

SATURDAY **1 JULY** 2023  
QEII CENTRE **LONDON** UK

## Patrick Holford

Leading spokesman on nutrition and mental health / Founder, Food for the Brain Foundation and the Institute for Optimum Nutrition

## Prof David Smith

Founder Compass Lifestyle & NHS England Clinical Entrepreneur

**PRESENTING:**

**Are Omega-3 Plus B vitamins the dynamic duo for Dementia prevention?**

 [ipmcongress.com](http://ipmcongress.com)



**food<sup>+</sup>on**  
**prescription**  
CONFERENCE 23

# Homocysteine and Omega-3 fatty acids

- Homocysteine builds up in B vitamin insufficiency  
Levels below 10 are safe; **half the elderly have levels > 11**
- Omega-3 fatty acids are vital membrane components and come from diet. **~ 2/3 have inadequate levels**

## Clinical trials

- Lowering homocysteine by B vitamins can slow cognitive decline
- 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: Why?**

In the Oxford VITACOG trial we found evidence of an **interaction** between B vitamins and omega-3 fatty acids

# The VITACOG trial: Mild Cognitive Impairment

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 to 'TrioBe Plus' (Recip/Meda) (0.8 mg folic acid; 0.5 mg B12; 20 mg B6)

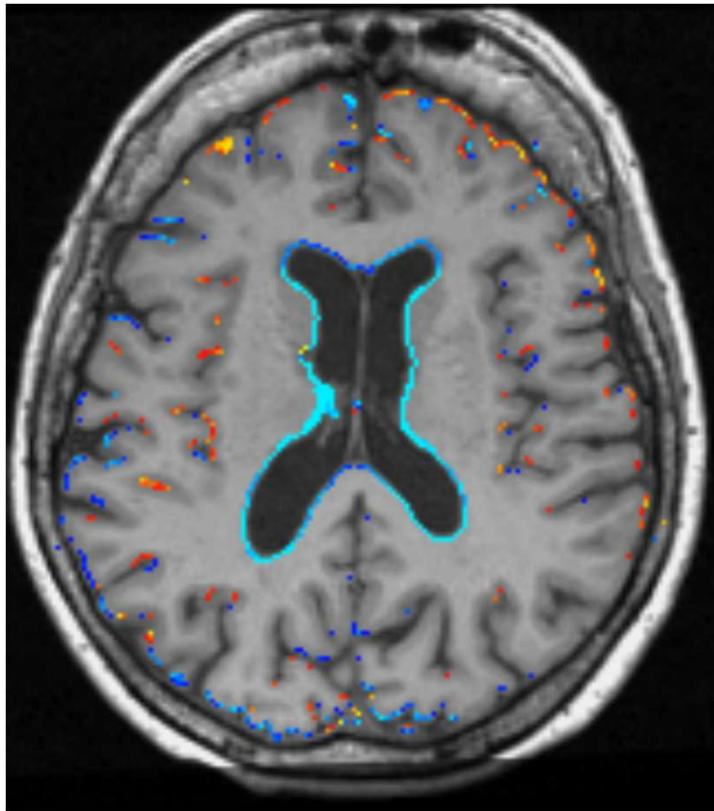
Volumetric MRI scans at start and end (2 years)

**Primary outcome: rate of brain atrophy.** Powered to detect a 20% slowing of atrophy

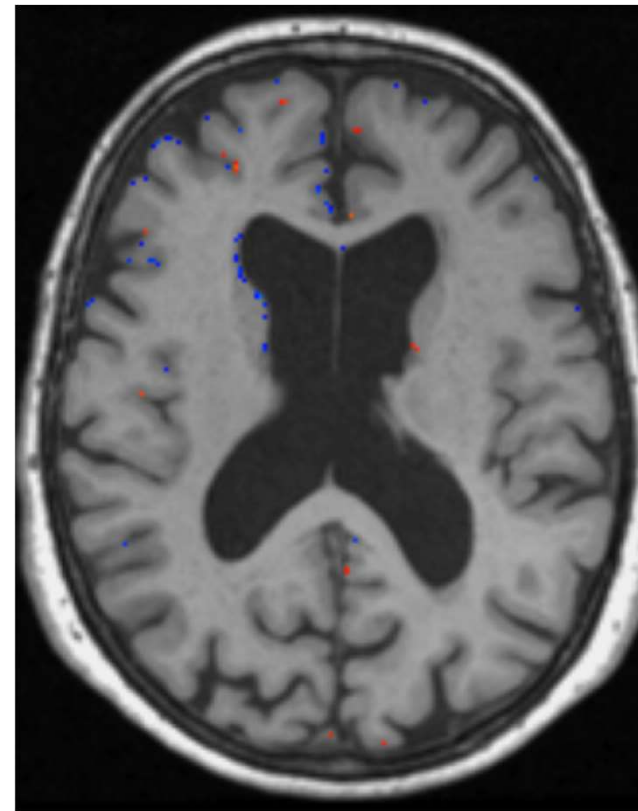
**Secondary outcome:** changes in cognitive test scores

**Homocysteine was lowered by 30%**

Blue indicates shrinkage: 0.3 to 1mm (brightest)



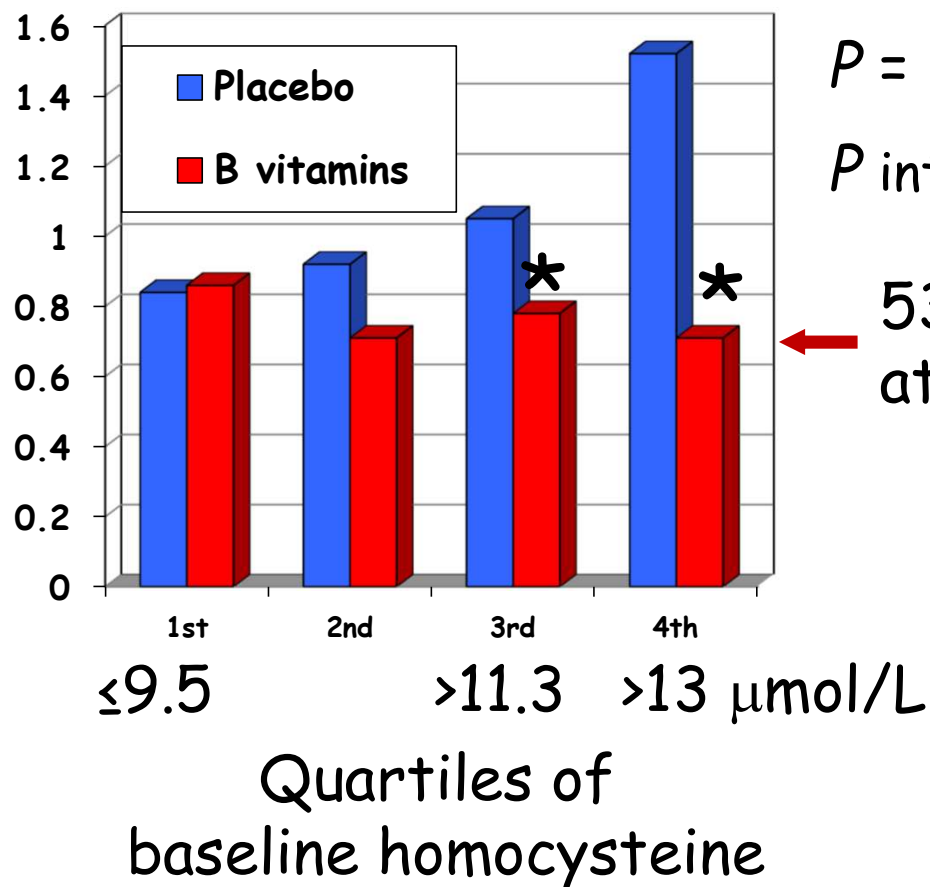
Atrophy 2.5% per y  
Placebo  
tHcy up from 22 to 30



Atrophy 0.46% per y  
Active treatment  
tHcy down from 24 to 12

# Slowing of atrophy depends on baseline homocysteine

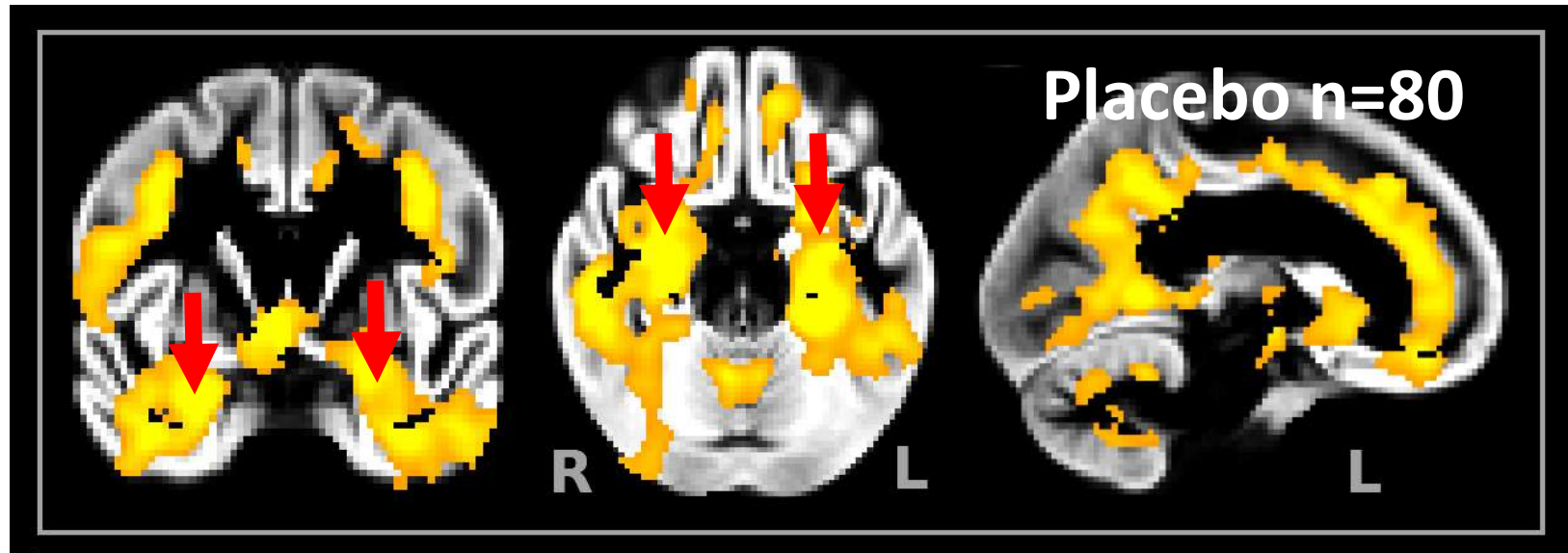
Rate of brain atrophy per year (%)



$P = 0.001$

$P$  interaction = 0.02

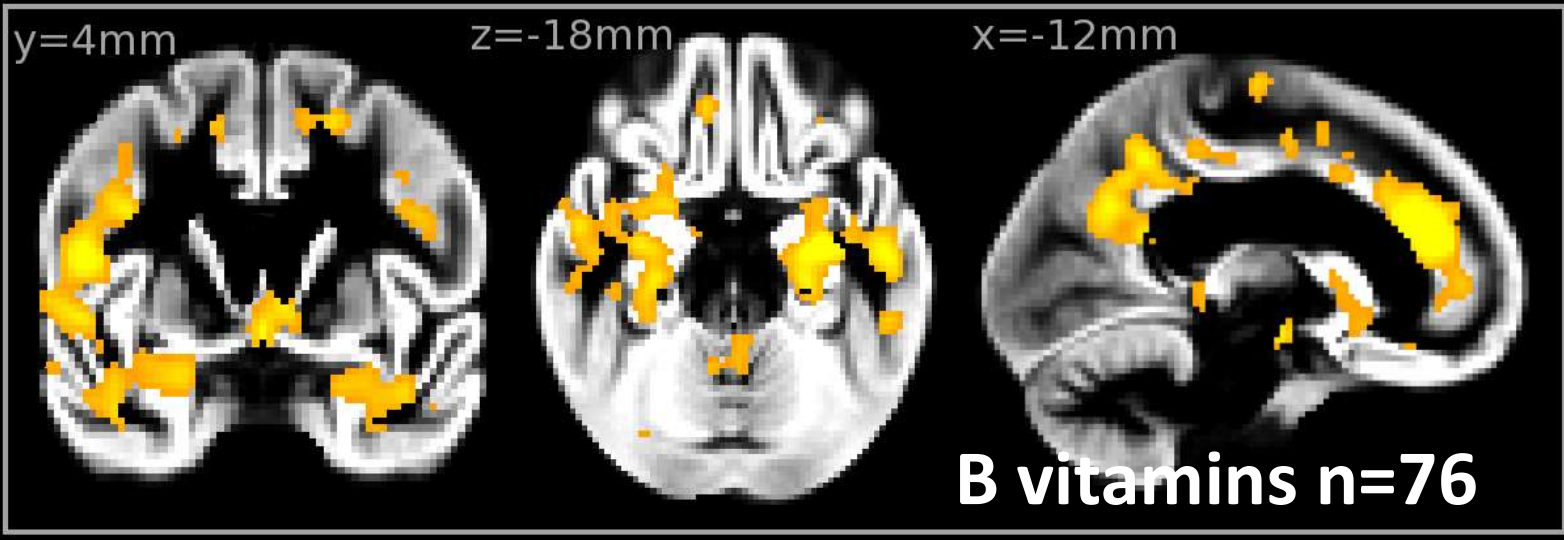
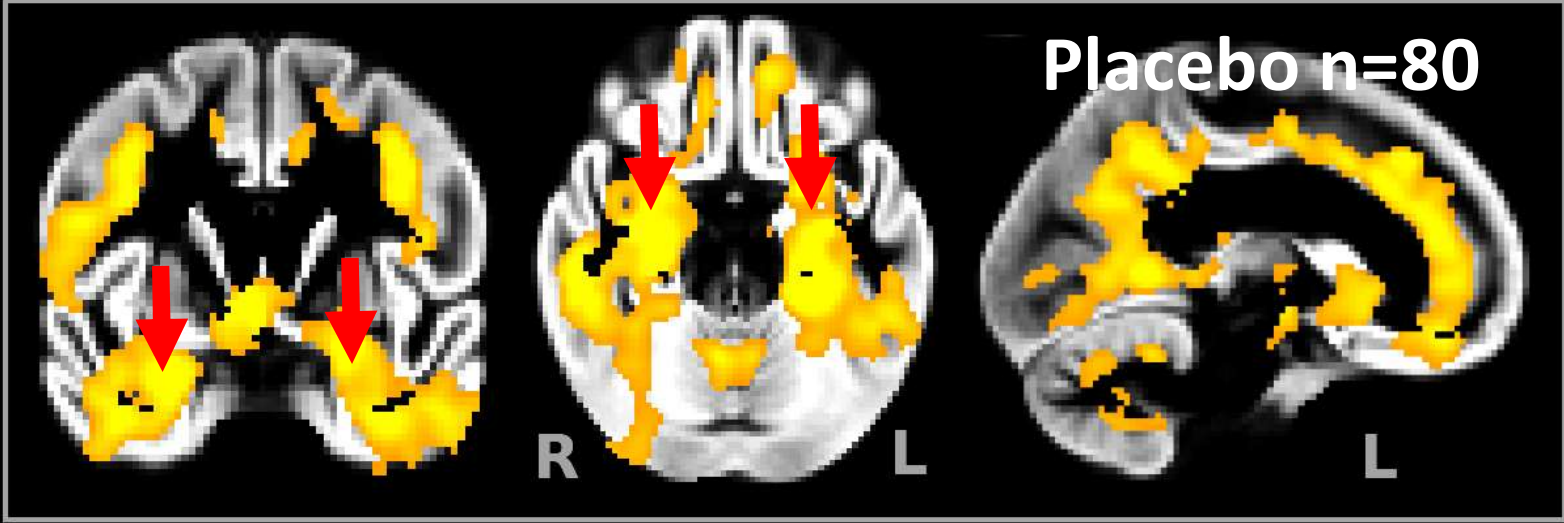
← 53% slower atrophy rate



↓ Medial temporal lobe

Regions (yellow) with significant atrophy over two years ( $P < 0.001$ ) in people with Mild Cognitive Impairment

What happens if we treat for 2 years with B vitamins?





## VITACOG trial

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

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

*Proc Natl Acad Sci* 2013, 110:9523

- Subjects with Mild Cognitive Impairment were treated for 2 years with high doses of folic acid, B6 and B12
- In those with high homocysteine (>11) at baseline, the B vitamin treatment:
  - Slowed whole brain atrophy by up to 53%
  - Slowed atrophy of specific brain regions by 86%
  - Slowed, or stopped, further cognitive decline
  - Improved clinical status assessed by CDR

## Outcomes of the VITACOG trial: effect of B vitamins

**Overall, B vitamins had a disease-modifying effect**

These responses only occurred in subjects with baseline tHcy levels above  $\sim 11 \mu\text{mol/L}$  and, as I will now show, in those with a good omega-3 fatty acid status

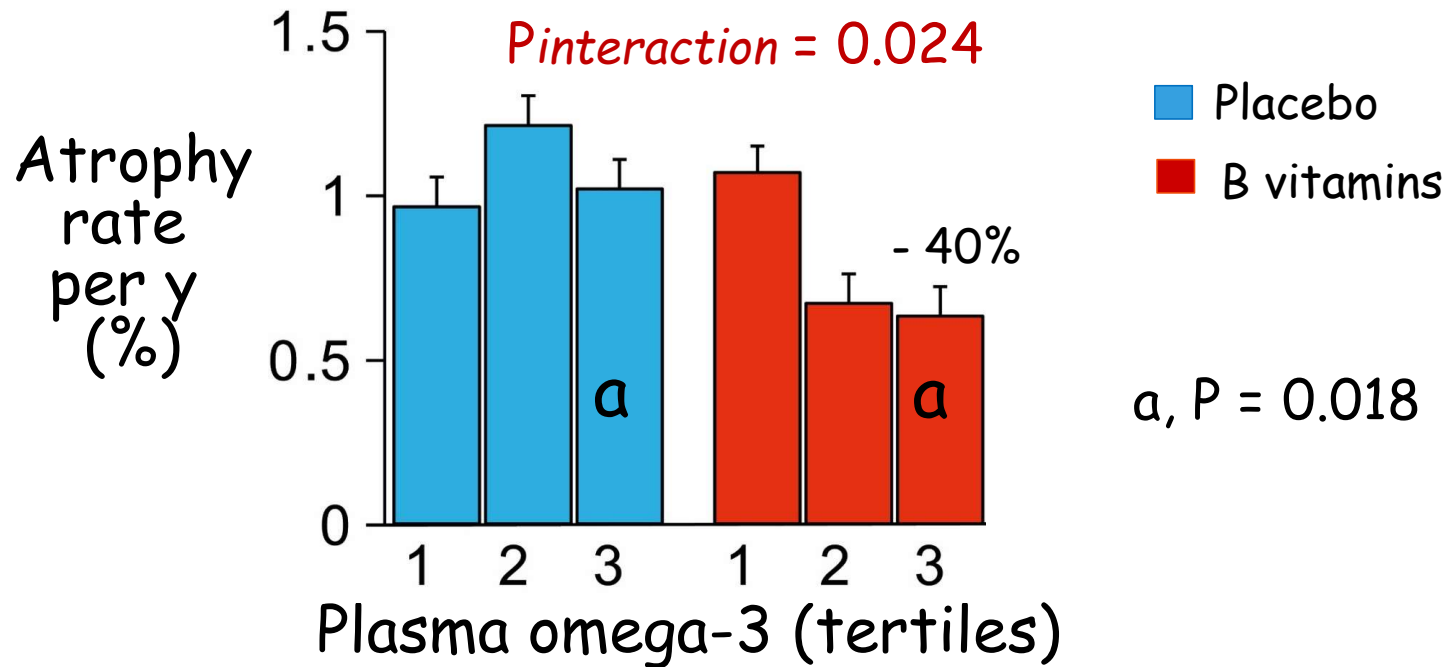
# Omega-3 fatty acids and response to B vitamins

## VITACOG

We asked the question:

- Does baseline omega-3 status influence the atrophy and cognitive *responses to B vitamins?*

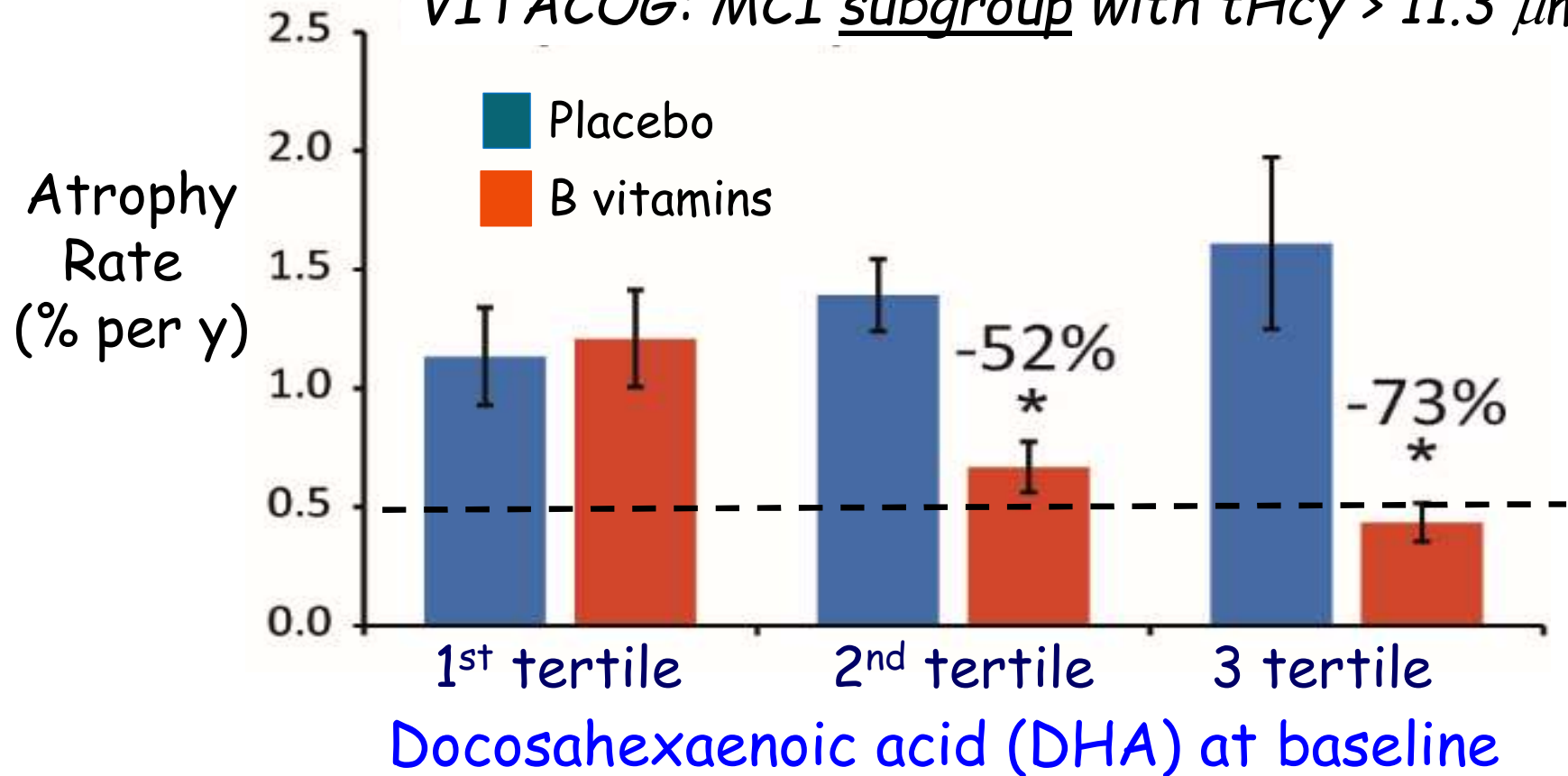
## Omega-3 and atrophy response to B vitamins



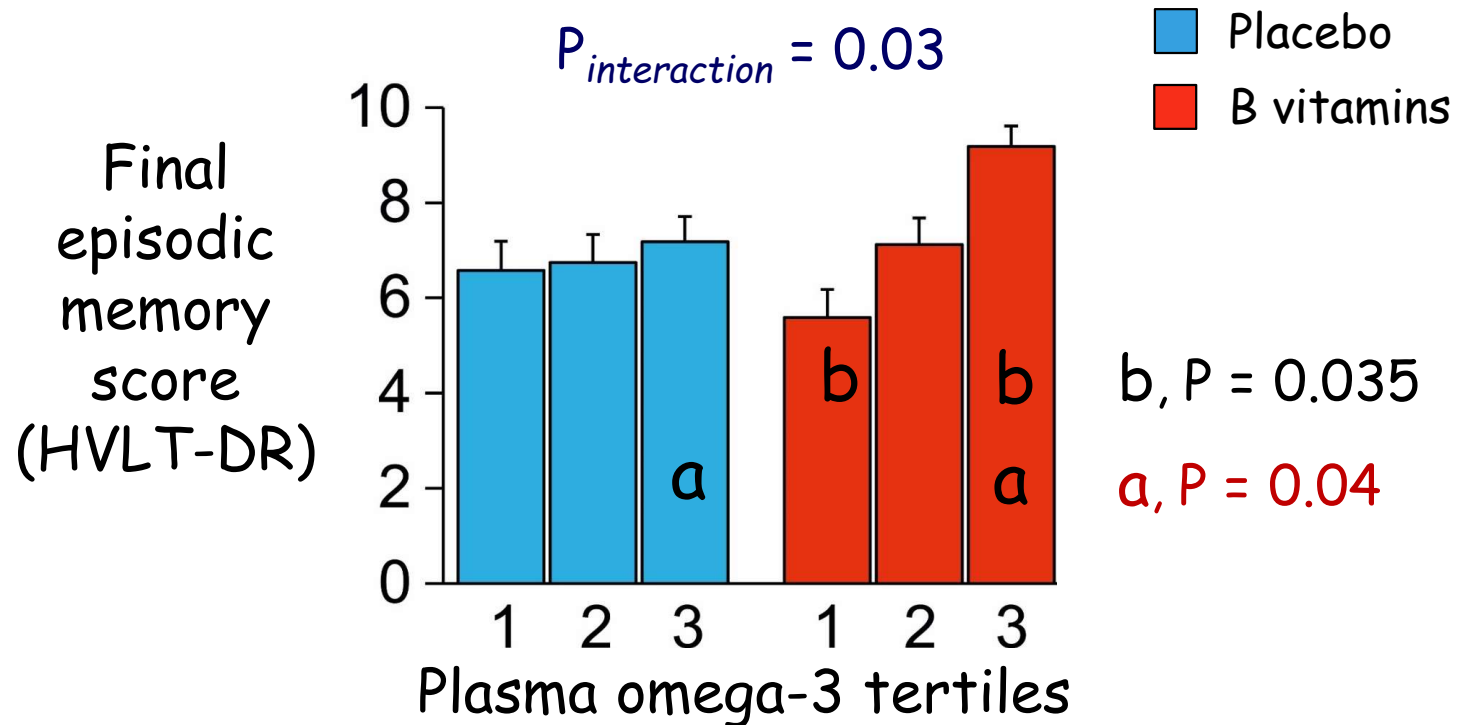
- B vitamin treatment reduces brain atrophy rates by 40% in subjects with high omega-3 levels
- No effect of B vitamins in those with low omega-3 status

Combination of B vitamin treatment with high baseline omega-3 slows atrophy rate to normal in those with high tHcy

VITACOG: MCI subgroup with tHcy > 11.3  $\mu\text{mol/L}$



# 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

## 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 those 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)

## Tentative conclusions from VITACOG trial

- 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 also why some B vitamin trials have failed



# Clinical trials of B vitamins and cognition

## *Positive trials*

- FACIT trial, Netherlands, normal ageing (Durga 2007)
- VITACOG trial Mild Cognitive Impairment (Oxford 2010)
- Mild Cognitive Impairment (China, Ma 2019)
- AD (China, Chen 2021)

## *Negative trials*

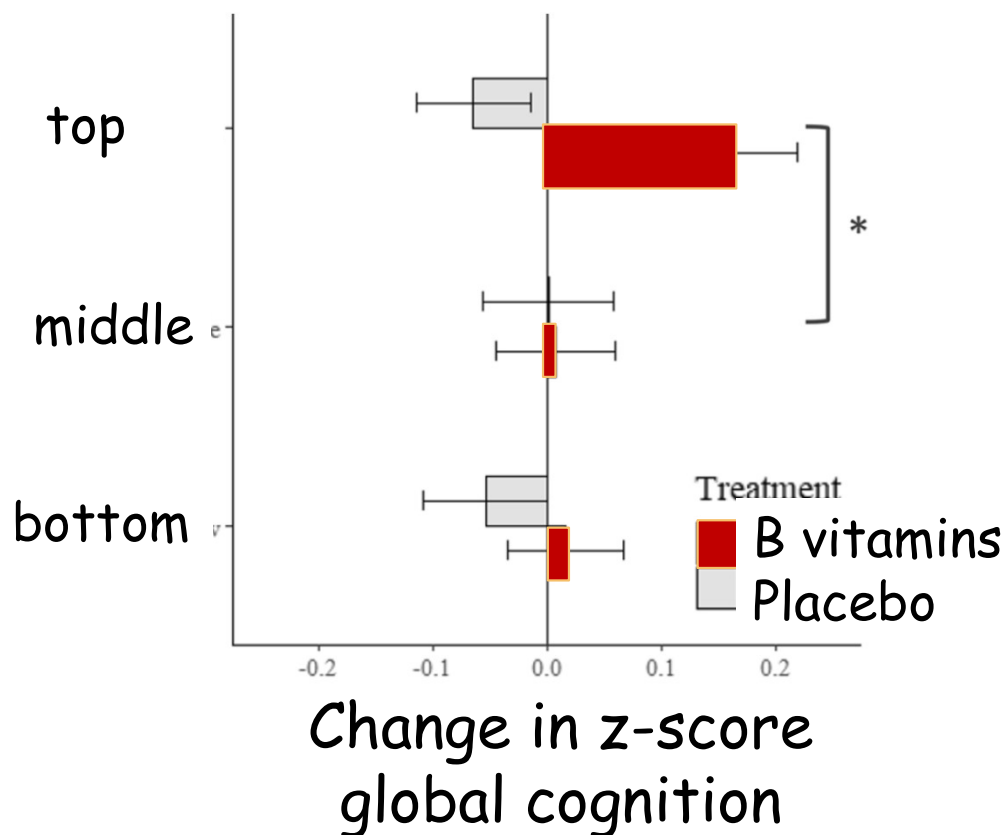
- B-proof trial, normal ageing (van der Zwalu 2014)
- MCI, Hong Kong (Kwok 2020)

*Hypothesis:* did the trial populations in the negative trials have **insufficient omega-3 status?**

# Clinical trials of B vitamins and cognition

B-proof trial, post-hoc (van Soest 2022)

Tertiles of  
docosahexaenoic  
acid  
DHA



Cognitive  
benefit from  
B vitamins  
only those in  
top tertile of  
DHA

# Clinical trials of omega-3 fatty acids and cognition

## *Positive trials*

- Cognitive aging DHA (Yurko-Mauro 2010)
- Mild Cognitive Impairment (China) 6 mo (Bo 2017)
- Mild Cognitive Impairment(China) 12 mo (Zhang 2017)

## *Negative trials*

- OmegAD trial in Uppsala (Freund-Levi 2006)
- Alzheimer's Disease Cooperative Study DHA (Quinn 2010)
- MAPT trial in France (Andrieu 2017)

*Hypothesis:* did the trial populations in the negative trials have insufficient B vitamins?

## $\omega$ -3 Fatty Acid Treatment in 174 Patients With Mild to Moderate Alzheimer Disease: OmegAD Study

### *A Randomized Double-blind Trial*

Yvonne Freund-Levi, MD; Maria Eriksdotter-Jönhagen, MD, PhD; Tommy Cederholm, MD, PhD; Hans Basun, MD, PhD; Gerd Faxén-Irving, PhD; Anita Garlind, MD, PhD; Inger Vedin, MSci; Lars-Olof Wahlund, MD, PhD; Jan Palmblad, MD, PhD

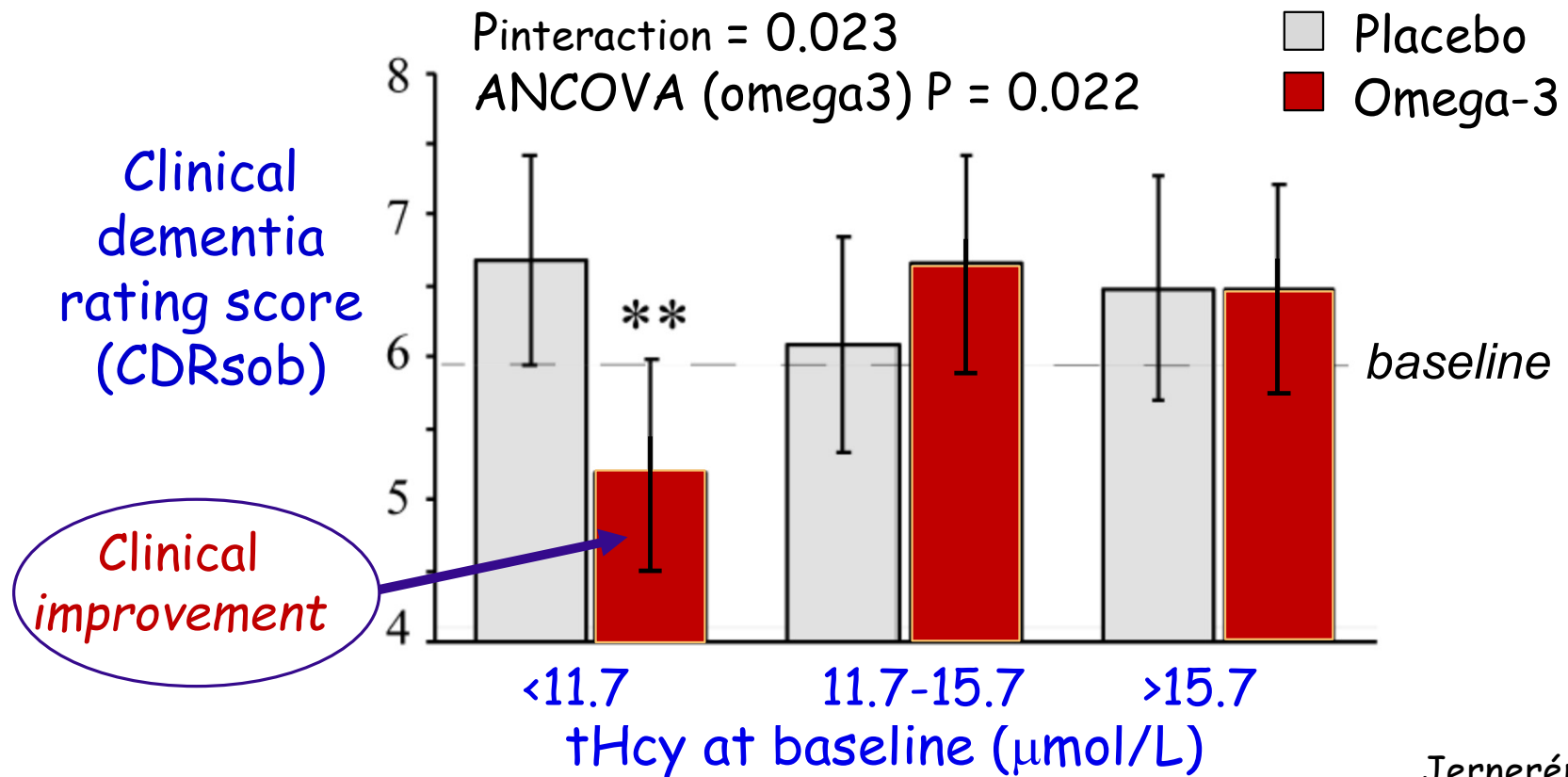
*Arch Neurol.* 2006;63:1402-1408

No beneficial effect on cognition of supplementation with 2.3g/day omega-3 fatty acids (DHA & EPA) - apparently a failed trial

- We asked the question: **does omega-3 treatment need a good B vitamin status to work in Alzheimer's?**
- We measured tHcy as a marker for B vitamin status

# Importance of B vitamin status for beneficial effect of omega-3 fatty acids in Alzheimer's disease

**OmegAD trial: omega-3 treatment for 6 months**



# New meta-analysis confirms the findings

The effects of multi-nutrient formulas containing a combination of *n*-3 PUFA and B vitamins on cognition in the older adult: a systematic review and meta-analysis

*British Journal of Nutrition* (2023), 129, 428–441

Paul Fairbairn<sup>1\*</sup>, Simon C. Dyllal<sup>2†</sup> and Fotini Tsofliou<sup>1†</sup>

<sup>1</sup>*Department of Rehabilitation and Sport Sciences, Bournemouth University, Poole, UK*

<sup>2</sup>*School of Life and Health Sciences, University of Roehampton, London, UK*

“The results indicate that providing a combination of *n*-3 PUFA and B vitamins as part of a multi-nutrient formula benefits cognition in older adults versus a placebo, and the potential for an interaction between these key nutrients should be considered in future experimental work.”

## What next?

Urgent need for a trial in Mild Cognitive Impairment of a *combination* of B vitamins and omega-3 fatty acids to see if this combination slows, or prevents, conversion to dementia

“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