen vs placebo HR = 2.35 (CI:0.95- 5.77)
- Celecoxib or naproxen do not appear to prevent AD

ADAPT Research Group (2007). Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology*. 68(21): 1800-1808

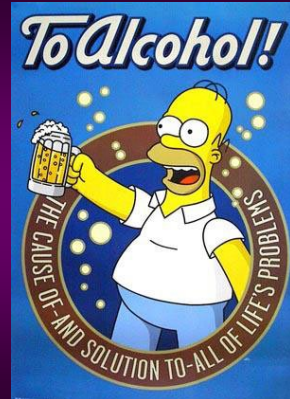
NSAIDS/Aspirin meta-analyses

- Etminan et al *BMJ* 2003;327:128
- NSAIDs lower risk of AD, esp if L/T use
- Aspirin has effect – result n.s., small N
- de Craen et al, *Am J Epidemiol* 2005;161:114-120
- Prevent dementia or cognitive decline
 - ↓50% if studies report prevalent dementia
 - ↓20% if studies report incident dementia
 - Absent if cognitive decline is end point

Nutrition / Supplements



- Alcohol
- Fish/Seafood
- Caffeine
- Vitamin E
- Vitamin C
- Fats
- Ginkgo biloba



Alcohol & Dementia

- Many negative studies (mainly X-sectional)

Longitudinal studies → alcohol beneficial

- Orgogozo et al, 1997 (PAQUID)
- Ruitenberg et al, 2002 (Rotterdam study)
- Truelsen et al, 2002 (Copenhagen study)
- Mukamel et al, 2003 (Cardiovascular health study)
- Huang et al, 2002 (Stockholm)
- Solfrizzi et al, 2007 (Italian; MCI → AD)

Alcohol & Dementia

- Copenhagen City Health Study – no relationship with alcohol intake; but those who drank wine (v beer or spirits) had lower risk
- Several studies: interaction with Apo E
 - Moderate alc → protection in ε4-
 - Any alcohol → risk factor if ε4+

Mechanism for alcohol protection?

- Effects on cerebral vasculature
 - Rotterdam: protection mainly w. VaD
 - Mod alc assoc^d with ↓DWMH
- Actions on clotting factors
- ↑ HDL
- Antioxidants, polyphenols
 - Differential effect of wine v spirits, beer
- Why interaction with ApoE4??

Fish



Fish/Seafood & AD: PAQUID¹

- N = 1674 aged 68+, 7 yr f/u
- 170 developed dementia (135 AD)
- Fish & seafood consumption ↑ in higher educated
- Controlling for educⁿ, age, sex:
eating fish/seafood ≥ 1 X week
OR (dementia) = 0.73, 95% CI 0.52-1.03
OR (AD) = 0.69, 95% CI 0.47-1.01

¹Barberger-Gateau et al *BMJ* 2002;325:932-3

Omega-3

- Insufficient evidence re dietary or supplemental omega-3 polyunsaturated fatty acid reduces risk of cognitive impairment or dementia prevention^{1,2}
- Results of two clinical trials expected in 2008³

¹Issa et al, 2006; ²Lim et al 2006; ³ Australian Dementia Research Mapping Project: www.aro.gov.au

Kame Project: Fruit/Vegetable Juice (Polyphenols)



- 1836 dementia-free Ss; f/u 7-9 yrs
- Protective effect for developing dementia for drinking juice v < 1x/wk
– ≥ 3x/wk (OR = 0.24; CI 0.09-0.61)
– 1-2x/wk (OR = 0.84; CI 0.31-2.29)
- Association stronger if APOE4 + & – if not physically active
- No association for dietary intake of Vit E, Vit C, beta-carotene, tea

Dai Q. et al. (2006) Fruit and Vegetable Juices and Alzheimer's Disease: The Kame Project. *American Journal of Medicine*. 119(9):751-759

Caffeine & AD: Lisbon¹

- Case-control study of 54 AD & 54 controls
- Self & informant reports on caffeine, alcohol & tobacco from age 25 onwards
- Caffeine intake in 20 yrs preceding AD diagnosis: OR 0.40, 95% CI 0.25-0.67
- AD subjects reported lower caffeine intake in young adulthood
- Alcohol & tobacco not associated

¹Maia & de Mendonca, *Euro J Neurol* 2002;9:337-382

Caffeine & AD cont...

- Caffeine added to drinking water of mice
- Ave. daily intake of caffeine = human equivalent of 5 cups of coffee per day
- Tg mice given caffeine performed better in spatial learning/reference memory, working memory, and recognition/identification
- ↓ hippocampal Aβ observed
- ↓ Aβ production a likely mechanism of caffeine's cognitive protection
- Moderate daily intake of caffeine may delay or reduce the risk of AD

Arendash GW. et al. (2006). Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain Aβ production. *Neuroscience*. 142(4): 941-952

Dietary Antioxidants & AD: Chicago Health & Ageing Project¹

- Cohort of 815 non-demented
- 3.9 yrs mean f/u, 131 developed AD
- Self-report food frequency for past year completed 1.7 yrs after baseline
- Nutrient intakes calculated & divided into quintiles (lowest = reference)
- Vit E from diet, RR for highest quintile 0.30, 95% CI 0.10-0.92, dose effect significant
- Vit C, β-carotene & Vit E supplements not protective

¹Morris et al *JAMA* 2002;287:3230-3237

Vitamin E & C supplements & AD: Honolulu-Asia Ageing Study¹

- N = 3385 Japanese-US males aged 71-93
- 10 yr f/u, 132 developed dementia (47 AD)
- Self-report mail survey on # of multivitamins, Vitamin A, E or C pills in past year
- OR for AD if taking Vit E or C pills not sig.
- OR for AD if E+C = 1.81, 95% CI 0.91-3.62
- But both protective for VaD or mixed/other dementia

¹Masaki et al *Neurology* 2000;54:1265-1272

Antioxidants & AD: MRC/BHF Heart Protection Study¹

- Sample as previously described
- 5 yr RCT of 600mg Vit E, 250 mg Vit C & 20 mg β -carotene daily vs placebo
- Rx did not significantly affect rate of mortality, myocardial infarction, stroke or revascularisation
- No difference between groups on incidence of dementia or cognitive impairment

¹Heart Protection Study Collaborative Group. *Lancet* 2002;360:23-33

Is Vit E harmful?

- Meta-analysis : 0.4% increased mortality rate when several studies of people taking Vit E for chronic medical conditions were pooled ¹
- Many clinicians no longer recommending Vit E for treatment or prophylaxis

Miller et al, *NEJM* 2005

Other compounds



- Ginkgo biloba
- DHA
- Curcumin
- Selenium
- Cat's claw
- Peony root
- Lemon balm, Melissa
- Lavender oil

Does Fat Matter?



Does Fat Matter?¹

- Rotterdam cohort study, f/u 6.0 \pm 1.3 yrs
- N = 5395, 179 developed dementia (146 AD)
- Diet assessed through self-report and dietician assessment of food-frequency
- Increase of 13.5 g/day (1 SD) total fat intake \downarrow risk of AD by 14% (rate ratio 0.86, 95% CI 0.73-1.01)
- Similar rate ratios for saturated fat, trans fat and cholesterol individually

¹Engelhart et al *Neurology* 2002;59:1915-1921

Calories & AD: Manhattan¹

- N = 480, 4 yr f/u, 242 developed AD
- Telephone food frequency questionnaire - total caloric intake
- Highest quartile total calories
HR for AD 1.5, 95% CI 1.0-2.2
- If ApoE4 +, highest calorie quartile
→ HR 2.3, 95% CI 1.1-4.7

¹Luchsinger et al *Arch Neurol* 2002;59:1258-63

BMI & dementia: PAQUID¹

- N = 3,646 ≥ 65 yrs, 8 yr f/u
- Subjects with low BMI (< 21) ↑ risk of dementia v normal BMI (OR = 1.48, 95% CI 1.08-2.04)
- But relationship not significant if individuals who developed dementia in first 3 yrs excluded from analysis (who may have experienced weight loss as a result cognitive and functional loss as part of early dementing process)

¹Nourhashemi et al *Neurology* 2003;60:117-119

BMI & AD cont

- Being overweight found to be a risk factor for developing AD¹
- In women, every 1.0 ↑ in BMI at 70 yrs = AD risk ↑ by 36%¹
- In men & women, association between BMI
 - < 76 yrs U shape dementia risk
 - ≥ 76 yrs, dementia risk ↓ with ↑ BMI²

¹Gustafson et al (2003) *Arch Int Med*;163:1524-8;

²Luchsinger JA. et al. (2007) *Archives of Neurology*; 64: 392-398

Other Factors

- Diabetes
- Depression
- Smoking
- Head injury
- Environmental toxins

Type 2 Diabetes & AD

- **Canadian SHA - OR 1.30, 95% CI 0.83-2.03¹**
- Honolulu-Asia - OR 1.8, 95% CI 1.1-2.9²
- Rotterdam - OR 1.9, 95% CI 1.3-2.8³
- Cambridge - OR 1.4, 95% CI 1.1-17.0⁴
- **Manhattan - OR 1.3, 95% CI 0.8-1.9⁵**
- Systematic review: ↑ incidence of 'any dementia' (including AD and VaD) in Ss with diabetes in 7/10 studies⁶

¹MacKnight et al *Dem Ger Cog Disord* 2002;14:77-83; ²Peila et al *Diabetes* 2002;51:1256-62; ³Ott et al *Neurol* 1999;53:1937-80; ⁴Brayne et al *Dem Ger Cogn Disord* 1998;9:175-80; ⁵Luchsinger et al *Am J Epidemiol* 2001;154:635-41; ⁶Biessels GJ. et al. 2006. *Lancet Neurology*; 5: 64-74

Type 2 Diabetes

Insulin resistance

- ↓ insulin signalling
- Attenuates positive effects of insulin on memory
- Disrupts insulin effect on clearing β amyloid

Insulin degrading enzyme has role in clearing β amyloid

Implications for prevention

- Public health efforts to address
 - Obesity epidemic
 - Metabolic syndrome
- Better treatment of Type 2 DM
- Trials of anti-diabetic drugs
 - Thiazolidinediones, PPAR γ agonists
 - Rosiglitazone, pioglitazone

Depression and AD: Meta-analyses and review^{1,2}

- Case control studies: RR 2.01¹ 2.03², (1.16, 3.50)¹
- Prospective studies: RR = 1.87¹, 1.90² (1.09, 3.29)²
- Likely hypotheses:
 - depression is early dementia prodrome
 - depression brings forward clinical syndrome
 - depression damages hippocampus
- Interval between diagnoses positively and significantly related to AD risk

¹Jorm AF, ANZJP 2001;35:776-781;

²Ownby RL et al, Arch Gen Psych 2006;63:530-8

Protection against depression

- NIA consensus statement
- Link between the depression and dementia and
- Overlap of risk and protective factors

Hendrie H et al (2006) J Alz and Dem

Happiness and Memory

- Happier people have higher current cognitive function, such as memory, but not intelligence
- Well-established link between mood and memory, i.e., as mood goes down, so does memory



Happiness Not Just Good for Memory

- Laughter and positive mood boosts:
 - Immune function
 - Cardiovascular function e.g., lowers blood pressure
 - The body's ability to cope with stress

Increase Happiness Levels

- Absence of role identity in later life. Volunteering found to increase mood & buffer against this
- “Three Good Things” exercise - write down 3 things daily that went well & why each happened
- Get active! Exercise can improve both memory AND your mood



Smoking

- Studies contradictory
- 21 case control studies (>5000 Ss) → protective
- 8 cohort studies (>43,000) → risk factor
- Majority consider it risk factor with survival bias and other methodological differences explaining paradox

Almeida O et al *Addiction* 2002;97:15-28

Smoking

- Meta-analysis of 19 studies: smoking vs dementia, AD, VaD and annual cognitive ↓
- Current smokers had higher risk of dementia and cognitive decline = 40- 80%, depending on type of dementia or cognitive outcome
- No increased risk of dementia or cognitive decline for ever smoking vs never smoking
- However former smokers show an increased risk of yearly decline in cognitive ability vs never smokers

Anstey K, *Am J Epidemiology* 2007;10:1093;116

Head Injury

- Increased risk reported by many
- Severity may be important, eg LOC
- Meta-analysis: HI + :OC → OR 1.58 (1.21-2.06) of developing AD¹
- Association with ApoE4 remains ?

Fleminger et al, *JNNP* 2003; 74:857-862

Environmental toxins

- Pesticide exposure linked to dementia in men¹
- Industrial solvents – toluene²
- Paraquat³
- MPTP (mixed with heroin) → PD⁴

¹ Baldi et al 2003; ² Rosenberg et al 2002

³ Langston et al 1999; ⁴ Liou et al 1997

Prevention Trials

- Randomised controlled trials
 - Large
 - Lengthy
 - Expensive
 - Multiple confounds
 - Ethics?

Drug prevention trials

- Cholinesterase inhibitors for MCI
 - Donepezil
 - Galantamine
 - Rivastigmine
 - all –ve on primary outcome measure
 - Some +ve results with post-hoc analyses eg ApoE, BuChE K
- Immunotherapy ??

In summary

- Age
- Family history
- Apoe4
- Down's syndrome
- Other genes
- FH of Downs
- Foetal origins
- Education
- Midlife ↑ BP
- Midlife ↑ cholesterol
- Homocysteine
- Statins
- HRT
- NSAIDS
- Alcohol
- Seafood
- Caffeine
- Vitamin E
- Vitamin C
- B12, folate
- Ginkgo
- Fats
- Leisure activity
- Cognitive activity
- Physical activity
- Depression
- Diabetes
- Head injury
- Vaccines

Potentially Modifiable

- Age
- Family history
- Apoe4
- Down's syndrome
- Other genes
- FH of Downs
- Foetal origins
- Education
- Midlife ↑ BP
- Midlife ↑ cholesterol
- Homocysteine
- Statins
- HRT
- NSAIDS
- Alcohol
- Seafood
- Caffeine
- Vitamin E
- Vitamin C
- B12 & folate
- Ginkgo
- Fats
- Leisure activity
- Cognitive activity
- Physical activity
- Depression
- Diabetes
- Head injury
- Vaccines

Conclusions

- Accumulating evidence for benefits of
 - Physical activity
 - Mental activity
 - Social engagement
 - Vascular factors
- Weaker evidence for diet & supplements
- Investigation of gene-diet interaction continues
- New ethical dilemma re genetic screen

Conclusions

- Public health measures that can be instituted now
- Current Alzheimer's Assoc campaigns
 - Train the Brain in USA
 - Mind your Mind in Australia
 - Mind Your Head in UK
- "What's good for your heart is good for your brain"
- Lessons from dramatic reduction in CAD

Mind your Mind

- Mind your brain – cognitive stimulation
- Mind your body – exercise
- Mind your head – protect head
- Mind your habits – smoking
- Mind your health – check BP, cholesterol
- Mind your diet – antioxidant, polyphenol
- Mind your social activities - engagement

Thank to Louisa Gibson and Lee-Fay Low

To get back my youth I would do anything in the world, except take exercise, get up early or be respectable.

Oscar Wilde

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www.dementia.unsw.edu.au