Beneficial interaction between B vitamins and omega-3 fatty acids in slowing brain atrophy and cognitive decline in Mild Cognitive Impairment

A. David Smith and Helga Refsum,
Oxford Project to Investigate Memory and Ageing (OPTIMA)
Department of Pharmacology, University of Oxford

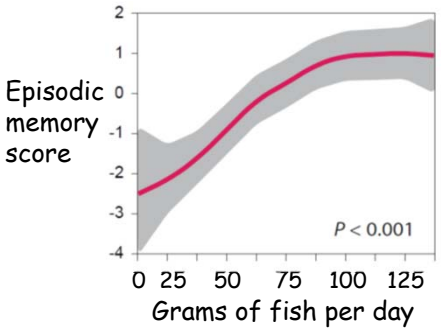
Risk factors for Alzheimer's disease

- Low fish intake,
- or low blood levels of long chain omega-3 fatty acids,

are risk factors for AD

Cognition in the elderly: intake of fish

2,027 Norwegian elderly



Nurk, 2007

Eating fish protects against Alzheimer's Disease

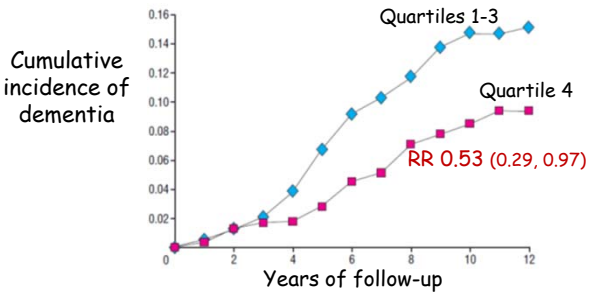
Eating fish once or more each week reduces risk of AD by 33%
- compared with those who eat fish less than once a week.

Meta-analysis by Beydoun, 2014

Fish is a rich source of several micronutrients:
- Omega-3 fatty acids (DHA, EPA)
- Vitamin B12
- Selenium

Plasma DHA and later risk of dementia

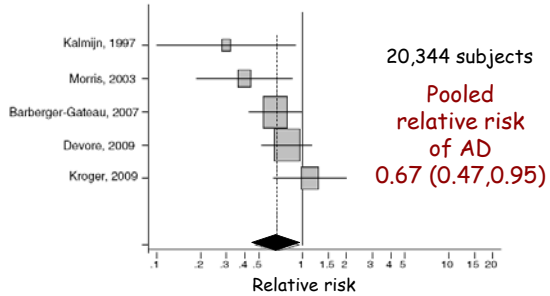
Framingham Heart Study (N = 899, age 76, no dementia)



Schaefer 2006

Omega-3 fatty acids and Alzheimer's disease

Meta-analysis by Beydoun et al. BMC Public Health 2014, 14: 643



20,344 subjects

Pooled relative risk of AD 0.67 (0.47,0.95)

n-3 fatty acids (high vs. low) and risk of incident AD

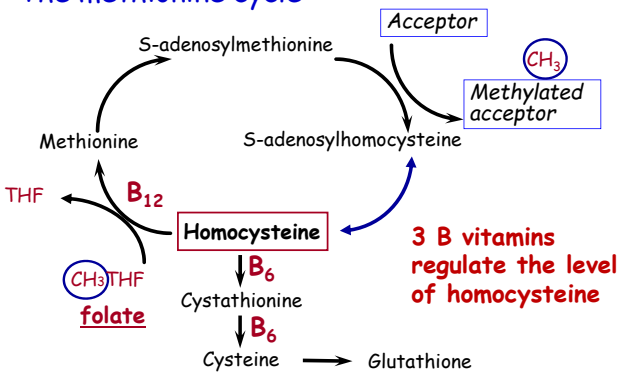
Population attributable risk of AD for low omega-3 is 22%

david.smith@pharm.ox.ac.uk

Risk factors for Alzheimer's disease

- Low fish intake, or low blood levels of long chain omega-3 fatty acids, are risk factors for AD
- Low folate and B12 status and raised plasma total homocysteine (tHcy) are risk factors for cognitive decline and for AD

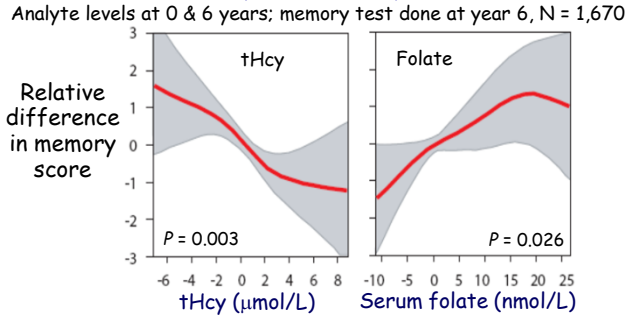
The methionine cycle



3 B vitamins regulate the level of homocysteine

Effect of changes in homocysteine (tHcy) or folate over time on episodic memory test scores

Analyte levels at 0 & 6 years; memory test done at year 6, N = 1,670



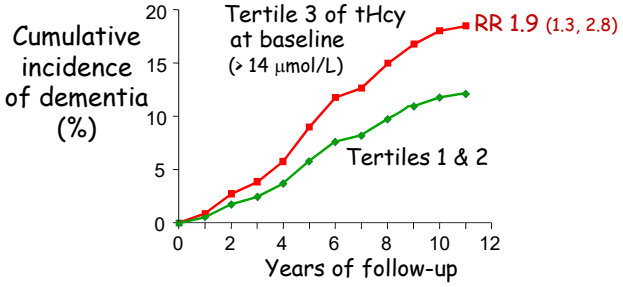
Change from baseline to follow-up 6 y later

Nurk 2005

Homocysteine and dementia in the Framingham study

N=1092 without signs of dementia, mean age 76 y

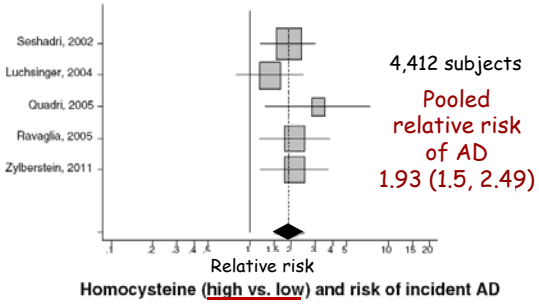
Median follow-up time of 8 years: 111 developed dementia



Seshadri 2002

Raised homocysteine and Alzheimer's disease

Meta-analysis by Beydoun et al. BMC Public Health 2014, 14: 643



4,412 subjects

Pooled relative risk of AD 1.93 (1.5, 2.49)

Homocysteine (high vs. low) and risk of incident AD

Population attributable risk of AD for raised tHcy is 22%

Risk factors for Alzheimer's disease

- Low fish intake, or low blood levels of long chain omega-3 fatty acids, are risk factors for AD
- Low folate and B12 status and raised plasma total homocysteine (tHcy) are risk factors for cognitive decline and for AD
- Each of these risk factors has a population attributable risk of about 20%
- What is the effect of modifying these risk factors on cognitive decline?

david.smith@pharm.ox.ac.uk

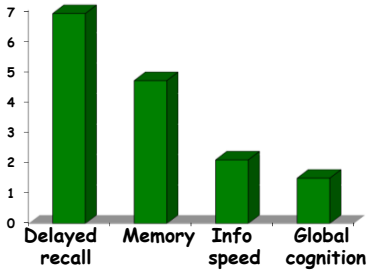
Clinical trials

- Lowering homocysteine by B vitamins can slow cognitive decline: FACIT trial, VITACOG trial
- Eating fish or supplementing diet with omega-3 fatty acids can slow cognitive decline
- BUT, for both risk factors, trial results have not been consistent, many negative. Why?

Effect of folic acid treatment on age-related cognitive decline (FACIT trial)

818 people with high homocysteine treated for 3 years

Performance equivalent to someone younger by 'x' years, in those on folic vs. placebo



Durga, 2007

The shrinking brain

- As we age (over ~ 60) the brain shrinks at a rate of ~ 0.5% per year, i.e. ~ 7 mL per year
- Those of us with memory problems – 'mild cognitive impairment' or 'MCI' – show a faster rate of shrinkage of ~ 1.0% per year
- In patients with Alzheimer's disease, the rate is higher still, at ~ 3% per year

Many risk factors for AD are associated with an increased rate of brain atrophy: smoking, diabetes, low omega-3, physical inactivity, low Med diet, high blood pressure, atrial fibrillation, high homocysteine, low B vitamins

Vitamin B_{12} status and rate of brain volume loss in community-dwelling elderly

A. Vogiatzoglou, et al. *Neurology*® 2008;71:826-832

Association of Vitamin B_{12}, Folate, and Sulfur Amino Acids With Brain Magnetic Resonance Imaging Measures in Older Adults

A Longitudinal Population-Based Study

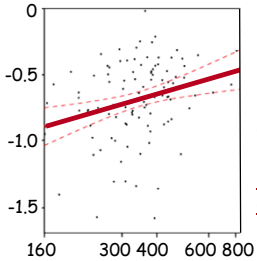
Babak Hooshmand, MD, PhD, MPH; Francesca Mangialasche, MD, PhD; Grégoria Kalpouzos, PhD; Alina Solomon, MD, PhD; Ingemar Kåreholt, MD, PhD; A David Smith, PhD; Helga Refsum, MD, PhD; Rui Wang, PhD; Marc Mühlmann, MD; Birgit Ertl-Wagner, MD; Erika Jonsson Laukka, PhD; Lars Bäckman, PhD; Laura Fratiglioni, MD, PhD; Miia Kivipelto, MD, PhD

JAMA Psychiatry. 2016;73(6):606-613

Serum B12 is related to rate of brain atrophy

107 community-dwelling elderly, not impaired at baseline

% change in total brain volume per year, over 5 years



$r = 0.33$
$p < 0.001$

Brain volume changed over the normal range; No-one was B12 deficient

Vogiatzoglou 2008

The VITACOG trial

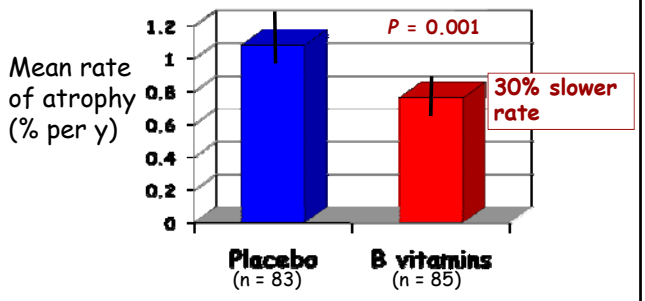
P.I.s AD Smith, H Refsum and R Jacoby

Do B vitamins slow the rate of brain atrophy in those with MCI?

- 270 community-dwelling subjects > 70 years old with *mild cognitive impairment (MCI)*, in Oxford
- Randomised to placebo or 'TrioBe Plus' (Recip/Meda) (0.8 mg folic acid; 0.5 mg B12; 20 mg B6)
- Treated for 2 years
- Volumetric MRI scans at start and end
- Powered to detect a 20% slowing of brain atrophy
- Secondary outcomes: cognitive and clinical changes
- Pre-specified analysis according to nutrients and tHcy

david.smith@pharm.ox.ac.uk

B vitamin treatment slows the mean rate of brain atrophy (ITT)

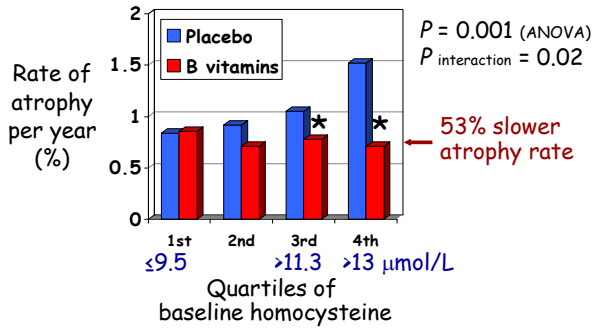


Smith, PLoS ONE 2010, 5: e12244

VITACOG

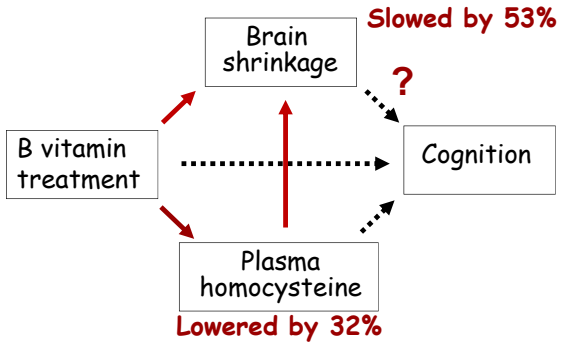
- The main effect is a highly significant slowing of the rate of atrophy by B vitamin treatment
- Pre-specified subgroup analysis: do baseline homocysteine levels interact with effect of B vitamin treatment?

Slowing of atrophy depends on baseline homocysteine

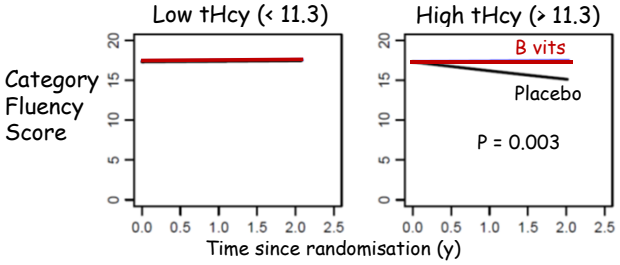


Smith, PLoS ONE 2010

VITACOG matrix



Effect of B vitamin treatment on semantic memory (GLMM model)



At low tHcy, no cognitive decline; no effect of B vits

At high tHcy, B vits prevent cognitive decline

Beneficial effects of B vitamin treatment on cognition

Generalized linear model

Only significant in those with raised tHcy	P value
• Episodic memory (HVLT delayed recall)	0.001
• Semantic memory (category fluency)	0.037
• Global cognition (MMSE)	0.001
• *Clinical dementia rating (CDR)*	0.020
• *IQCODE*	0.011
Independent of baseline tHcy	
• Executive function (CLOX)	0.015

De Jager, *Int J Geriatr Psych*, 2012

david.smith@pharm.ox.ac.uk

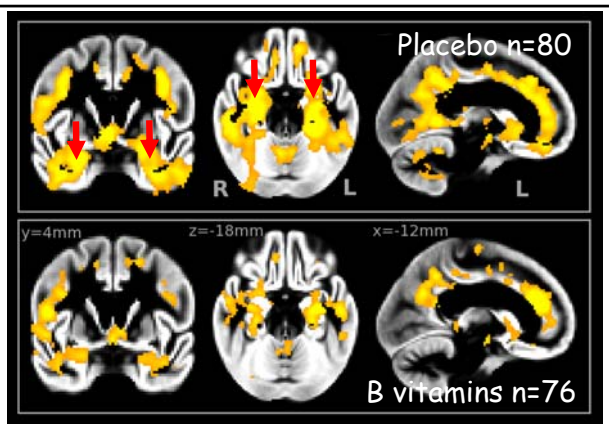
Which brain regions were protected by B vitamins?

- Particular cognitive functions are known to be associated with different brain regions
- What is the effect of B vitamin treatment on the rate of atrophy of these brain regions?
- We used voxel-based morphometry (VBM) to answer this question

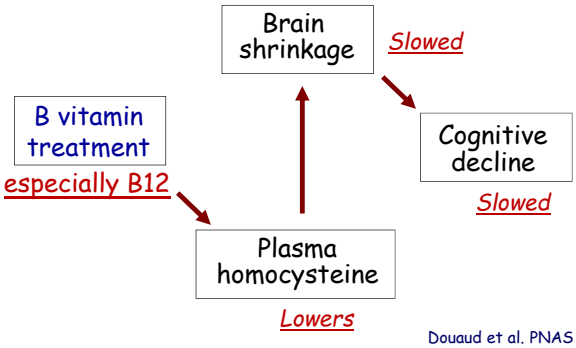
Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

Gwenaëlle Douaud[a,b,1], Helga Refsum[b,c,d], Celeste A. de Jager[e], Robin Jacoby[e], Thomas E. Nichols[a,f,g], Stephen M. Smith[a], and A. David Smith[b,c]

PNAS 2013, 110:9523



VITACOG – causal links by Bayesian network



Douaud et al. PNAS 2013

Outcomes of the VITACOG trial: effect of B vitamins

- Slowed whole brain atrophy in Mild Cognitive Impairment
- Slowed atrophy in those brain regions affected in Alzheimer's, by as much as 9-fold
- Slowed cognitive decline in several domains and improved clinical status
- **Overall, B vitamins had a disease-modifying effect**

  These responses only occurred in subjects with baseline tHcy levels above ~ 11 μmol/L and, as I will now show, in those with a good omega-3 fatty acid status

Omega-3 fatty acids and brain atrophy

Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging

Neurology 2012

Z.S. Tan, MD, MPH
W.S. Harris, PhD
A.S. Beiser, PhD
R. Au, PhD
J.J. Himali, MS
S. Debette, MD
A. Pikula, MD
C. DeCarli, MD
P.A. Wolf, MD
R.S. Vasan, MD
S.J. Robins, MD
S. Seshadri, MD

Low levels of red blood cell omega-3 fatty acids were associated with

- smaller whole brain volume,
- greater white matter hyperintensity
- poorer cognition

in non-demented Framingham cohort (n=1575)

Omega-3 fatty acids and brain atrophy

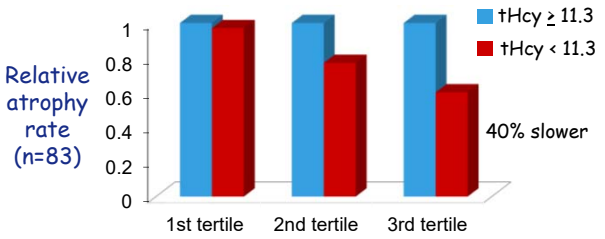
VITACOG

We asked two questions:

- Does baseline omega-3 status influence the rate of atrophy in the *placebo group*?
- Does baseline omega-3 status influence the atrophy and cognitive *responses to B vitamins*?

david.smith@pharm.ox.ac.uk

VITACOG: effect of omega-3 levels on brain atrophy in placebo group at different tHcy levels



Baseline omega-3 fatty acid concentration

High omega-3 status only protects the brain in those with low tHcy

Jerneren AJCN 2015

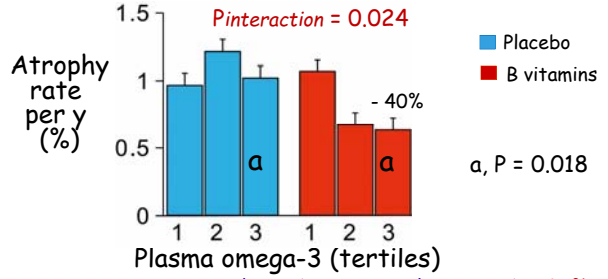
Omega-3 fatty acids and brain atrophy

VITACOG

We asked two questions:

- Does baseline omega-3 status influence the rate of atrophy in the placebo group?
  - YES, in those with low tHcy
- Does baseline omega-3 status influence the atrophy and cognitive *responses to B vitamins*?

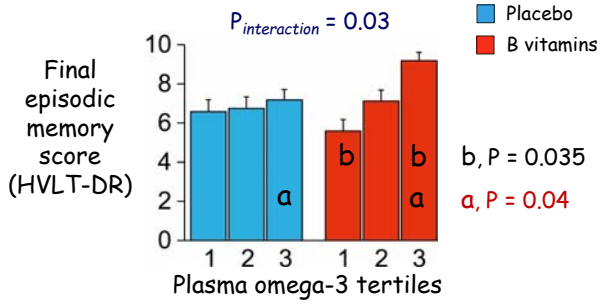
Omega-3 and atrophy response to B vitamins



- B vitamin treatment reduces brain atrophy rates by 40% in subjects with high omega-3 levels
- No effect of B vitamins in those with poor omega-3 status

Jerneren AJCN 2015

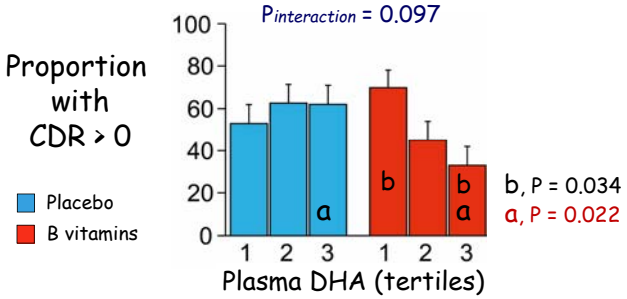
Omega-3 and cognitive response to B vitamins



Only those in the top tertile of omega-3 showed a beneficial cognitive response to B vitamins

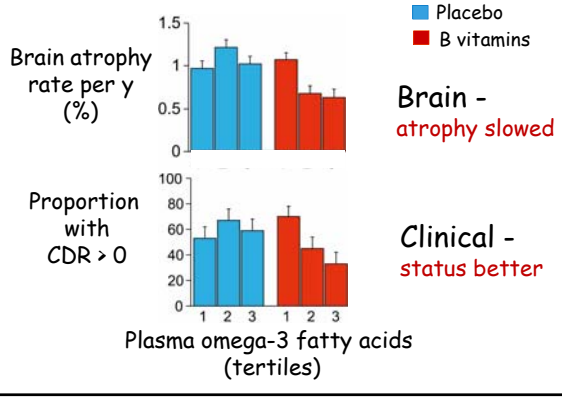
Oulhaj JAD 2016

Omega-3 and clinical response to B vitamins



At high DHA levels, B vitamins halved the proportion with scores > 0, i.e. they improved the clinical status

Oulhaj JAD 2016



david.smith@pharm.ox.ac.uk

How can we explain the interaction between B vitamins and omega-3 fatty acids on brain structure and function?

Neurobiology of Aging 28 (2007) 1834–1839

A metabolic link between *S*-adenosylhomocysteine and polyunsaturated fatty acid metabolism in Alzheimer's disease

Michael L. Selley *

Angiogen Pharmaceuticals Pty. Ltd., Level 31, ABN AMRO Tower, 88 Phillip Street, Sydney, NSW 2000, Australia

A landmark paper showing that increased plasma tHcy and S-adenosylhomocysteine (SAH) in AD is associated with a decrease in red cell phosphatidylcholine (PC) and in omega-3 (DHA) content of red cell PC

How can we explain the interaction between B vitamins and omega-3 fatty acids on brain structure and function?

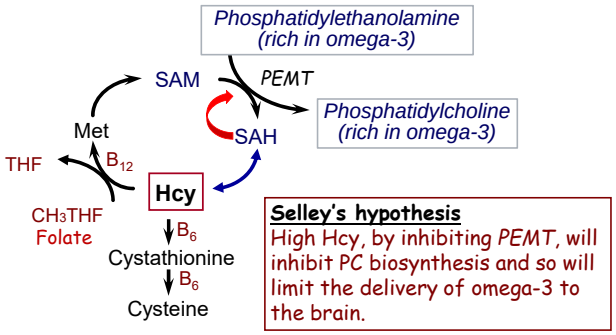
- In AD, there is a deficit in the brain, red cell and plasma of the species of phosphatidylcholine (PC) that *are rich in omega-3 fatty acids*
  (Selley, 2007, Astarita 2010, Yuki 2014, Whiley 2014)
- This form of PC is crucial for normal brain structure and function, especially at the synapse
- This form of PC is generated by the sequential methylation of phosphatidylethanolamine, a process requiring B vitamins (DeLong 1999)

Formation of phosphatidylcholine (PC)

1. Kennedy pathway (about 70% in liver):
   CDP-choline + diacylglycerol → PC
   PC contains mainly saturated fatty acids
2. From phosphatidylethanolamine by sequential methylation (*PEMT*):
   PE → N-methylPE → N-dimethylPE → PC
   SAM SAH SAM SAH SAM SAH

PC enriched in polyunsaturated fatty acids (omega-3)

Homocysteine and omega-3 fatty acids



Selley's hypothesis
High Hcy, by inhibiting *PEMT*, will inhibit PC biosynthesis and so will limit the delivery of omega-3 to the brain.

Selley's proposal

"The use of a combination of omega-3 polyunsaturated fatty acids, folic acid and vitamin B12 may be a more effective means of increasing the uptake of DHA into the brain than polyunsaturated fatty acids alone"

Selley, 2007

Conclusions from VITACOG

- Omega-3 fatty acids only appear to protect the brain in people with low tHcy, i.e. with good B vitamin status
- B vitamins only appear to protect the brain in people with good omega-3 fatty acid status
- These unexpected interactions could explain why some omega-3 trials have failed and why some B vitamin trials have failed

david.smith@pharm.ox.ac.uk

Summary and future directions

- The VITACOG trial has shown that lowering homocysteine by giving supplements of B vitamins will slow brain atrophy and slow cognitive decline
- The beneficial effect of B vitamins was limited to subjects who also had a good omega-3 fatty acid status at baseline
- A trial is needed to see if a combination of B vitamins and omega-3 fatty acids will slow conversion from MCI to AD
- MCI: ~ 6% of the elderly: ~ 250,000 in Australia
- With a combination treatment of B vitamins and fish oil it may be possible to prevent dementia in several thousand elderly in Australia

Nutrition is important!

Nutritional intervention is a valid approach to the prevention of dementia

Combinations of different nutrients are likely to be needed, which might explain why dietary patterns are so important in prevention

We would like to thank all our colleagues in in Oxford for their expert participation in VITACOG, especially Robin Jacoby, Celeste de Jager, Fredrik Jernéren, Abderrahim Oulhaj, Steve Smith, Gwen Douaud and the nurses who ran the trial

david.smith@pharm.ox.ac.uk