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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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

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.

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)

Omega-3 fatty acids and Alzheimer’s disease

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

Omega-3 fatty acids (high vs. low) and risk of incident AD
Population attributable risk of AD for low omega-3 is 22%

20,344 subjects
Pooled relative risk of AD
0.67 (0.47,0.95)

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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

![The methionine cycle diagram]

3 B vitamins regulate the level of homocysteine

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

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

Homocysteine and dementia in the Framingham study

![Homocysteine and dementia in the Framingham study graph]

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?

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.

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

Baseline vitamin B12 (pmol/L) vs. % change in total brain volume over 5 years

Serum B12 is related to rate of brain atrophy

Baseline vitamin B12 (pmol/L)

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)

Mean rate of atrophy (% per y)

Placebo (n = 83)

B vitamins (n = 85)

30% slower rate

$P = 0.001$


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

Rate of atrophy per year (%)

Quartiles of baseline homocysteine

≤ 9.5

>11.3

>13 μmol/L

$P = 0.001$ (ANOVA)

$P_{interaction} = 0.02$

53% slower atrophy rate

VITACOG matrix

Brain shrinkage

Slowed by 53%

B vitamin treatment

Plasma homocysteine

Lowered by 32%

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

Low tHcy (< 11.3)

High tHcy (> 11.3)

Category Fluency Score

Time since randomisation (y)

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


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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

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

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

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?
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

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 fatty acids and brain atrophy

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

Omega-3 and cognitive response to B vitamins

Final episodic memory score (HVLT-DR)

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

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

Proportion with CDR > 0

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

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)

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

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 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
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.

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