

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

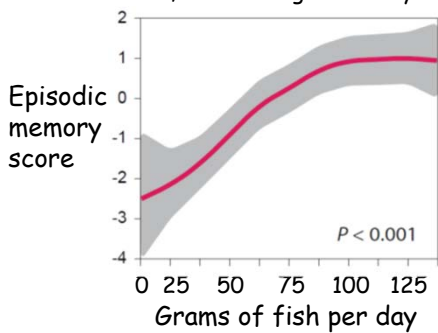
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Oxford Project to Investigate Memory and Ageing (OPTIMA)
Department of Pharmacology, University of Oxford



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

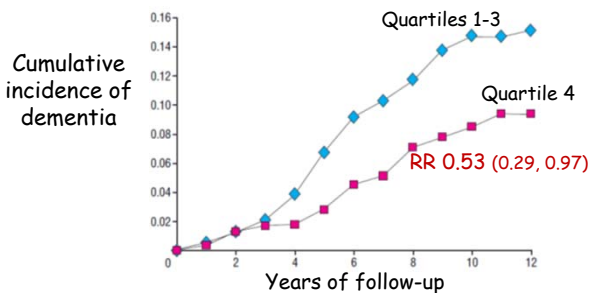
Eating fish once or more each week
reduces risk of AD by 33%
- compared with those who eat fish less than once a week.

Meta-analysis by Beydoun, 2014

Fish is a rich source of several micronutrients:

- Omega-3 fatty acids (DHA, EPA)
- Vitamin B12
- Selenium

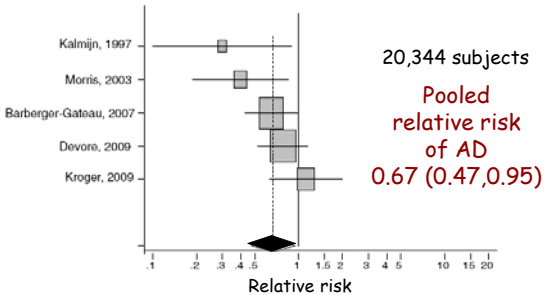
Plasma DHA and later risk of dementia
Framingham Heart Study (N = 899, age 76, no dementia)



Schaefer 2006

Omega-3 fatty acids and Alzheimer's disease

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

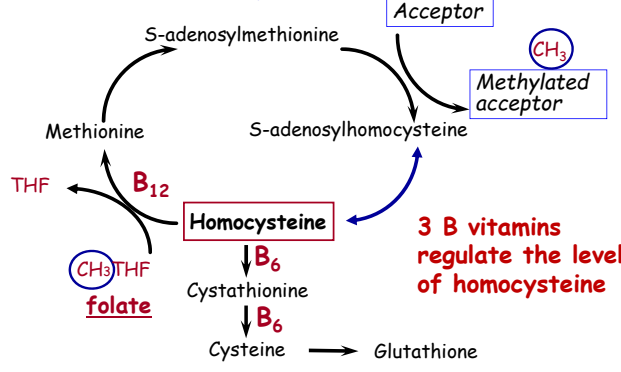


Population attributable risk of AD for low omega-3 is 22%

Risk factors for Alzheimer's disease

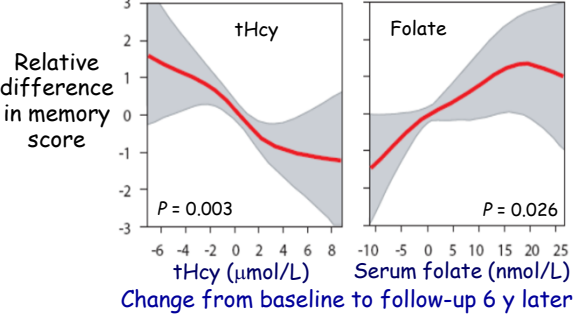
- Low fish intake, or low blood levels of long chain omega-3 fatty acids, are risk factors for AD
- Low folate and B12 status and raised plasma total homocysteine (tHcy) are risk factors for cognitive decline and for AD

The methionine cycle



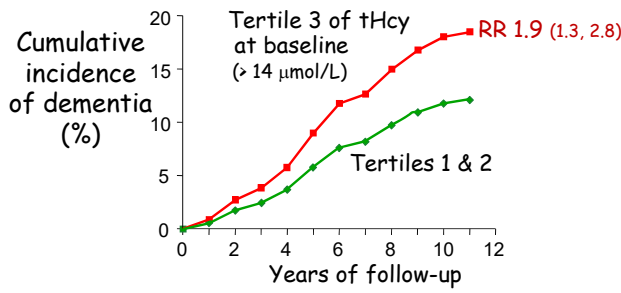
Effect of changes in homocysteine (tHcy) or folate over time on episodic memory test scores

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



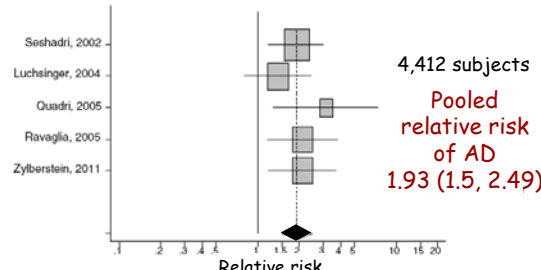
Homocysteine and dementia in the Framingham study

N=1092 without signs of dementia, mean age 76 y
Median follow-up time of 8 years: 111 developed dementia



Raised homocysteine and Alzheimer's disease

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



Population attributable risk of AD for raised tHcy is 22%

Risk factors for Alzheimer's disease

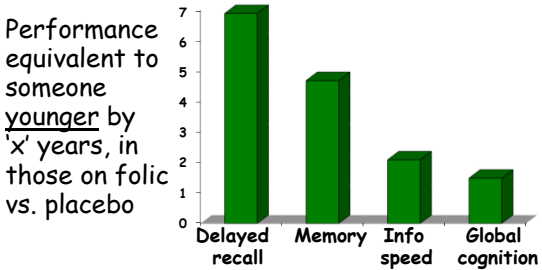
- Low fish intake, or low blood levels of long chain omega-3 fatty acids, are risk factors for AD
- Low folate and B12 status and raised plasma total homocysteine (tHcy) are risk factors for cognitive decline and for AD
- Each of these risk factors has a population attributable risk of about 20%
- What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

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



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 B₁₂ status and rate of brain volume loss in community-dwelling elderly

A. Vogiatzoglou, et al.

Neurology® 2008;71:826-832

Association of Vitamin B₁₂, Folate, and Sulfur Amino Acids With Brain Magnetic Resonance Imaging Measures in Older Adults

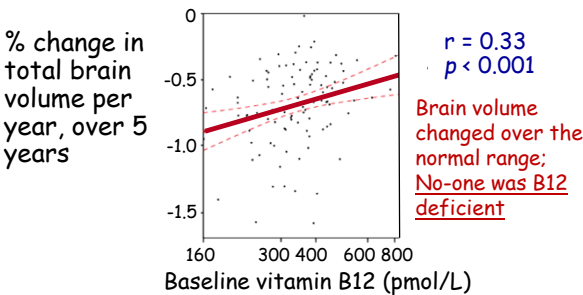
A Longitudinal Population-Based Study

Babak Hooshmand, MD, PhD, MPH; Francesca Mangialasche, MD, PhD; Grégoria Kalpouzos, PhD; Alina Solomon, MD, PhD; Ingemar Käreholt, 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; Mila 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



Vogiatzoglou 2008

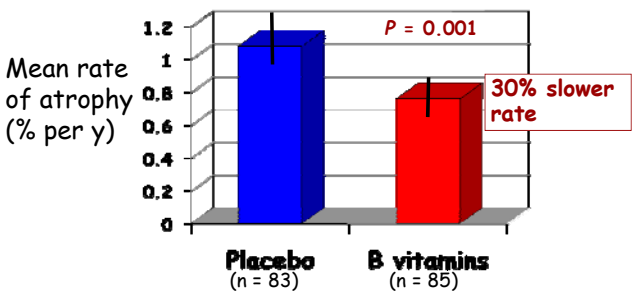
The VITACOG trial

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

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

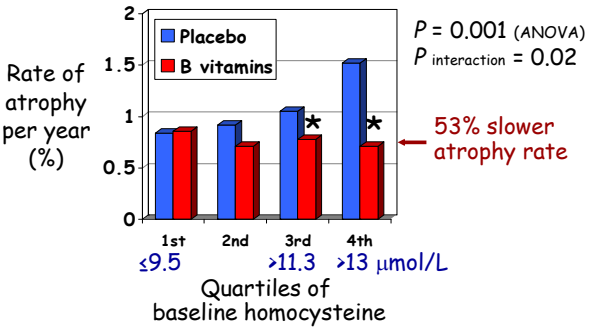


Smith, PLoS ONE 2010, 5: e12244

VITACOG

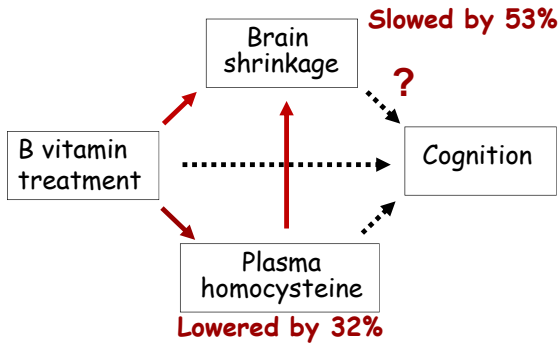
- The main effect is a highly significant slowing of the rate of atrophy by B vitamin treatment
- Pre-specified subgroup analysis: do baseline homocysteine levels interact with effect of B vitamin treatment?

Slowing of atrophy depends on baseline homocysteine

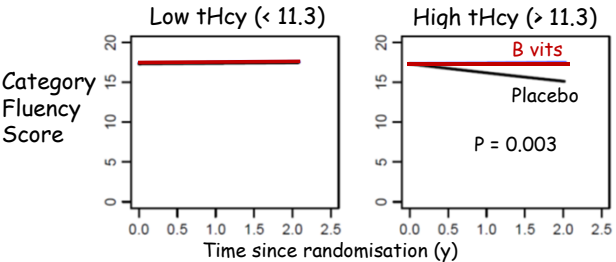


Smith, PLoS ONE 2010

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 (HVL T 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
- | | P value |
|-----------------------------|---------|
| • Executive function (CLOX) | 0.015 |

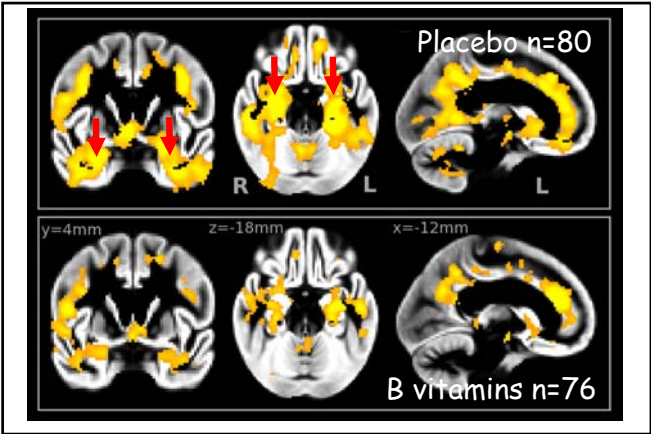
De Jager, Int J Geriatr Psych, 2012

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

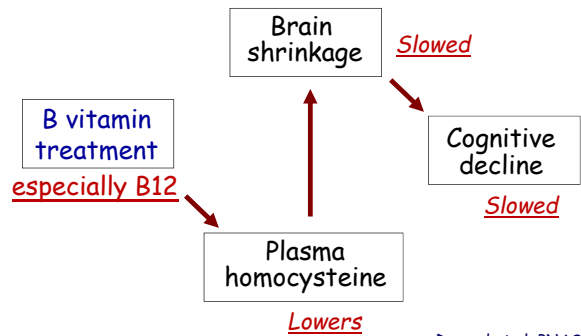
Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

Gwenaelle 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,h,i}
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

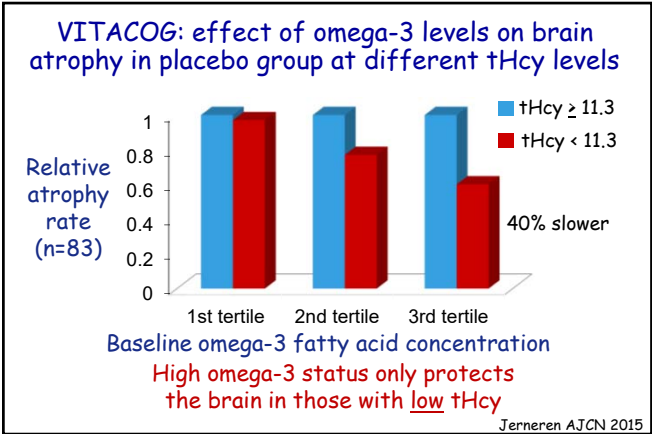
in non-demented Framingham cohort (n=1575)

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?

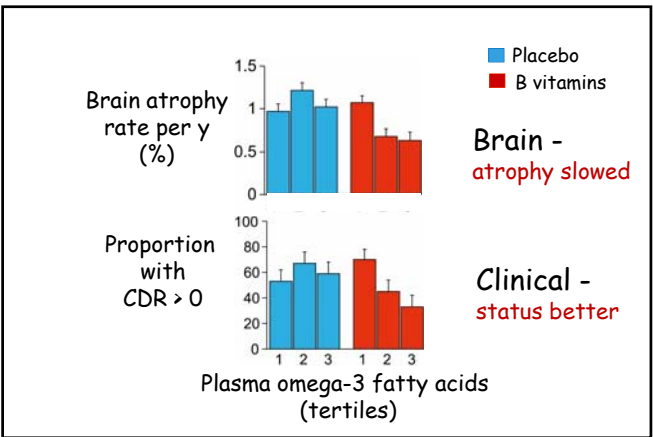
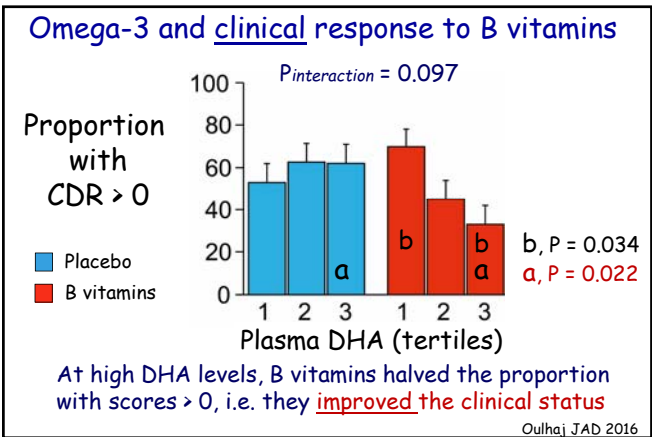
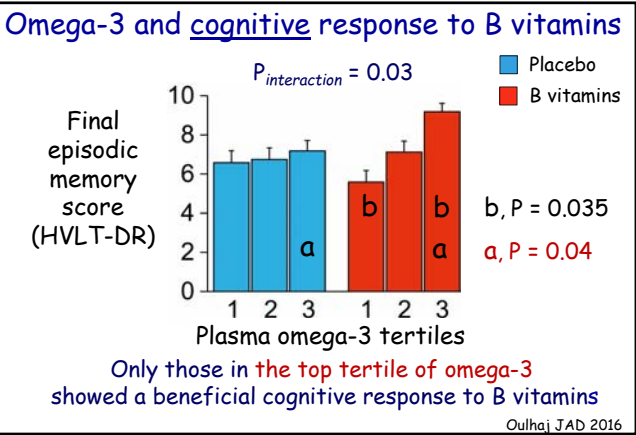
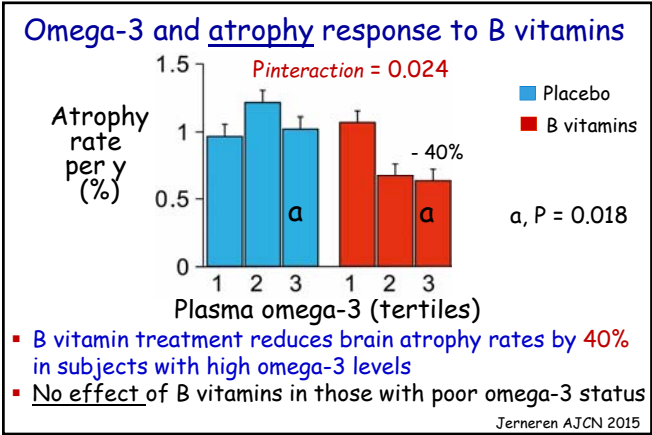


Omega-3 fatty acids and brain atrophy

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?



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?

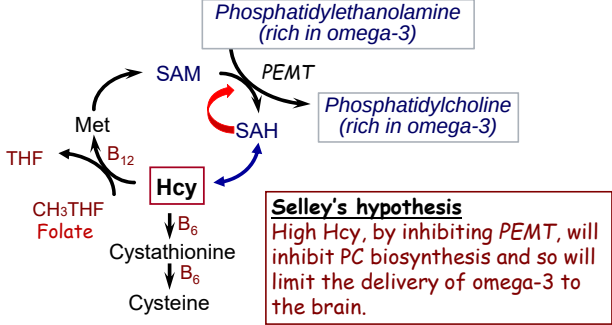
- In AD, there is a deficit in the brain, red cell and plasma of the species of phosphatidylcholine (PC) that are rich in omega-3 fatty acids
(Selley, 2007, Astarita 2010, Yuki 2014, Whiley 2014)
- This form of PC is crucial for normal brain structure and function, especially at the synapse
- This form 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

PC enriched in polyunsaturated fatty acids (omega-3)

Homocysteine and omega-3 fatty acids



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

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