ALINEA

NUTRITION

JUNE 2020

www.alineanutrition.com

TABLE OF

CONTENTS

Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette S, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology. 2012;78(9):658–64.

What We Know, Think We Know, or Are Starting to Know

What we know concretely is that the human brain is a highly costly evolutionary development, a fatty organ with enormous energy cost. Occupying only 2% of total body mass, the brain consumes 20% of daily energy, indicating the high metabolic cost to human cognition.

Over half - up to 60% - of the brain' s dry weight is lipid (fat), and of that up to 30% is comprised of polyunsaturated essential fatty acids [EFAs]. In particular, the omega-3 docosahexaenoic acid [DHA] comprises over 90% of omega-3 fatty acids in the brain - both eicosapentaenoic acid [EPA] and the precursor, alpha-linolenic acid [ALA] are low in brain tissue, comprising less than 1% of total brain fatty acid composition [(1)]. The critical role of DHA in neural growth and development suggests an important evolutionary requirement for this long-chain omega-3*. Analysis of the protective effect of fish intake against Alzheimer' s Disease have found that the protective effect was attributable to DHA intake, not EPA or ALA [(2)].

However, while EPA levels in brain tissue, i.e., in brain cell membrane phospholipids, may be low, this does not imply that EPA has no neurological role to play. With particular regard to depression, it appears that EPA is the fatty acid primarily associated with improvement of symptoms [(3)]. EPA acts a precursor to molecules known as 'resolvins' , named for their role in resolving inflammation and returning inflamed tissues to homeostasis [(3)]. Higher plasma EPA levels have also been associated with protection against atrophy of the amygdala, and depression associated with dementia [(4,5)]. The evidence for EPA in depression is robust, and this may relate to the precursor anti-inflammatory effect of EPA [(3,6)].

The present study sought to objectively assess markers of dietary intake of DHA and EPA, and the relationship with cognitive risk factors for dementia and Alzheimer' s Disease.

*Geek Box: A "Shore-Based" Perspective of Evolution

This predominant role of DHA in the brain has generated a "shore-based perspective" of human evolution, theorising that early Sapien migration and the process of encephalisation [the growth of the brain] occurred along coastal regions with access to direct food sources of DHA, in particular fish. Stable isotope analysis of bones of early Sapiens have indicated that marine protein sources constituted significant proportions of daily energy in the human diet. Anthropological evidence for the expansion of the genus Homo from the African rift valley suggests a migration along coastal and inland watercourses, provided access to both marine and freshwater sources of fish, and in particular long-chain omega-3 fatty acids. The evidence suggests that the consistent access to such food sources coincided with the period of exponential encephalisation, preceding the rapid development of language, complex reasoning, and problem solving cognitive capacities associated with the prefrontal cortex. Relative to other mammalian species, and indeed our primate cousins, the human brain is disproportionately large compared to body size. A number of lines of nutritional evidence support the anthropological research. First, other mammals with high levels of other polyunsaturated fats in membranes, but without a direct dietary source of preformed DHA, did not develop large brains, indicating a foundational need for preformed DHA in the early modern human diet. Secondly, humans lost the full activity of the delta-6-desaturase enzyme responsible for converting ALA to EPA and ultimately to DHA. While it is highly active in neonatal periods, in adulthood there is very little conversion of ALA through to DHA, which again suggests a direct source of preformed DHA as a foundational dietary characteristic associated with human encephalisation. While the Paleo narrative fantasies have often focused on our cavemen forebears huddled around the slain wooly mammoth, the reality is that the cost of obtaining land mammals as prey may have been quite high. Shore-based evolution has more anthropological, and nutritional, support, given the ease of access and low risk of obtaining freshwater and coastal marine sources, which are energy dense.

The Study

The Framingham Offspring Study is an ongoing cohort study in middle-aged participants, which has collected data from periodic in-person examinations. 1,575 participants had provided blood samples for red blood cell [RBC] fatty acid composition measurement, and also undertaken a brain MRI and neuropsychological [NP] tests.

MRI and NP tests were conducted on the same day, with the NP tests examining cognitive domains associated with increased risk of Alzheimer' s Disease [AD]; memory, recall, and abstract reasoning.

RBC fatty acid composition was analysed to calculate the HS-Omega-3 Index*, which is the level of EPA and DHA as a percentage of total RBC fatty acids. The associations between the Omega-3 Index and RBC DHA levels, and brain MRI volume and NP tests, were examined. DHA comprised 87.4% of the sum total of omega-3s [DHA + EPA].

The relationships were examined linearly, i.e., increasing levels of RBC DHA, and also comparing the lowest quartile of DHA [Q1] against the combined upper 3 quartiles [Q2-4].

- Q1 for RBC DHA was <3.9% of total fatty acids;
- Q2-4 was >3.9% [Q4 was 5.7% DHA].

For the Omega-3 Index [DHA + EPA]:

- Q1 was <4.4%
- Q2-4 was >4.4% [Q4 was 6.5% DHA+EPA].

Mean age of participants at baseline was 67yrs, 54% of the cohort were women.

*Geek Box: The HS Omega-3 Index

The question over what to measure to obtain reliable measures of DHA + EPA levels has been examined in numerous studies, ultimately leading to an argument in favour of erythrocyte - red blood cell - measures. The Omega-3 Index was first characterised in 2004, as the sum of DHA + EPA in RBCs, expressed as a percentage of the total fatty acids in the RBC measure. Because DHA is the predominant omega-3 fatty acid in membrane phospholipids, DHA makes up the majority of the Index, but this is not to suggest that EPA does not have important roles, however, it may mean that looking at EPA alone would not yield any meaningful findings. The Omega-3 Index was found to be a more robust predictor of cardiovascular disease. In addition, the Omega-3 Index appears to be stable and not easily altered by a given meal high in DHA + EPA, thus is a more reliable biomarker that is not easily influenced by recent dietary intake alone. An attractive feature of the Omega-3 Index is that the analytical laboratory procedure has been standardised, which means the measure should be reproducible across populations: the standardised method is known as the HS-Omega-3 Index®. Of particular note since the use of the standardised index, populations in Korea and Japan - with generally higher fish consumption - have exhibited significantly higher indices than American populations. Lower Omega-3 Index is also quite consistently associated with worse outcomes compared to higher levels.

Results: Participants in the lowest quartile of DHA exhibited significantly lower total cerebral brain volume [TCBV], which associated persisted after adjusting for key covariates, including ApoE-e4 and homocysteine levels.

This finding was repeated for the Omega-3 Index, where the lowest Q1 was associated with significantly lower TCBV after adjustment for multiple relevant covariates.

In cognitive testing, both DHA levels and the Omega-3 Index were significantly associated with visual memory, executive function, and abstract thinking tests. After adjusting for smoking, prevalent cerebrovascular disease, atrial fibrillation, and cholesterol, the relationship with visual memory and executive function was attenuated. Participants in the lowest Q1 of DHA performed worse on visual memory, executive function, and abstract thinking tests compared to Q2-4, which remained significant after adjustment for all covariates.

The Critical Breakdown

Pros: EPA and DHA was measured from RBCs, which is more reflective of dietary intake over the previous 3-4 months. The mean age reflects the decade wherein risk for dementia and AD increases significantly, and the cohort contained 54% women, which is close to reflecting the demographic distribution of dementia [~60-65%F/35-40%M]. MRI and NP tests provided objective assessments of brain health, and were conducted in close proximity to the blood sampling.

Cons: No dietary assessment was undertaken, to relate RBC fatty acid composition to potential food sources of dietary fats. The cross-sectional design, comparing RBC omega-3s with a single point-in-time MRI/NP examination, precludes any inference of the effects on dementia risk over time. The Framingham Offspring Cohort is also predominantly White/Caucasian, limiting inference to other ethnic groups, and both Blacks and Hispanics in the US have higher risk of dementia [(7)].

Key Characteristic

This was the first study to investigate the relationship between the long-chain omega-3 fatty acids and dementia/AD risk through erythrocyte [RBC] measures of fatty acids. As we' ve discussed in previous Deepdives, the use of biomarkers is a critical piece in the epidemiological puzzle, but is highly dependent on what nutrient is being measured, and what tissue the sample is derived from. There are a number of factors that make RBC measures of fatty acids more attractive. Fatty acids in RBCs have low variability, providing a stable assessment of fatty acid composition, and a reflection of tissue fatty acid composition. In addition, the average turnover time of RBCs - 120 days - means that fatty acid composition is more reflective of recent habitual dietary intake (generally, obviously dietary intake wasn' t assessed in this study, so we are left inferring). A number of studies have investigated plasma levels of omega-3s on dementia risk, however, plasma measures of fatty acids only reflect dietary intake in recent days, so it is difficult to attribute a chronic protective effect to plasma omega-3 levels. While the present was cross-sectional, further research has prospectively examined RBC omega-3 levels and brain volume [more under ***Relevance***, below].

Interesting Finding

The cerebral cortex volume was greater in the higher DHA quartiles, compared to the lowest. This may suggest that higher DHA levels are protective of the cerebral cortex in particular, and this gives us some interesting insight into the role of evolutionary role of DHA, and perhaps why intervention studies have generally been 'null'.

DHA turnover in the brain is very protracted, with a half-life of 2.5yrs in humans. The adult brain has been estimated to consume around 3.8-4.5mg/d DHA, and the brain contains up to 5g total DHA by total weight. This slow turnover and the brain, and high concentrations of required brain DHA, may provide an insight into why many short-term supplemental interventions have failed to produce an effect. This has cast doubts over the consistent epidemiological findings associating higher DHA levels - and fish consumption - with lower risk for dementia/AD. However, it may be a case of methodological discord, and thus studies like the present are important to provide corroborating evidence for the proposed role for DHA in protecting against neurodegenerative disease.

In particular, the "shore-based" evolutionary perspective indicates that the growth of the cerebral cortex facilitated the development of language and higher cognition, following access to consistent high-quality sources of preformed DHA [7]. The finding of greater cerebral volume in the present study could be seen as a modern technological insight into the ancient and crucial role of nutrition in facilitating the disproportionate brain to body size that characterises *Homo sapiens*.

Relevance

Epidemiology has consistently drawn correlations between dietary fish intake and lower risk of dementia, and the effect may be particular to fatty fish [2,8,9]. In the Chicago Health and Ageing Project, Morris et al. observed a significant reduction in risk for Alzheimer's from fatty fish consumption, an association attributable to DHA levels, not EPA or ALA [2]. EPA may have beneficial effects through acting as an anti-inflammatory mediator, but may not influence brain tissue itself [3].

The predominance of DHA in brain tissue and associations in epidemiology have been frustrated by a relative lack of success of supplemental interventions, but as outlined above these intervention studies may be too short to see any effect given the extended turnover time of DHA in the brain. The protective effect of DHA may relate to longer, sustained dietary intake - and higher tissue levels - and the present study indicated a preservation of cerebral cortex volume, albeit in a cross-sectional design.

In the Women's Health Initiative Brain MRI Study [WHIMS-MRI], women had MRI scans conducted 8yrs after baseline RBC omega-3 samples were collected [11]. High baseline Omega-3 Index levels correlated with a 2.1cm larger brain volume determined by MRI. While it would have been more insightful for baseline MRI scans to be conducted, suggesting higher DHA + EPA levels may protect against age-related brain atrophy. The pieces of the puzzle are beginning to come together, and taking the evidence as a whole, it does appear that DHA + EPA are important nutrients for prevention of cognitive decline associated with dementia risk.

Application to Practice

The minimum effective dose evident in the literature for fatty fish intake appears to be 1-2 servings per week. With the growing popularity of vegan diets, there are suggestions that sufficient ALA intake will cover biological needs for DHA, however, until we have actual data confirming this, best practice argues for the precautionary principle to apply, and algae-based DHA supplements are now more commonly available. Consider it an insurance policy.

References

1. Weiser M, Butt C, Mohajeri M. Docosahexaenoic Acid and Cognition throughout the Lifespan. Nutrients. 2016;8(2):99.
2. Morris M, Evans D, Bienias J, Tangney C, Bennett D, Wilson R et al. Consumption of Fish and n-3 Fatty Acids and Risk of Incident Alzheimer Disease. Archives of Neurology. 2003;60(7):940.
3. Sublette M, Ellis S, Geant A, Mann J. Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression. The Journal of Clinical Psychiatry. 2011;72(12):1577-1584.
4. Serhan C, Arita M, Hong S, Gotlinger K. Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their endogenous aspirin-triggered epimers. Lipids. 2004;39(11):1125-1132.
5. Samieri C, Maillard P, Crivello F, Proust-Lima C, Peuchant E, Helmer C et al. Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. Neurology. 2012;79(7):642-650.
6. Samieri C, Féart C, Letenneur L, Dartigues J, Pérès K, Auriacombe S et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. The American Journal of Clinical Nutrition. 2008;88(3):714-721.
7. Plassman B, Langa K, Fisher G, Heeringa S, Weir D, Ofstedal M et al. Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. Neuroepidemiology. 2007;29(1-2):125-132.
8. Crawford M, Bloom M, Broadhurst C, Schmidt W, Cunnane S, Galli C et al. Evidence for the unique function of docosahexaenoic acid during the evolution of the modern hominid brain. Lipids. 1999;34(S1):S39-S47.
9. Kalmijn S, van Boxtel M, Ocke M, Verschuren W, Kromhout D, Launer L. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004;62(2):275-280.
10. Barberger-Gateau P. Fish, meat, and risk of dementia: cohort study. BMJ. 2002;325(7370):932-933.
11. Pottala J, Yaffe K, Robinson J, Espeland M, Wallace R, Harris W. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI Study. Neurology. 2014;82(5):435-442.