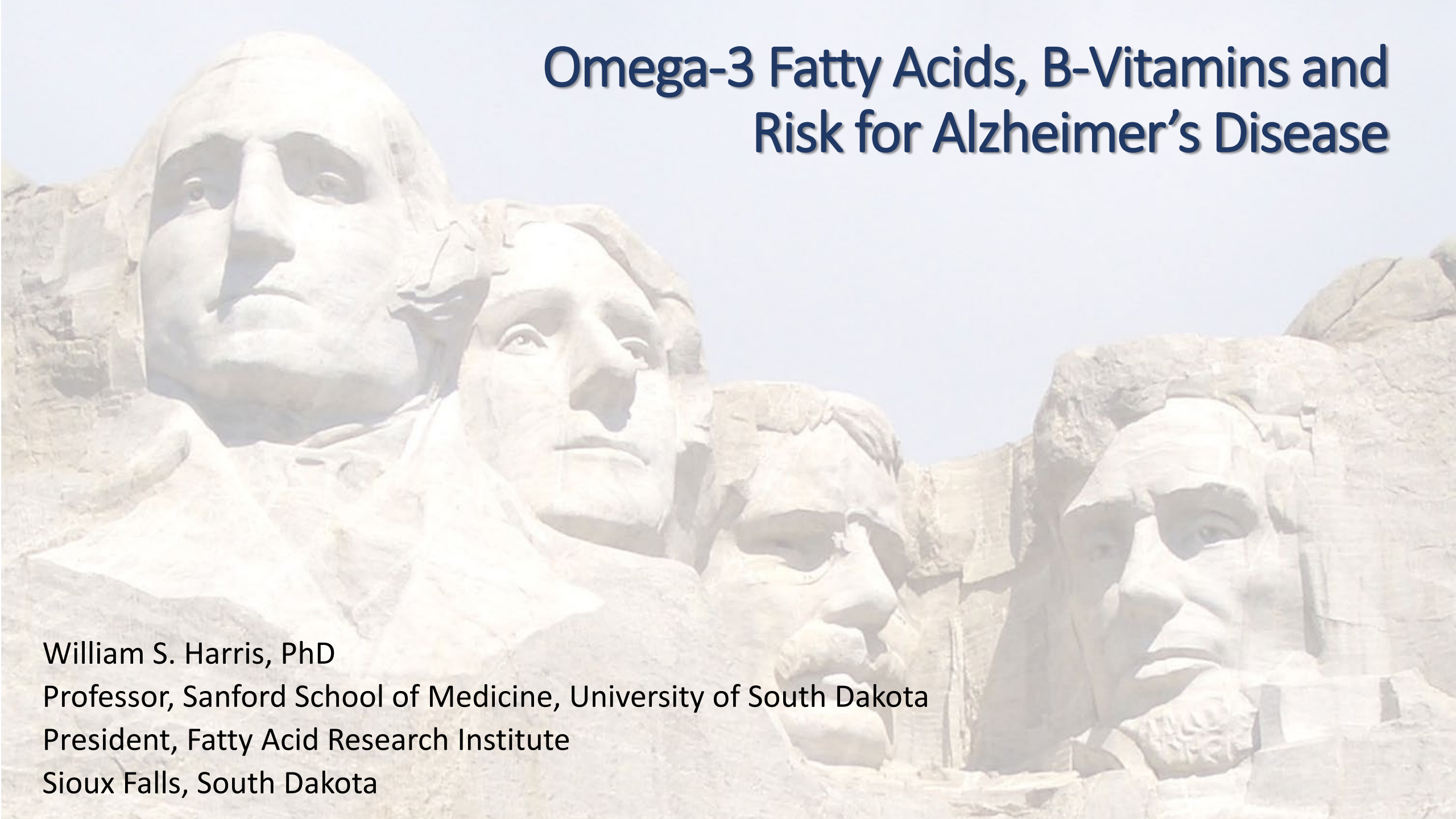
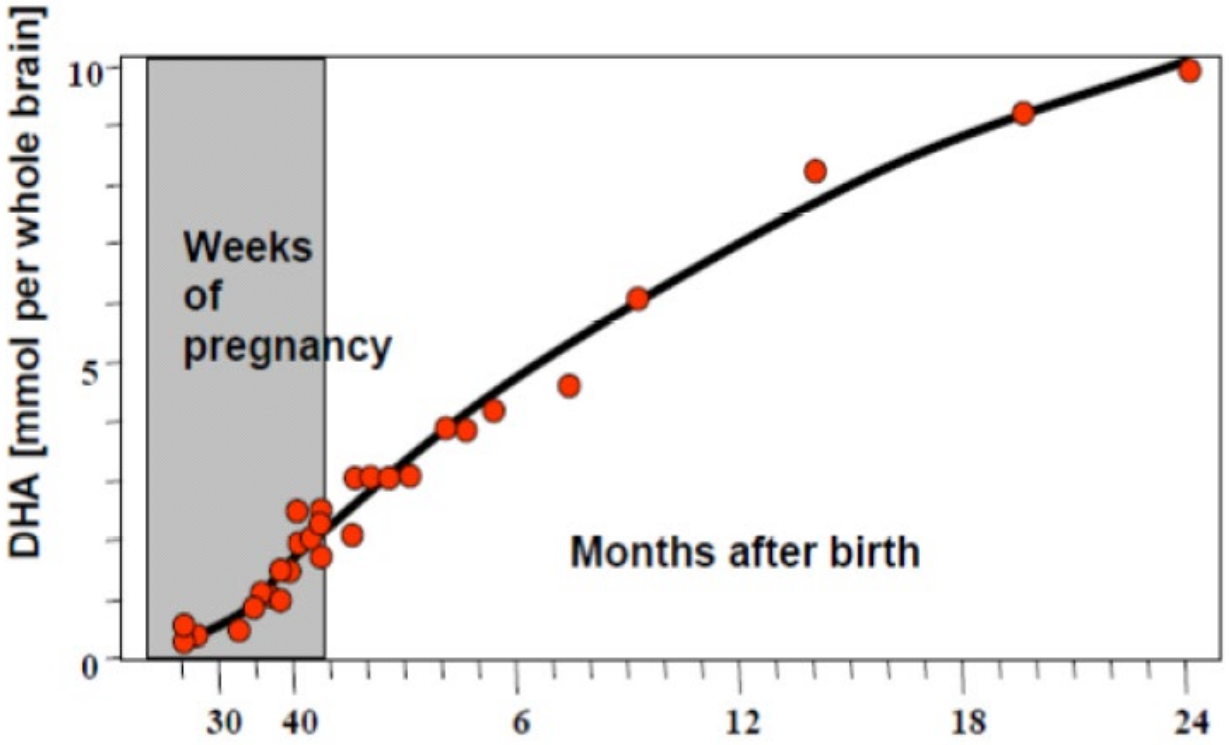
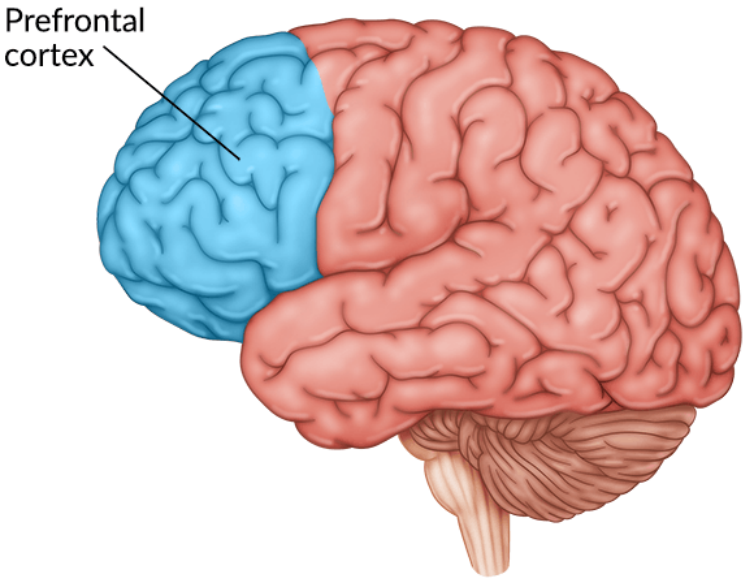
Omega-3 Fatty Acids, B-Vitamins and Risk for Alzheimer's Disease



William S. Harris, PhD
Professor, Sanford School of Medicine, University of South Dakota
President, Fatty Acid Research Institute
Sioux Falls, South Dakota

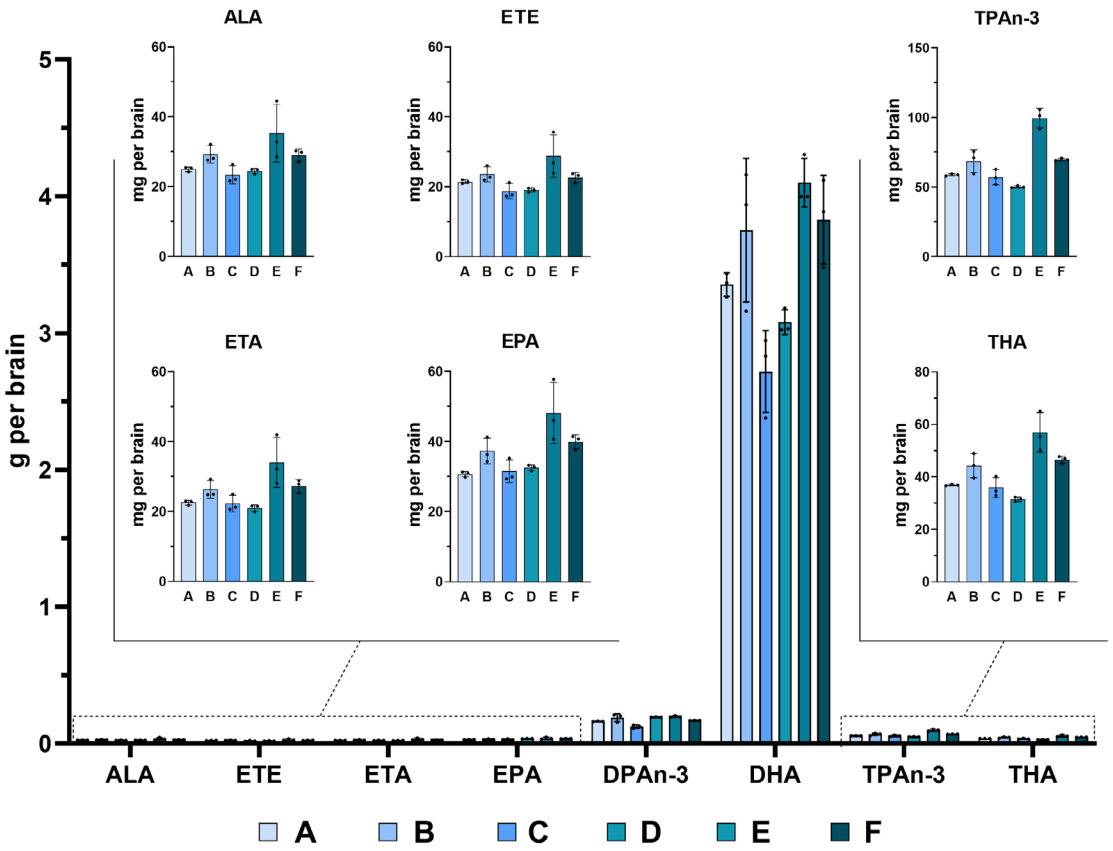
DHA brain accretion starts even before birth

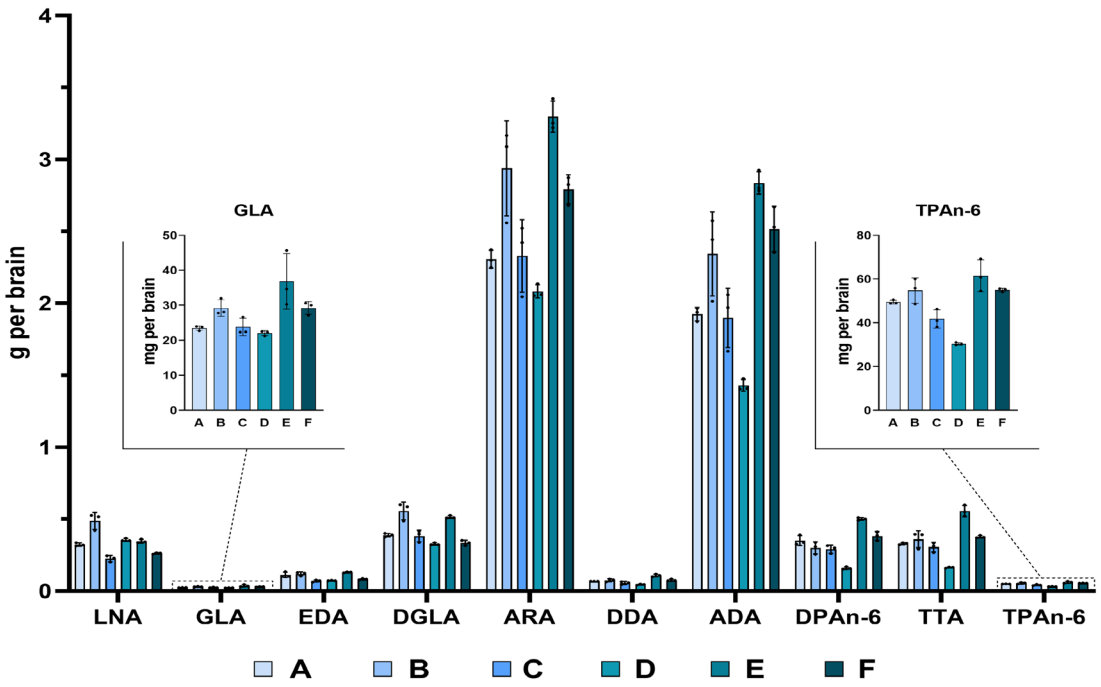




Adapted from Martinez M, World Rev. Nutr. Diet. 1991;66:87–102

DHA and ARA – Primary Polyunsaturated Fatty Acids in the Human Brain



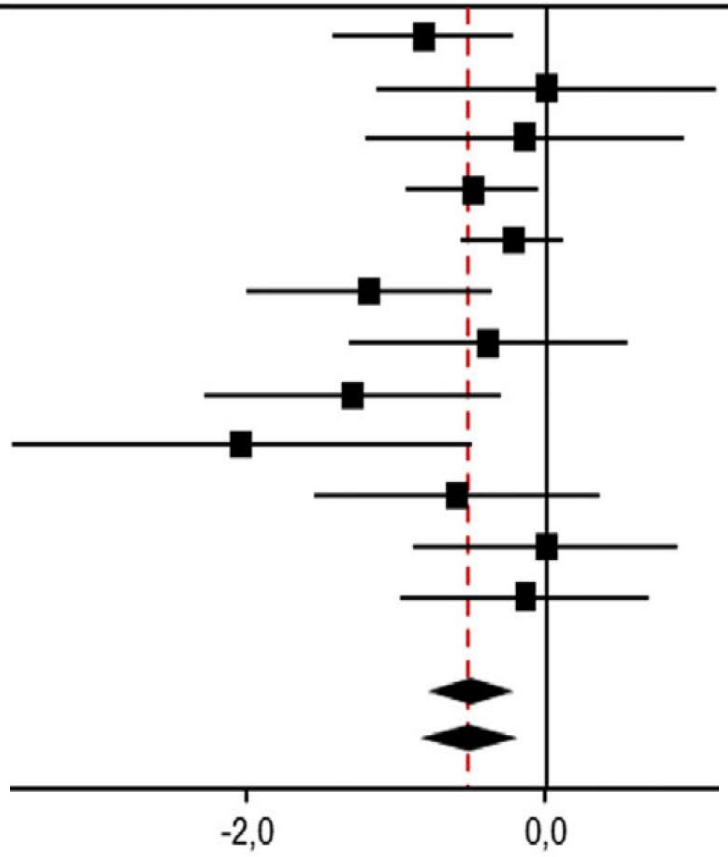


Lacombe, et al. J Neurochem 2023;164:44–56.

Estimated total lipid content of the brain = 7.5% of wet weight

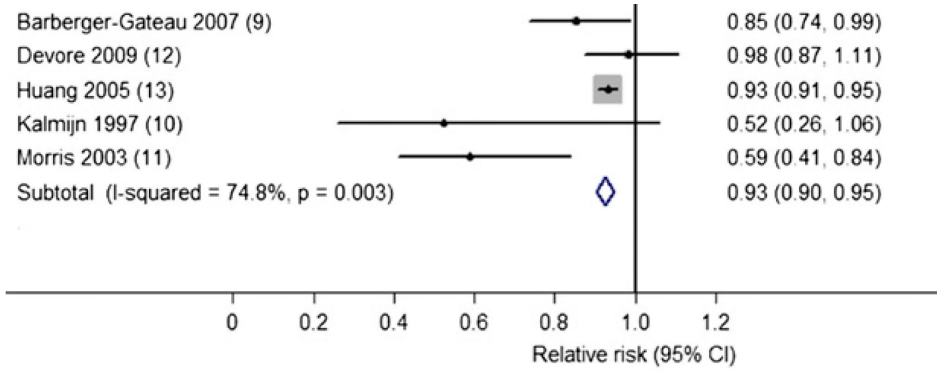
Lower DHA in brains of donors with Alzheimer's Disease

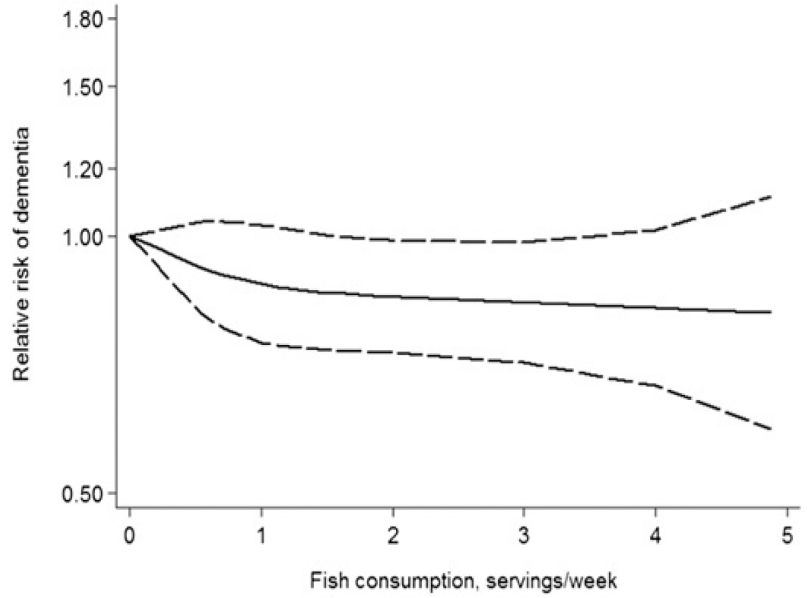
Study	Mean	SD	N	Mean	SD	N	Hedges-g	95% CI	Weight (%)
Astarita, 2010[61]	8,26	4,06	37	11,52	3,58	17	-0,82	(-1,42; -0,22)	11,7
Brooksbank, 1989[65]	25,9	3,67	6	25,9	1,54	6	0,00	(-1,13; 1,13)	4,2
Corrigan, 1998[66]	1,39	2,04	8	1,64	1,17	6	-0,14	(-1,2; 0,92)	4,7
Fonteh, 2014[62]	15,3	2,2	29	16,8	3,3	69	-0,49	(-0,93; -0,05)	17,0
Fraser, 2010[67]	14,51	2,42	86	14,98	1,53	55	-0,22	(-0,56; 0,12)	21,8
Guan, 1999[68]	0,82	0,19	15	1,09	0,25	13	-1,19	(-2,01; -0,38)	7,4
Igarashi, 2011[69]	6626	1038	10	7244	1903	9	-0,39	(-1,30; 0,52)	6,1
Martin, 2010[63]	4,91	1,74	10	6,87	1,07	10	-1,30	(-2,28; -0,31)	5,5
Nakada, 1990[64]	0,53	0,3	5	1,71	0,67	5	-2,05	(-3,59; -0,52)	2,4
Prasad, 1998[70]	84	54	9	121	63	9	-0,60	(-1,55; 0,35)	5,7
Reich, 2001[71]	14,3	0,4	9	14,3	0,4	11	0,00	(-0,88; 0,88)	6,4
Skinner, 1993[72]	17,1	4,07	13	17,57	1,34	10	-0,14	(-0,97; 0,68)	7,1
Total			**237**			**220**			
Random unadjusted Overall (REML) p = 0,0018							**-0,51**	**(-0,77; -0,24)**	
Random centr, age adjusted Overall (REML) p = 0,0025							**-0,52**	**(-0,81; -0,23)**	



De Wilde et al., Alzheimers Dement (NY). 2017;3:416-31

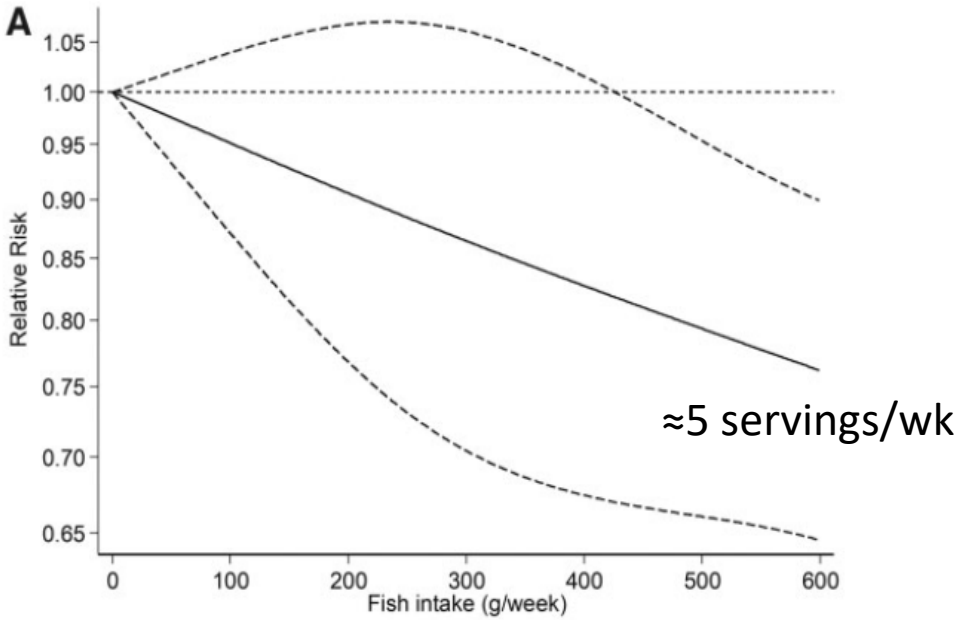
So… can fatty fish prevent Alzheimer's disease?





Zhang et al., Am J Clin Nutr. 2016;103:330-40

"Based on findings with low/moderate risk of bias, fish intake of up to 2 portions (250 g) per week was associated with a 10% reduction in all-cause dementia and a 30% reduction in AD risk. Changes in EPA and DHA body status had a positive impact on participants' executive functions, but not on their overall cognitive performance."



≈5 servings/wk

Kosti et al., Nutr Rev. 2022;80:1445-1458

Clinical Nutrition 41 (2022) 589–598

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Association of fish oil supplementation with risk of incident dementia: A prospective study of 215,083 older adults

Xiaohui Liu [a], Pan Zhuang [b], Yin Li [a], Fei Wu [a], Xuzhi Wan [b], Yu Zhang [b], Jingjing Jiao [a, *]

Table 2
HRs (95% CIs) of dementia according to fish oil supplement use in the UK Biobank study.

	Fish oil supplement non-users (n = 130,222)	Fish oil supplement users (n = 84,861)	*P* Trend
No of cases (%)	1304 (1.0)	750 (0.9)	
Person-years	1,027,321	675,926	
Age- and sex-adjusted HR (95% CI)	1 [Reference]	0.84 (0.77–0.92)	0.001
Model 1[a]	1 [Reference]	0.87 (0.79–0.96)	0.006
Model 2[b]	1 [Reference]	0.87 (0.79–0.96)	0.007
Model 3[c]	1 [Reference]	0.87 (0.79–0.96)	0.004

Even after adjusting for multiple possible confounders, FOS users were still 13% less likely to develop dementia than non-users

RBC DHA levels predict risk for incident dementia/Alzheimer's Disease in Framingham

- DHA content of RBC membranes were measured in 1490 dementia-free subjects from Framingham Offspring cohort over the age of 65
- Average age 73 yrs
- Incidence of dementia/AD tracked over median of 7.3 yrs

Sala-Vila et al. *Nutrients* 2022;14:2408

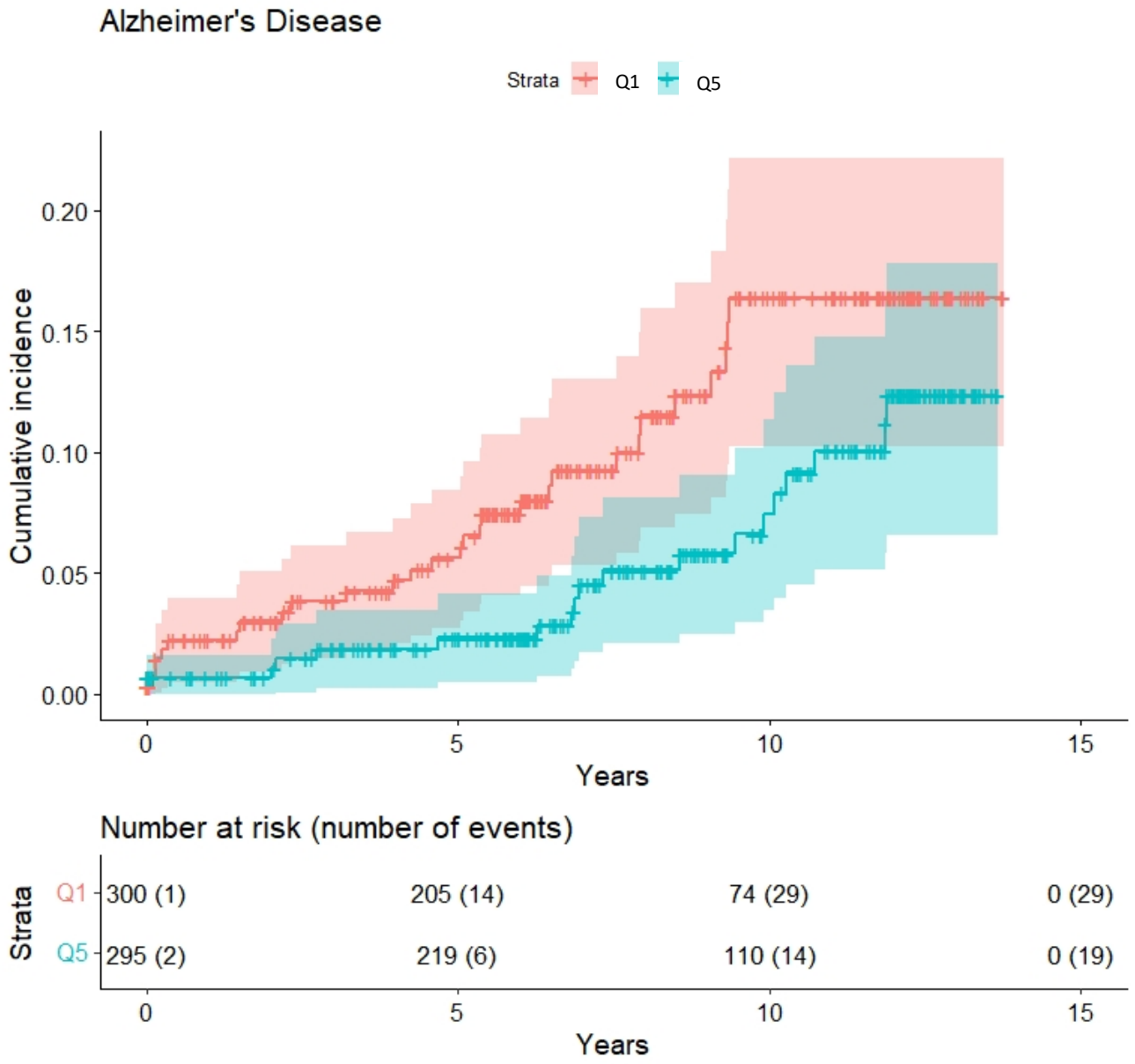
Risk for developing Alzheimer's disease over an average of 7.3 years as a function of baseline RBC DHA in Framingham

Endpoint	HR (95% CI) for quintiles of red blood cell DHA				
	Q1 (<3.8%, median = 3.4%) (n = 300)	Q2 (3.8% to <4.5%, median = 4.2%) (n = 298)	Q3 (4.5% to <5.2%, median = 4.8%) (n = 297)	Q4 (5.2% to 6.1%, median = 5.6%) (n = 297)	Q5 (>6.1%, median = 6.97%) (n = 295)
Alzheimer's disease					
N. of cases	29	30	24	29	19
Hazard Ratio	1.00	0.77 (0.45, 1.33)	0.64 (0.35, 1.18)	0.75 (0.42, 1.33)	0.51 (0.27, 0.96)
All-cause dementia					
N. of cases	35	38	29	40	26
Hazard Ratio	1.00	0.79 (0.49, 1.29)	0.64 (0.37, 1.11)	0.87 (0.53, 1.44)	0.56 (0.32, 0.97)

49% lower risk for AD comparing Q5 to Q1

Sala-Vila et al. *Nutrients* 2022;14:2408

Rate of developing Alzheimer's disease over ~13 years as a function of baseline RBC DHA in Framingham



Sala-Vila et al. *Nutrients* 2022;14:2408

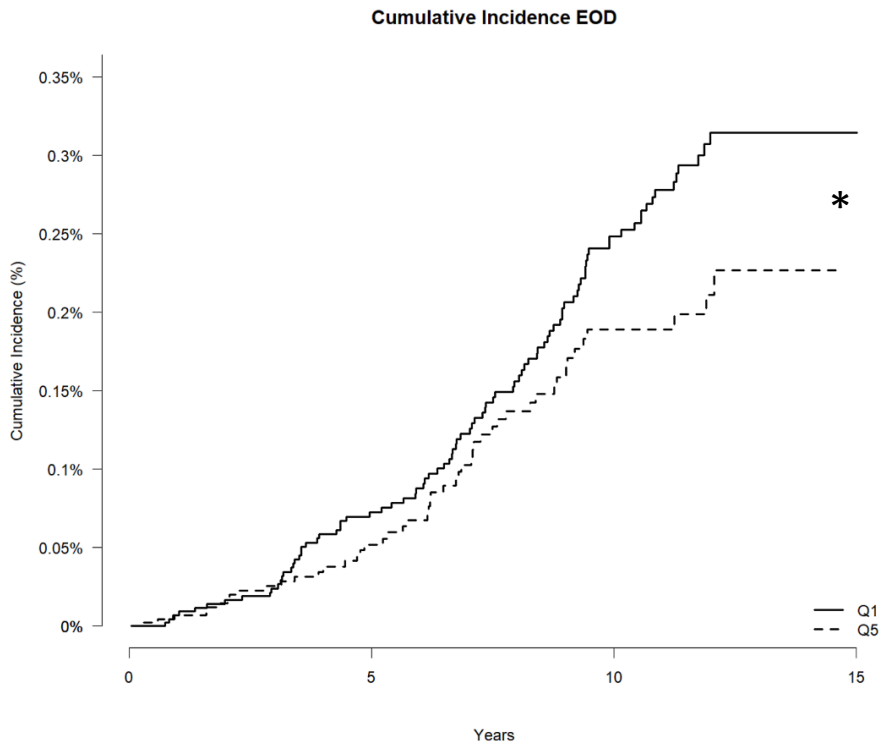
Plasma Omega-3 Levels and Risk for Early Onset Dementia: UK Biobank

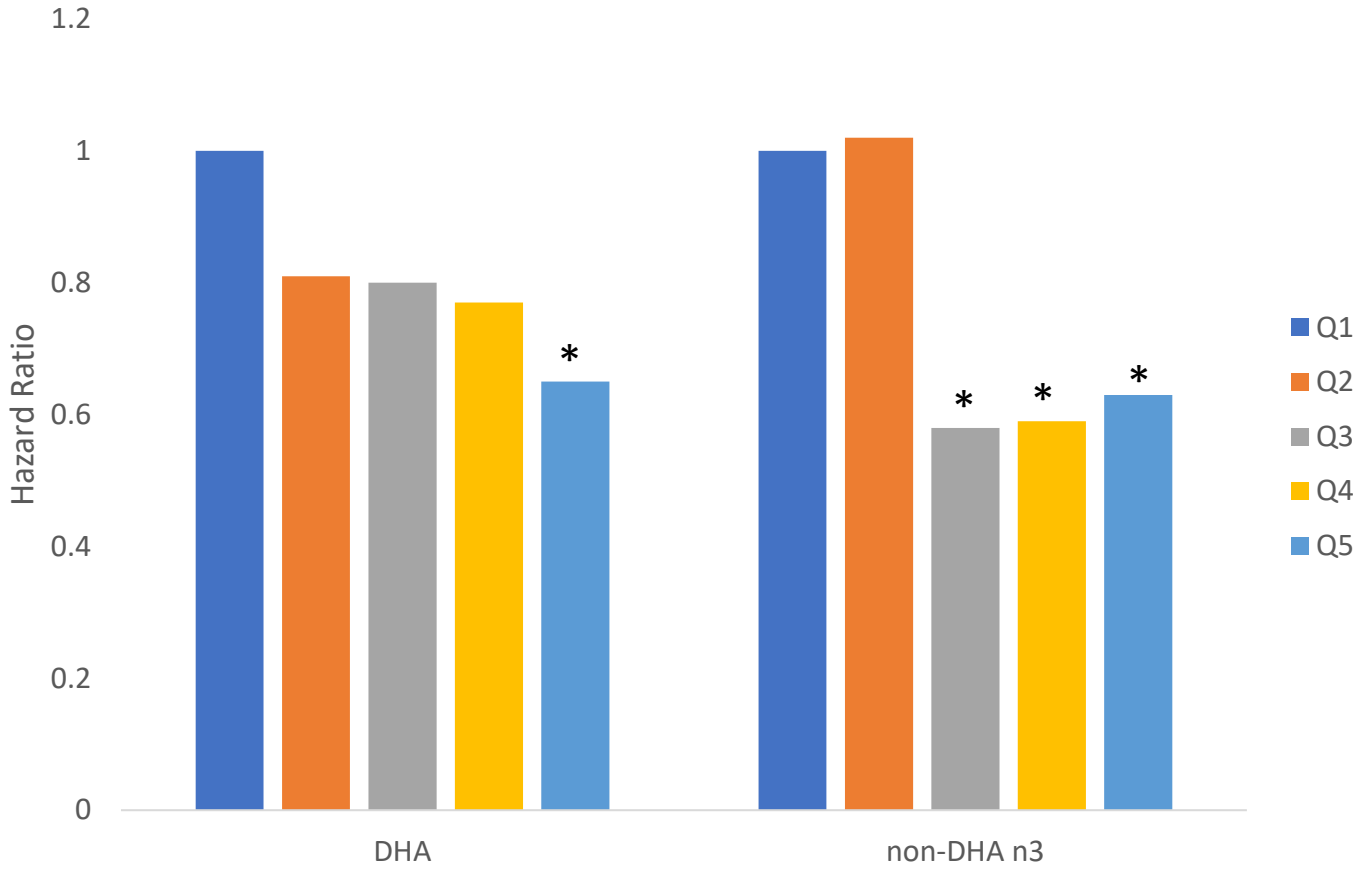
- Early onset = dementia diagnosis before age 65
- UKBB participants 40-64 yr old at baseline without diagnosis of dementia
- 217,222 participants included
- After 8.3 years of follow-up, 325 incident cases of early onset dementia
- Compared risk for early onset dementia as a function of quintiles of total omega-3, DHA and non-DHA omega-3

Sala-Vila, et al. Clin Nutr 2026;57:106559

Plasma Omega-3 Levels are Inversely Related to Risk for Early Onset Dementia: UK Biobank

Total Plasma Omega-3





Sala-Vila, et al. Clin Nutr 2026;57:106559

*p<0.05

ω-3 Ethyl ester results in better cognitive function at 12 and 30 months than control in cognitively healthy subjects with coronary artery disease: a secondary analysis of a randomized clinical trial

Abdulaziz Malik, Amira Ramadan, Bhavya Vemuri, Wardah Siddiq, Maral Amangurbanova, Aamir Ali, and Francine K Welty

Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

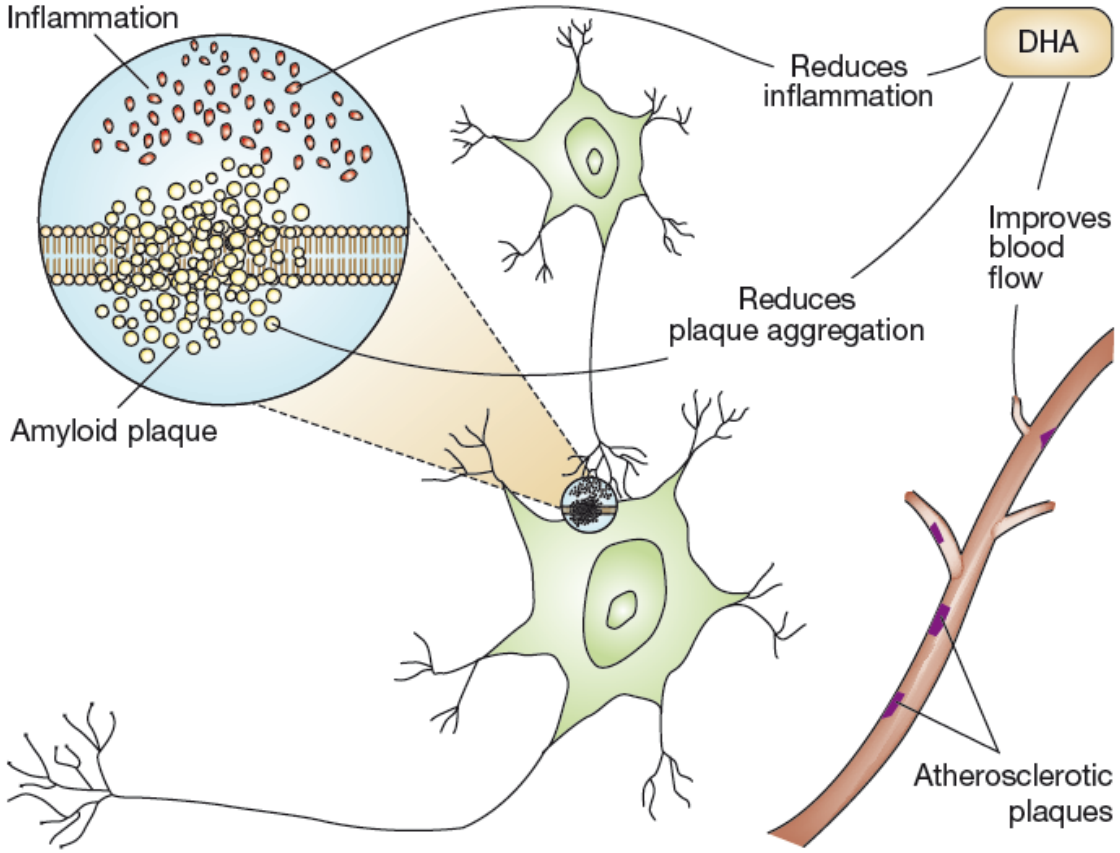
285 patients with stable CAD were randomized to **4 g of Lovaza** or not (control) for 30 months. Effects on neuropsychological tests were evaluated.

"In the current trial, subjects randomly assigned to EPA and DHA had significantly better cognitive function scores for **verbal fluency**, **language**, and **memory** and 2 tests of **visual-motor coordination** than the control group over the 30-mo period."

"The improvement in the EPA and DHA group is **clinically important** and suggests that EPA and DHA should be considered to improve cognitive function."

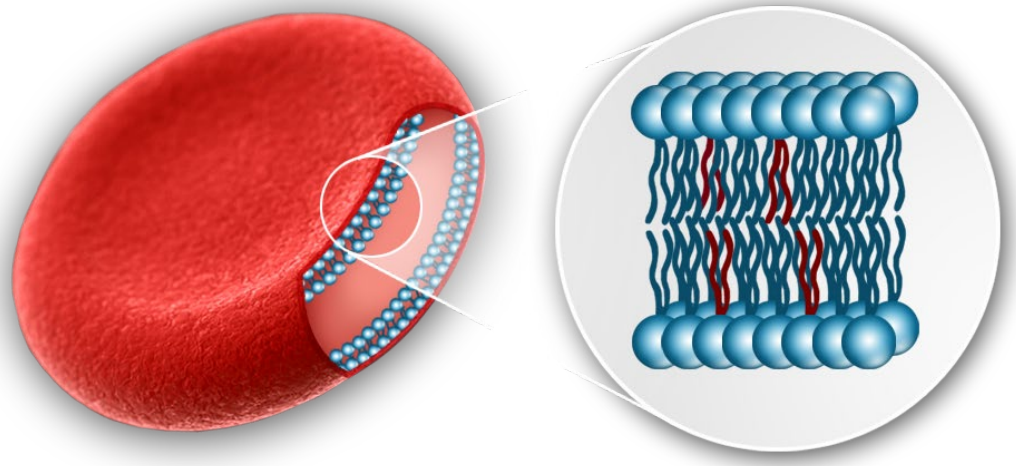
Malik, et al. Am J Clin Nutr 2021;113:1168-1176

Mechanistic link between DHA and Alzheimer's Disease



Fotuhi M et al., Nat Clin Pract Neurol 2009;5:140-52

The Omega-3 Index: Biomarker and Risk Factor



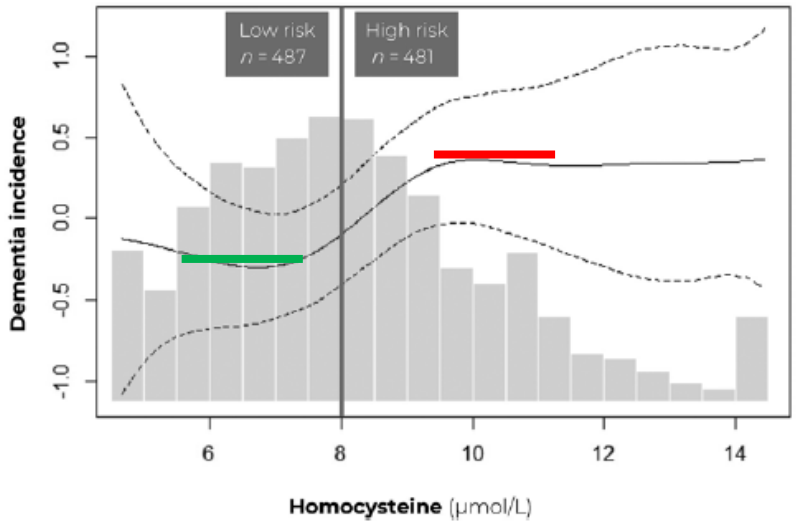
The Omega-3 Index (EPA+DHA as a % of erythrocyte fatty acids) is a marker of tissue levels of EPA and DHA.

- Having an Omega-3 Index in the desirable range (8%-12%) has been associated with improved heart, brain, and eye health.

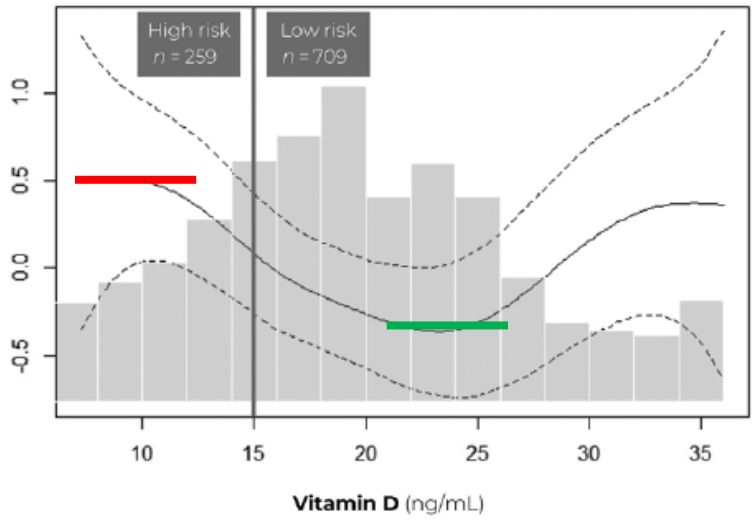
Harris WS and von Schacky C. *Prev Med* 2004;39:212-220.

The effects of 3 nutritional deficiencies on risk for dementia in Framingham Offspring

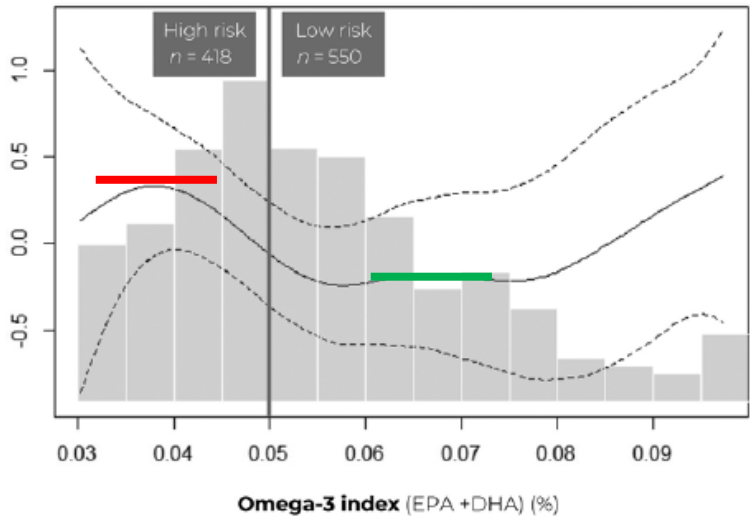
Homocysteine > 8 µM



Vit D < 45 mg/mL



Omega3 Index
<5%



Those with all 3 deficiencies were at 4.6 x increased risk for dementia

Van Soest et al. Alzheimer's Dement. 2024;20:4594–4601

VitaCog and OmegAD Post-Hoc Analyses

Feature	VITACOG Study (2015/2016)	OmegAD Study (2019)
Participant Group	Mild Cognitive Impairment (MCI)	Mild to Moderate Alzheimer's (AD)
Active Intervention	**B Vitamins** (B6, B12, Folic Acid)	**Omega-3s** (EPA and DHA)
The "Modifier"	Baseline **Omega-3** status	Baseline **Homocysteine** status
Condition for Efficacy	Benefits only seen with **High Omega-3s**	Benefits only seen with **Low Homocysteine**
Optimal Thresholds	Omega-3 > 590 µM	Homocysteine <11.7 µM
Key Result (Atrophy)	**40% slower brain shrinkage**	Not the primary focus of this analysis
Key Result (Cognition)	Significant slowing of cognitive decline	**7.1% improvement** in MMSE score
Main Conclusion	B vitamins need good om3 status to slow atrophy.	Omega-3s need good B vitamin status to help memory.
	Oulhaj A, et al. J Alz Dis 2016:50:547-557	Jerneren F, et al. J Alz Dis 2019;69:189-197

B-Proof Post Hoc Analysis

Study Population	191 cognitively healthy adults (age > 65) with high homocysteine (>12 µM).
Intervention	Daily oral **400** µg **Folic Acid** and **500** µg **Vitamin B12** for 2 years.
Primary Outcome	Change in **Global Cognition** (composite score of memory, attention, and executive function).
The "Modifier"	Baseline plasma **DHA** levels.
Effect of B Vitamins	**No significant effect** across the entire group regardless of nutrient status.
Interaction Result	A significant interaction was found between B-vitamins and **DHA** (p = 0.03$).
High DHA Status	Participants in the highest tertile of DHA saw a **significant improvement** in global cognition.
Low/Mid DHA Status	B vitamin supplementation had **no measurable benefit** on cognitive performance.
EPA vs. DHA	Unlike DHA, baseline **EPA** levels did *not* significantly modify the treatment effect.

Van Soest A, et al. European Journal of Nutrition https://doi.org/10.1007/s00394-022-02924-w

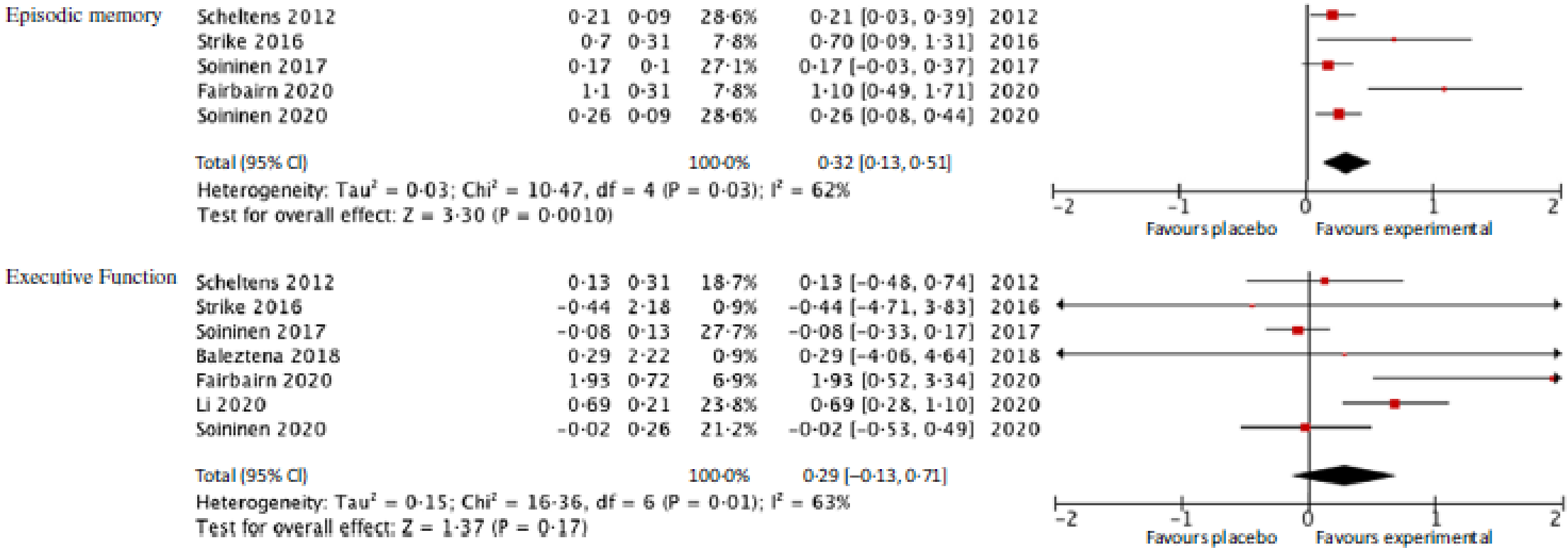
Multidomain Alzheimer Prevention Trial

Feature	Low Homocysteine (≤16.8µM) - Good	High Homocysteine (>16.8µM) - Bad
Effectiveness	**Significant Benefit**	**No Significant Benefit**
Executive Function	Significant association between high omega-3 levels and better scores in the **Trail Making Test (TMT-A)**.	No association between omega-3 levels and cognitive performance at baseline.
Cognitive Domains	Improvements observed in **motor activity**, **selective attention**, and **executive function**.	No measurable improvements across cognitive domains.
Long-term Outcome	Participants maintained cognitive stability or showed improvement compared to the high Hcy group.	Participants showed a **significant worsening** in executive function (TMT-B) over 5 years.
Conclusion	**Omega-3s were effectively utilized to protect the brain.**	**High Hcy likely blocked the cognitive benefits of the omega-3 supplements.**

Maltais M, et al. J Nutr Health Aging.2022;26(6):615-620

Meta-Analysis of n-PUFA + B vitamins on Cognitive Function

Meta-analysis and forest plots for the effects of multi-nutrient interventions containing both n-3 PUFA and B vitamins on composite scores from neuropsychological test batteries, single measures of global cognition, episodic memory and executive function.



Fairbairn, Dyall and Tsofliou. British Journal of Nutrition (2023), 129, 428–441

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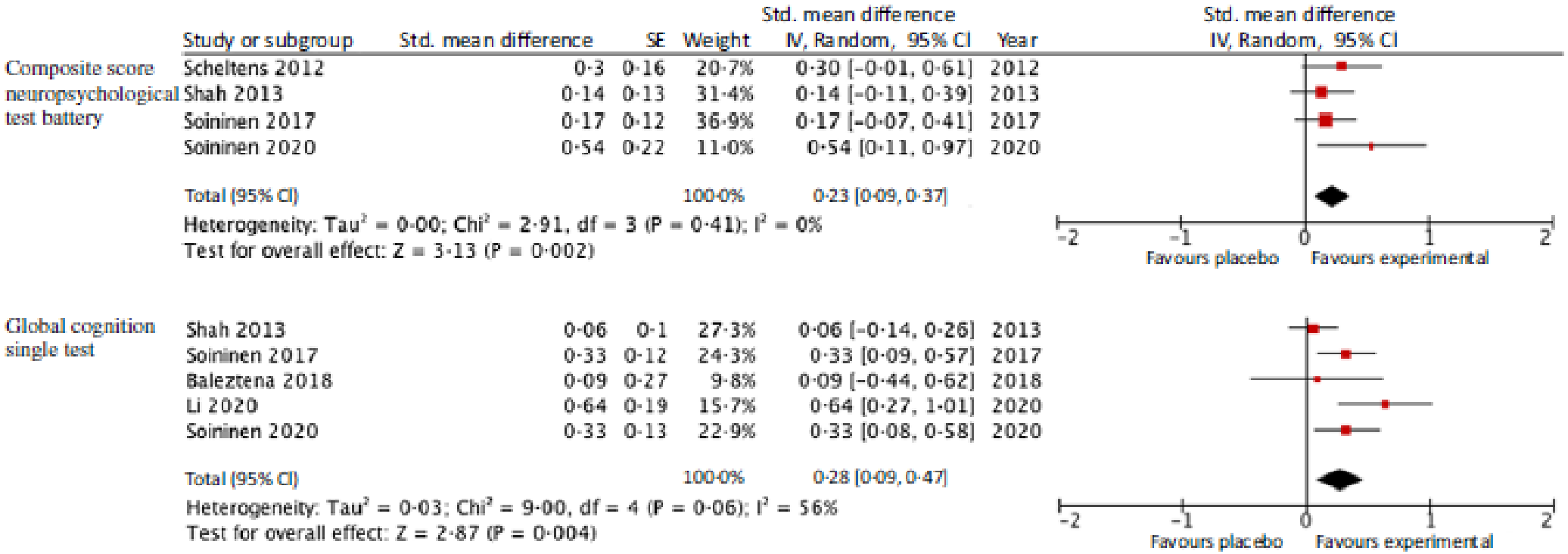
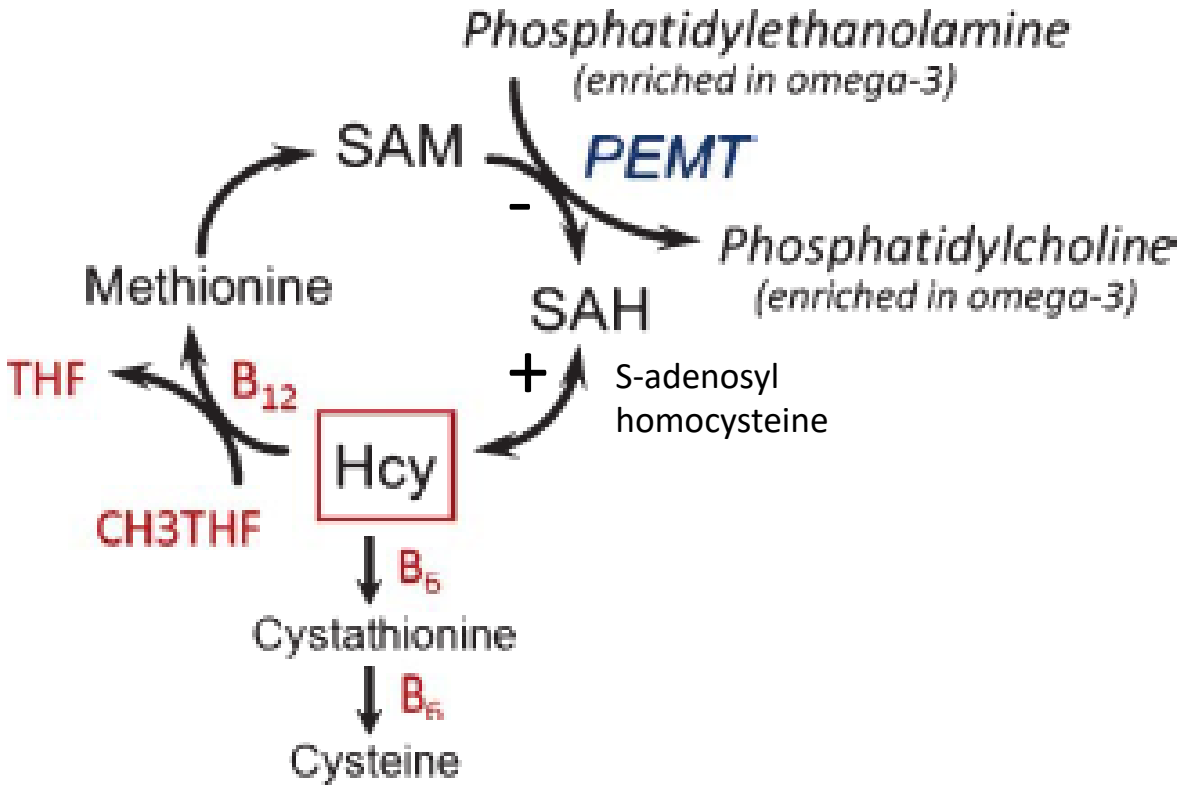


Fairbairn, Dyall and Tsofliou. British Journal of Nutrition (2023), 129, 428–441

Potential Mechanism behind a B-Vitamin - Omega-3 Interaction



Observations

- In AD patients, plasma SAH is high and RBC PC om3 is low.
- Exposure of chick embryos to Hcy increased PE and lowered PC and brain DHA levels
- In rats, a B-vit enriched diet increased plasma DHA vs a B-vit depleted diet

Possible Mechanism

- High Hcy raises S-adenosyl homocysteine (SAH) levels.
- High SAH inhibits PE methyl transferase (PEMT) which
- Reduces the conversion of om3 enriched PE to om3 enriched PC
- Lowers the levels of om3 enriched PC
- Reduced uptake of om3 PC into brain

Oulhaj A, et al. J Alz Dis 2016:50:547-557

Conclusions

1. Brain is a lipid-rich organ that accumulates omega-3 (DHA in particular).
2. Observational studies have linked higher seafood intake, fish oil supplement use and higher blood DHA levels with lower risk for AD/dementia and improved cognitive function.
3. Current evidence supports the need for both optimal B-vitamin and omega-3 nutrition for brain health.