Essential Fatty Acids: Recommendations for Plant Based Diets – Do vegans and vegetarians require a DHA supplement?

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Background

Current: *DrPH and PhD in Public Health Academic Coordinator/Faculty*
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Previous:
Assistant Professor of Nutrition and Dietetic Internship Director
College of Health Sciences, Appalachian State University

Senior Research Program Manager
Cancer Prevention Institute of California, Fremont, CA

Director of Nutrition
Physician's Committee for Responsible Medicine, Washington DC

Loma Linda University – M.P.H.,Dr.PH, RDN -Leader in investigating relationship between vegetarian diet and health and disease outcomes. Credentialed as a Registered Dietitian Nutritionist for almost 20 years

John McDougall M.D. Program - Interned

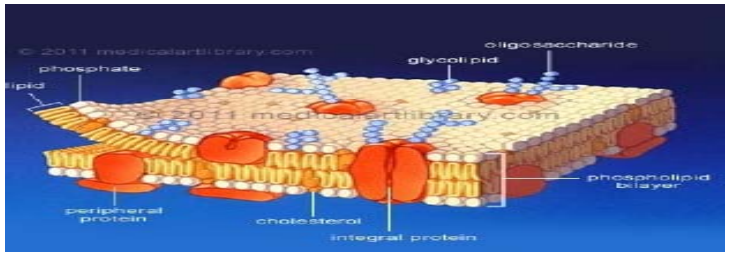
Studying, doing research, and publishing in the fields of Nutrition and Chronic Disease for over 20 years with a particular focus on answering the question of whether plant foods confer healthful benefits for minimizing disease and optimizing health. Published in 2013 the first ever entire chapter in academic text on plant based diets for food and ecology text.

Essential Fatty Acids: Recommendations for Plant Based Diets – Do vegans and vegetarians require a DHA supplement? - Objectives/Learning Outcomes

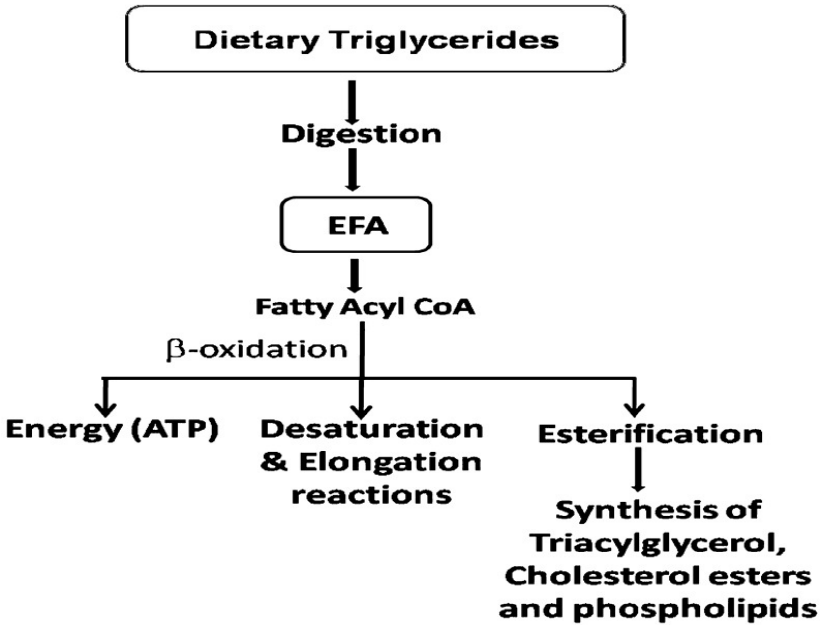
- 1) Be able to define types and sources of EFA
- 2) Understand what most plant-based researchers are recommending
- 3) Discuss omega-3 and 6 pathways, what they make
- 4) Discuss summary of health benefits of omega 3 and 6 in both omnivores, vegetarian/vegan populations and controversies (CVD, Brain, Eye)
- 5) Issue #1: EFA current intakes/status for vegetarian/vegans
- 6) Issue #2: Discuss omega-3 and omega-6 ratio
- 7) Issue #3: Conversion rates. Are the pathways of EFA inefficient?
- 8) Issue #4: The standard omnivore: should we be taking an algae supplement to obtain equal status?
- 9) Understand examples of products marketed to vegans
- 10) Discuss guidelines for suggested intakes and proposed recommendations for vegans/vegetarians and address the question: do vegans/vegetarians need to take a DHA Omega 3 supplement?

Essential Fatty Acids – Introduction

- Omega-3 and 6 PUFA are essential fats that cannot be derived or synthesized from other fats in the diet. This makes them unique with regard to fats and lipids, similar to essential amino acids in that they must be exogenously sourced.
- There are other omega fatty acids such as omega 7 or 9 that are non essential as they can be synthesized from other fats/lipids (MUFA).
- While requirements for intake of EFA are very small they play a role in the health or function of every tissue in the body and produce potent substances and compounds and are involved in a variety of processes.
- Unlike carnivores (Cats/most fish) who cannot elongate fats to create long chain PUFA, humans can via a elongation and desaturation process (Kothapalli, 2016).
- Both omega 3 and 6 fatty acids are incorporated in the membrane of phospholipids (the building blocks for cell membranes) and play a variety of roles in cell signaling and functioning. Both are required for growth, reproduction, neuronal function, skin maintenance and are involved in cholesterol regulation and metabolism and affect gene expression



Essential Fatty Acids – Introduction



Kaur N, Chugh V, Gupta AK Essential fatty acids as functional components of foods- a review. J Food Sci Technol. 2014 Oct;51(10):2289-303.

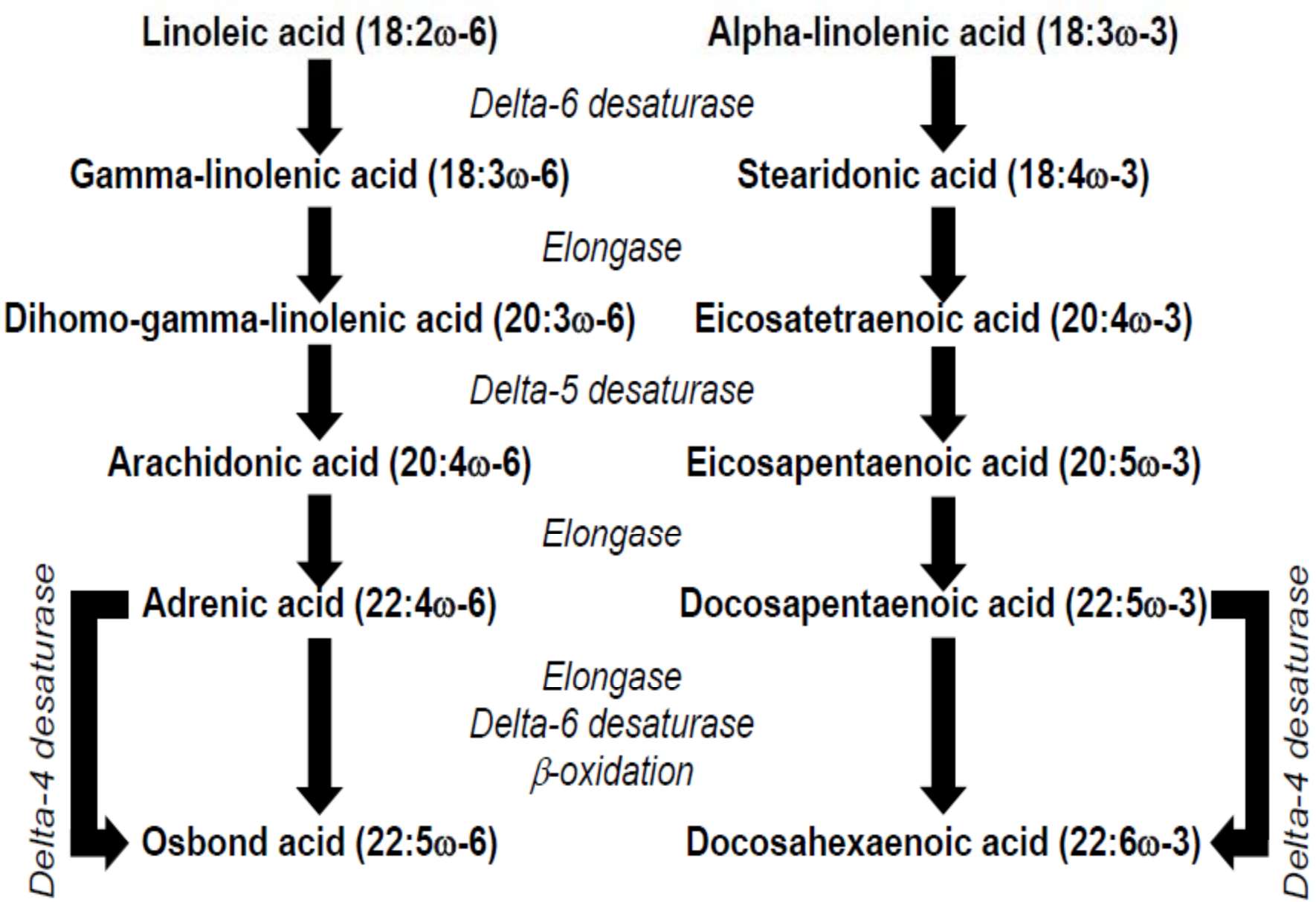


Table 3. Djuricic, 2021

Where EFA are processed

- **Omega 3 and 6 Interactions:** “DHA and ARA require a number of common enzymes, namely, fatty acid desaturase 1 (FADS1), FADS2, and elongation of very long fatty acid protein-5 (ELOVL5) In the case of PUFAs with >22 carbon chains, such as DHA, an additional enzyme, ELOVL2, is also required. All these PUFA biosynthetic enzymes are highly expressed in the liver; therefore, the liver has been considered as a central organ for the systemic metabolism and distribution of PUFAs“ (Hishikawa, 2020). As will be discussed evaluating EFA status via blood may not be the best indicator given the importance of the liver in EFA synthesis and distribution to tissues.

Current recommended intake for all diets

- **Government recommendations:**
- It wasn't until 2002 that govt recommendations were created for n-3 FA n-6 FA. The Institute of Medicine (IOM) considered the evidence inadequate to establish an Recommended Dietary Allowance (RDA) or Estimated Average Requirement (EAR) for n-3 FA n-6 FA. Thus the IOM established only an Adequate Intake (AI) values for ALA and LA, based on the highest median intake of ALA and LA for the current population and an apparent absence of deficiency symptoms (Balk, 2016).
- No Estimated Average Requirement or Adequate Intake was established for EPA or DHA or AA, but it was mentioned that 10% of ALA can come from EPA/DHA .
- Advises caution with Omega 3 supplements for those who use hypoglycemic medications, or anti-coagulants (IOM, 2006).
- The IOM did not establish a UL for any omega-3s, although it noted that high doses of DHA and/or EPA (900 mg/day of EPA plus 600 mg/day DHA or more for several weeks) might reduce immune function due to suppression of inflammatory responses (IOM, 2019).
- FDA notes increased bleeding times with high EPA/DHA (fish oil) intakes and combined food/supplement should not exceed 3g/day (Lewis, 2000).

Current recommended intake for all diets

Institute of Medicine, 2002 –	Men	Women	Adequate intake
ALA	1.6g/d	1.1g/d Pregnant 1.4g/d Lactation 1.3g/d	for.6-1.2% total energy
			(up to 10% of ALA can come from EPA/DHA)
LA	17g/d	12g/d	5-10% total energy
US National data from NHANES (Vannice, 2014)			
ALA	1.77g	1.3g	
LA	17.8g	13.3g	
EPA	.4g	.3g	
DHA	.8g	.6g	

Current Recommendations for Fish/Seafood

Dietary Guideline for Americans/MyPlate USDA

"Twice a week, make seafood—fish and shellfish—the main protein food on your plate. Seafood contains a range of nutrients, including healthy omega-3 fats. According to the 2010 Dietary Guidelines for Americans, eating about 8 ounces per week (less for young children) of a variety of seafood can help prevent heart disease." – Ten Tips, Eat Seafood Twice a Week (USDA, 2011).

The ***2010 Dietary Guidelines for Americans*** – increase amount of seafood to replace some meat and poultry (healthy population); 8-12oz seafood and limit tuna to 6oz and do not eat all high mercury containing fish (pregnant/breastfeeding)

The ***2015-2020 Dietary Guidelines for Americans*** specifically recommends that adults consume about eight ounces per week at 2,000 calorie level of a variety of seafood, including at least some choices higher in the omega-3 fatty acids EPA and DHA, because seafood has been associated with heart health benefits.

"provide an average consumption of 250 mg per day of EPA and DHA, is associated with reduced cardiac deaths among individuals with and without preexisting CVD" and "strong evidence from mostly prospective cohort studies but also randomized controlled trials has shown that eating patterns that include seafood are associated with reduced risk of CVD." - **Note. Not all research supports these recommendations. Alternatives? Plant-based diet? Plant sourced FA?**

Dietary Guideline for Americans – 2015-2020

"The DGAC supports the current FDA and EPA recommendations that women who are pregnant (or those who may become pregnant) and breastfeeding, or small children should not eat certain types of fish—tilefish, tuna – big eye, marlin, swordfish, and king mackerel—because of their high methyl mercury contents. Attention should be paid to local fish advisories when eating fish caught from local rivers, streams, and lakes." (DGFA 2015-2020)

"Understand that seafood is just one component of a healthy eating pattern. If a person is vegetarian or vegan, allergic to seafood, or simply doesn't like it, that's ok! There are many ways to eat a healthy diet. Focus the conversation on other healthy changes that fit the person's needs and lifestyle" – **(Quam, 2017) Five Strategies for Encouraging Seafood Consumption: What Health Professionals Need to Know – March 2017**

Recommendations in Literature for EFA intake

Health effects of vegan diets

Winston J Craig

The American Journal of Clinical Nutrition, Volume 89, Issue 5, May 2009, Pages 1627S–1633S, https://doi.org/10.3945/ajcn.2009.26736N
Published: 11 March 2009

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ABSTRACT

Recently, vegetarian diets have experienced an increase in popularity. A vegetarian diet is associated with many health benefits because of its higher content of fiber, folic acid, vitamins C and E, potassium, magnesium, and many phytochemicals and a fat content that is more unsaturated. Compared with other vegetarian diets, vegan diets tend to contain less saturated fat and cholesterol and more dietary fiber. Vegans tend to be thinner, have lower serum cholesterol, and lower blood pressure, reducing their risk of heart disease. However, eliminating all animal products from the diet increases the risk of certain nutritional deficiencies. Micronutrients of special concern for the vegan include vitamins B-12 and D, calcium, and long-chain n-3 (omega-3) fatty acids. Unless vegans regularly consume foods that are fortified with these nutrients, appropriate supplements should be consumed. In some cases, iron and zinc status of vegans may also be of concern because of the limited bioavailability of these minerals.

Diets that do not include fish, eggs, or sea vegetables (seaweeds) generally lack the long-chain n-3 fatty acids, eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), which are important for cardiovascular health as well as eye and brain functions. The plant-based n-3 fatty acid α-linolenic acid (ALA; 18:3n-3) can be converted into EPA and DHA, albeit with a fairly low efficiency (62, 63). Compared with nonvegetarians, vegetarians, and especially vegans, tend to have lower blood concentrations of EPA and DHA (64). However, vegans can obtain DHA from microalgae supplements containing DHA, as well as from foods fortified with DHA.

Recommendations by veg professionals for EFA intake

- **Brenda Davis, RD/Vesanto Melina, MS, RD** –

  Omega-3 fatty acids**.** Balanced diet and adequate ALA sufficient to meet needs, but unknown if vegan health could be improved by supplementing. Decision is a personal one. Include at least one of the following:

  • 2 tablespoons (30 ml) of ground flaxseeds or chia seeds
  • ¼ cup (60 ml) of hempseeds, • ⅓ cup (85 ml) of walnuts
  • 1½ teaspoons (7 ml) of flaxseed oil, • 1½ tablespoons (22 ml) of hempseed oil
  • 2½ tablespoons (37 ml) of canola oil

  Taking supplement of 200 to 300 mg of supplemental vegan DHA two to three times per week may be beneficial for some individuals (such as during pregnancy or for those with diabetes). A supplement that combines DHA with EPA can also be used. (The Vegan Plate, 2014) https://www.brendadavisrd.com/my-vegan-plate/

- **Michael Klaper, MD** - Assure omega-3 fatty acid sufficiency by eating a small handful of walnuts every day, along with 1-2 tablespoons of freshly ground flaxseeds on your oatmeal. If there is any question of fatty acid deficiency, indicated by dry skin and/or depression, take 300 mg of *algae-derived* DHA (the content of one “vegi-cap” available at the natural food store) daily.
  http://www.nutrientrich.com/wp-content/uploads/guides/failure-to-thrive-the-nutritional-adequacy-of-100-plant-based-diets.pdf

Recommendations by veg professionals for EFA intake

- **Jack Norris, RD** –
  - No need to supplement with DHA. https://veganhealth.org/omega-3s-part-2/#Welch2008
  - Step 1: DHA Supplement – Option A – If you want your DHA levels to be the same as non-vegetarians, supplementing with 300 mg per day will likely accomplish that. Option B – If you just want some insurance that you are getting a source of DHA in case your body isn't efficient at making it, supplementing with 200 - 300 mg every 2-3 days will provide that.
  - Step 2: Minimize Omega-6 Oils - Do not prepare food with oils high in omega-6 such as corn, soy, safflower, sunflower, most vegetable oil blends (typically labeled "vegetable oil") and sesame oil. Instead, use low omega-6 oils like olive, avocado, peanut, or canola. Only cook canola under low heat and for short periods.
  - Step 3: Add some ALA http://www.veganhealth.org/articles/omega3

- **Joel Kahn, MD** – because of low Omega 3 status in patients, recommend supplement with 250mg each of combined DHA and EPA from algae, limit foods rich in omega-6, which may contribute to inflammation, add whole foods rich in ALA ie. Walnuts, chia, flax, leafy greens. https://drjoelkahn.com/supplements-recommend-plant-based-patients/
- **Ginny Messina, RD, MPH**– "at best, an upstream battle for vegans and vegetarians to try to get enough EPA and DHA through their diets.. It's likely that vegans [and vegetarians] may need to consume higher amounts of ALA to achieve [adequate EPA and DHA], but even then, there is no guarantee"

Recommendations by veg professionals for EFA intake

- **John McDougall, MD** –Hydrogenation of oils, low selection of omega 3 foods, milling, large intake of animal products have all caused lower Omega 3 in diet. Can obtain essential fats (ALA, LA) in whole foods low fat vegan diet, diet and no need to focus EPA/DHA and recommends to avoid use of oils in diet in general. Can use flax as ALA source is desired and for some conditions (rheumatoid arthritis or diabetic neuropathy) could consider primrose oil.
  https://www.drmcdougall.com/health/education/health-science/featured-articles/articles/vegetable-fat-as-medicine/
  https://www.drmcdougall.com/misc/2007nl/aug/oils.htm

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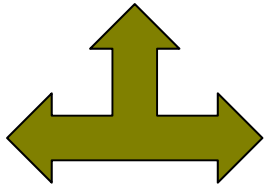


Inconsistency among health professionals but generally recommend a supplement. Could this be out of concern for veg/vegan populations not meeting a WFPBD? How much is due to lower intakes of EPA/DHA? How much is due to the believed CVD benefits? (one recent prominent vegan conference speaker advises patients to take DHA algae because of Omega 3 CVD benefits)

Fish Intake and CVD - Observational

Some association/modest benefit

Observational: Bulk of research is mainly CVD/mortality.
One of the earliest studies investigating fish intake and disease risk was the long running Zutphen study (one of the 7 countries studies) which followed more than 1000 men assessing long term fish intake.

Results suggested a benefit for sudden CHD death, but was not dose dependent and diminished when participants reached age 50 and above (Streppel, 2008; Kromhout, 1985). Study also found reduced stroke incidence with 1 serving or more of fish (Keli, 1994).

The New England
Journal of Medicine

Volume 312 MAY 9, 1985 Number 19

THE INVERSE RELATION BETWEEN FISH CONSUMPTION AND 20-YEAR MORTALITY FROM CORONARY HEART DISEASE

DAAN KROMHOUT, PH.D., M.P.H., EDWARD B. BOSSCHIETER, M.D., AND COR DE LEZENNE COULANDER, M.SC.

Abstract The low death rate from coronary heart disease among the Greenland Eskimos has been ascribed to their high fish consumption. We therefore decided to investigate the relation between fish consumption and coronary heart disease in a group of men in the town of Zutphen, the Netherlands. Information about the fish consumption of 852 middle-aged men without coronary heart disease was collected in 1960 by a careful dietary history obtained from the participants and their wives. During 20 years of follow-up 78 men died from coronary heart disease. An inverse dose–response relation was observed between fish consumption in 1960 and death from coronary heart disease during 20 years of follow-up. This relation persisted after multiple logistic-regression analyses. Mortality from coronary heart disease was more than 50 per cent lower among those who consumed at least 30 g of fish per day than among those who did not eat fish.

We conclude that the consumption of as little as one or two fish dishes per week may be of preventive value in relation to coronary heart disease. (N Engl J Med 1985; 312:1205-9.)

Fish Intake and CVD - Observational

Observational Studies on Fish Intake – Cardiovascular Diseases and All Cause Mortality

Fish intake or EPA/DHA status in blood in most observational studies or systematic reviews show significant benefit for CVD mortality, total mortality, CHD events (MI, sudden cardiac death, heart failure), or stroke (Takata, 2013; Villegas, 2015; He, 2004; He, 2002; Chowdhury, 2012; Sala-Vila, 2016; Balk, 2016 ; Alexander, 2017; Harris, 2021) especially in those who report regular consumption as compared to little or no fish intake (McLennan, 2015; Zheng, 2012). though some do not (Jayedi, 2018) nor for nonfatal CHD events (Alexander, 2017). and one new large study showed an increased risk for stroke caused by cardioembolism for higher intakes of dietary Omega 3 and DHA (Venø, 2019) while another large study showed significant increased overall and cause specific mortality from fish intake (van den Brandt, 2019)
A joint Food and Agriculture Organization/World Health Organization expert report suggests there is convincing evidence to support fish consumption decreasing risk for CVD mortality(WHO, 2011).

Despite the earlier studies suggesting benefit for fish intake, later observational studies and meta analysis of those studies linking fish intake with a reduction in mortality or other disease outcomes **are inconsistent** (Villegas, 2015; Virtanen, 2019; Zhuang, 2018) .

For example, one large systematic review suggested no benefit for any fish intake for healthy individuals while some benefit on reduction in CHD death was suggested in high risk individuals only (Marckmann, 1999). Other large prospective studies suggest little or no effect (Rhee, 2017; Amiano, 2014; Amiano, 2016; Villegas, 2015; Engeset, 2015). Three large studies suggested that all-cause mortality appeared or trended to increase with increasing frequency of fish intake

Fish Intake and CVD - Observational

Other prospective studies- **more mixed results**. Looking at outcomes such as atrial fibrillation, found no benefit to fish intake and suggest no general antiarrhythmic effect (Frost, 2005; Brouwer, 2006). No effect on heart failure incidence was seen from fish intake (Levitan, 2009) nor for mortality (except higher mortality in sub group analysis with↑ fish intake (Virtanen, 2019) while in another study a positive effect was seen for baked/broiled fish but a negative effect for fried fish (Belin, 2011). A global meta-analysis of 19 studies in those with or who died from CHD assessing biomarkers of ALA, DPA, DHA were all associated with lowering risk for CHD mortality and less so for non-fatal MI (Del Gobbo, 2016). About 30% were smokers, and medications varied between studies making conclusions less clear.

Possible explanations for differences in findings from observational studies

1. Some may be attributable to overall healthier diet patterns/lifestyle in fish eaters of which fish is only one part (Cundiff, 2007; Raji, 2014), which is well known (Engeset, 2015),
2. Those who consume fish may replace that for animal protein i.e meat/chicken known to carry health risks. So observational studies comparing those who mainly consume fish to those who mainly consume other animal proteins may "inflate" the benefits in the fish consumers, esp. as fish is lower in cholesterol and saturated fat.
3. It is unknown if the benefits are due to other nutrients in seafood. Fish contains Vit A, D, B-complex vitamins, iron, iodine, selenium and zinc.
4. Inconsistencies or variation possibly due to: methodological differences, accuracy of FFQ to assess true intake, type of cooking method or if raw, preservation method ie pickled, canned, smoked (nitrosamines?) etc, type of fish (i.e 27K species), gender, race, whether studies took into account contaminants in fish, genetic variability, or country of origin in population studied.

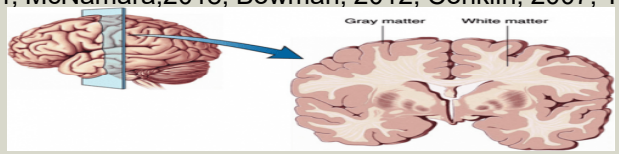
Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Brain Morphology

Brain morphology

Essential fatty acids (Omega 3 and 6) constitute about ~1/3 of total brain fatty acids mostly in the form of phospholipids of which DHA dominates for Omega 3 (trace amounts of ALA/EPA) and AA (trace amounts of LA for Omega 6) (Cederholm, 2013; Luchtman,2013). In general, DHA and AA have opposing effects on synaptic signal transduction and inflammatory signaling pathways. (McNamara, 2017) Brain weight typically shrinks about 5% per decade after age 40 (Peters, 2006). and brain size/reserve is still a hypothesis being debated in relationship to Alzheimer disease (AD) risk (Whitwell, 2010; An, 2016; Van Petten , 2004)

Regular fish consumption or total Omega 3 intake or EPA/DHA status was associated with preservation of brain size, gray matter, white matter, and lower white matter hyperintensities (WMH) which are associated with cognitive impairment/dementia, but not in all studies with one study suggesting benefit from marine Omega 3's that was attenuated when controlling for depression (Raji, 2014; Pottala, 2014; McNamara,2018; Bowman, 2012; Conklin, 2007; Tan, 2012; Luciano, 2017; Titova, 2013; Virtanen, 2013; Zamroziewicz, 2018)).



Some were small sample sizes, self reported dietary information, possible residual confounding and mostly cross-sectional (cannot draw conclusions on causality and it is unclear if low DHA in some but not all post mortem brain studies is a cause or consequence of AD(Pan, 2015) or other factors, and Cunnane, 2013 suggest is it puzzling that if low DHA status or low fish intake is associated with AD, why post-mortem studies do not consistently show lower brain DHA (Cunnane, 2013; Fraser, 2010) .

Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Cognitive impairment or decline

Cognitive impairment or decline/Alzheimer Disease
AD accounts for 60 – 80% of Dementia cases worldwide.

Observational studies on fish intake and risk for **mild cognitive impairment or decline** are conflicting in short term studies(Zhang, 2016, Wu, 2015; Beydoun, 2007; Roberts, 2010).

One study also found higher DHA levels to be associated slower learning performance in non-pregnant healthy women (de Groot, 2007).

Fish intake associated with **subclinical neurobehavioral abnormalities** (Carta, 2003), authors attribute 60% of result due to mercury blood concentrations.

Alzheimer disease or dementia - A sizable number of studies suggest reduced risk either for fish intake or high Omega status levels though some are conflicting (Raji, 2014; Zhang, 2016; Cole, 2009; Alsumari, 2019; Cunnane, 2012; Titova, 2017); Solfrizzi, 2017) and improvement in mental scores but not for probable dementia or cognitive impairment (Ammann, 2017), and some longer term studies (i.e 10 years) found no or minimal association with fish intake and long term risk of dementia (Devore, 2009). Fish combined with other seafood reduced risk but only among APOE ε4 carriers, and this was also correlated with mercury concentration levels in the brain in deceased subjects(Morris, 2016) .

Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Cognitive impairment or decline

Alzheimer disease or dementia - A recent meta-analysis of cohort studies suggest a strong effect for higher saturated fat intake: was associated with an increased risk of 39% and 105% for AD and dementia and no association found for PUFA in either AD or dementia (Ruan, 2018).

Why is this important?

Studies that looked at low status of EPA/DHA compared to higher status of DHA and suggested better brain volume size/compartments. Other dietary hazards like **meat**, **arachidonic acid** (competes w/DHA in brain), **cholesterol** and **saturated fat** may of been reduced/replaced by fish/seafood and in addition, also suggest an overall healthier lifestyle and diet i.e Med diet (including exercise) making observational study conclusions complex as these were often not controlled for (residual confounding) as well, some of the many chronic diseases linked with AD may not of been controlled for. Higher fish intake may be associated with higher socioeconomic status which is protective for AD/cognitive decline (Alsumari, 2019; Sattler, 2012). Dietary intake of seafood may have other nutrients related to brain health beyond EPA/DHA making linkages of DHA and brain health confounded. Pesticide exposure has been linked with cognitive function (Dardiotis, 2019)

Fish contains Vit A, D, B-complex vitamins, Mg, iron, iodine, selenium, zinc, and B-12 and has lower saturated fat and cholesterol than meat, the underlined items of which are related +/- to cognitive decline or AD risk (Raji, 2014; Annweiler, 2016; Andrási, 2009; Berti, 2015; Dominguez, 2018; Medawar, 2019)

Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Cognitive impairment or decline

Alzheimer disease or dementia -

Some studies did not control for trans-fat, or fruit and vegetable intake, blood glucose, exercise, all associated with cognition and brain size/atrophy or medications that are associated with brain atrophy (Raji, 2014; Walsh, 2018). or hypertension which can predict both vascular dementia and AD 20 years before onset (Janssen, 2014) Studies were done on Omnivores, while vegans have intakes/levels of all of these in a health promoting direction, however higher protein intakes are associated with plasma/brain amyloid-β (Aβ) accumulation and vegans tend to have lower protein intakes (Fernando, 2018).

Many of these studies occurred during a time when recommendations to reduce meat intake (typically as greater source of saturated fat than fish ie. same portion of ground beef to salmon fillet had 4.5 and .73 grams respectively) with healthier options such as fish, which may indicate that EPA/DHA status was a marker for a diet healthier than a meat-based diet.

Research suggests that those who eat fish, also increase their intakes of fruit, vegetables, legumes, whole grains as part of a 'prudent dietary plan' compared to a Western dietary plan (Shakersain, 2016) and it is well know that the Western diet is one of the worst for cognitive health. In the Greek cohort of the EPIC study, out of 9 dietary components, only fruit and vegetable intake (not fish) was associated with being protective for cognitive decline (Trichopoulou, 2014).

Another study evaluating brain atrophy and the Mediterranean diet found that adherence to the diet was beneficial but the benefit from the Med Diet was <u>not</u> due to fish (Luciano, 2017)

Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Cognitive impairment or decline

Alzheimer disease or dementia -

Greek cohort of the EPIC study following Mediterranean diet

Table 6 Multinomial logistic regression-derived odds ratios (ORs)[a] and 95 % confidence intervals (CI) of the change in MMSE by Mediterranean diet components, among 401 individuals

	Change in MMSE (−4 to −1) versus ≥0 OR (95 % CI) per 1 SD increment	*p*	Change in MMSE ≤ −5 versus ≥0 OR (95 % CI) per 1 SD increment	*p*
Vegetables	0.85 (0.64, 1.12)	0.244	0.39 (0.22, 0.69)	0.001
Legumes	0.90 (0.71, 1.15)	0.407	0.91 (0.60, 1.39)	0.673
Fruits and nuts	0.95 (0.75, 1.21)	0.682	0.95 (0.63, 1.42)	0.800
Diary products	1.01 (0.79, 1.28)	0.950	1.01 (0.69, 1.48)	0.942
Cereals	1.00 (0.77, 1.30)	0.998	1.21 (0.79, 1.85)	0.384
Meat	1.14 (0.89, 1.47)	0.307	1.09 (0.71, 1.69)	0.686
Fish	0.91 (0.72, 1.14)	0.398	0.90 (0.64, 1.28)	0.568
Alcohol[b]	0.78 (0.46, 1.30)	0.336	0.63 (0.27, 1.48)	0.285
Ratio of monounsaturated to saturated lipids	0.84 (0.55, 1.29)	0.431	0.78 (0.40, 1.52)	0.468

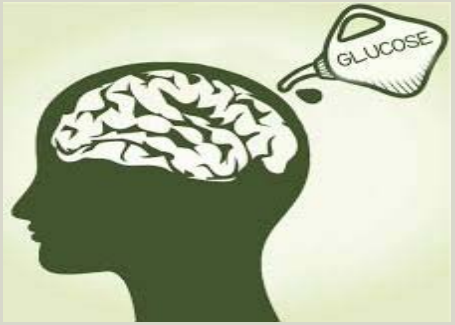
EPIC-Greece cohort

Fish Intake/Omega 3 Status and Brain - Observational

Observational Studies on Fish Intake/Omega 3 Status – Cognitive impairment or decline

Alzheimer disease or dementia -

Other areas of exploration: Studies assessing serum, plasma, and cerebrospinal fluid have identified several metabolic pathways that have association with AD: bile acids, sphingolipids, antioxidants, phospholipids, and amino acids (Snowden, 2017) and other factors like impaired cerebral glucose uptake and insulin resistance and resultant inflammation may play a role in the pathogenesis of AD suggesting that AD is a metabolic disease mediated by brain insulin and insulin-like growth factor resistance. (Toledo, 2017; Lazar, 2018)



The extent of cognitive decline in mildly cognitively impaired or who have AD is associated with the degree of glucose metabolism loss, nearly 35% in some brain regions (Weiser, 2016). Those who do not have diabetes or impaired fasting glucose and who have a slightly higher blood glucose level in the normal range experienced brain atrophy, predicted at a rate of approximately 0.06% reduction in total brain volume each year.(Walsh, 2018)

Some are calling AD, "**Type 3 Diabetes**".

The UK Biobank study (500K): strong associations with pre-diabetes or diabetes and AD; increased risk for cognitive decline; ↑white matter hyperintensity volume, ↓hippocampal volume (Garfield, 2021).

Brain – Omega 3 status

Observational Studies on Fish Intake/Omega 3 Status – Brain Morphology

Cardiovascular Health Study

- The Cardiovascular Health Study (CHS), a prospective cohort study of 5888 older adults assessed using brain MRI scans in relationship to plasma phospholipid Omega-3 levels and dietary intakes and found benefit with increased plasma levels of **DHA** and less white matter abnormalities, but not for improvement in markers that indicate less brain atrophy. Plasma phospholipid **ALA** was associated with improvement in markers that indicate brain atrophy, and dietary ALA was associated with less white matter abnormalities (Virtanen, 2013). This was also suggested in another study where not only plasma ALA status but several other fatty acids, including Omega 6 were related to memory function and white matter microstructure suggesting that both Omega 3 and 6 may slow age-related decline and memory (Zamroziewicz, 2017)

- Cardiovascular Health Study also found that frequency of fish consumption (did not correlate with mental score testing) but did show fish intake correlates with higher gray GM volumes in the brain areas responsible for memory and cognition but conversely omega 3 status in phospholipids was not related to higher gray GM volumes with authors suggesting dietary intake of fish are not necessarily the presumed biological factors that can affect the structural integrity of the brain and there are *other lifestyle reasons and that fish intake may be a marker of a healthier overall diet* (Raji, 2014) *or something else in fish like selenium content.* Authors say this is consistent with Omega 3 supplement studies which show little effect on prevention of dementia or cognition in AD patients.

Brain – Omega 3 Status

Observational Studies on Fish Intake/Omega 3 Status – Brain Morphology

Latest studies

Measured six plasma phospholipid omega-3 PUFAs, fluid intelligence, and regional gray matter volume in the frontal and parietal cortices in 100 cognitively intact older adults (65–75 years old).

Precursor **ALA** and downstream products like **stearidonic acid**, and **eicosatrienoic acid** (but not EPA or DHA) was linked to fluid intelligence, and preservation of total gray matter volume of the left frontoparietal cortex (FPC) which fully mediated the relationship between this omega-3 PUFA pattern and fluid intelligence. The authors suggest dietary consumption of **precursor n-3 PUFAs** may support neuronal health through the unique neuroprotective benefits of **ALA** and its immediate downstream products. (Zamroziewicz, 2018)

Fish Intake - Trials

Experimental Studies on Fish Intake

Most RCT have overwhelmingly focused on fish oil supplementation but some studies advising fish intake will be mentioned here. Many studies tend to group total Omega 3 sources together including on FFQ (i.e dietary, plus supplements, and could possibly include algae sources) so attempted to exclude studies/meta-analysis of this nature.

All cause mortality, CHD death, Angina: Burr, 1989 looked at 2033 men with a previous Myocardial Infarction by control group and experimental group to increase fatty fish intake Diet and Reinfarction Trial (DART). No effect was seen for risk for **CHD death** though increased fish intake suggested improved reduction in **all cause mortality** (Burr, 1989). A follow up study (DART-2) also looked at increasing fish intake in men with stable angina, followed for 3-9 years. Results suggested no effect from increased fish intake for **all cause mortality**, and instead was associated with a significant increase in **sudden cardiac death** (Burr, 2007). Other studies suggest lowered risk for **stroke** (ischaemic but not haemorrhagic) (Nestel, 2015)

Fish Intake - Trials

Experimental Studies on Fish Intake

Lipids, Blood Pressure: An 8 wk interventional study comparing 1 serving to 4 servings of fish per week found no effect on blood pressure or lipids compared to a diet low in fish (Grieger, 2014).

Fish Intake - Summary

Observational-Fish	Trials-Fish
Inconclusive/no risk or benefit: **CVD death, all cause mortality, atrial fibrillation, heart failure,** mixed for **preservation of white or grey matter; mild cognitive impairment** or **decline** in short term studies and no or minimal benefit in long term studies, higher DHA levels associated with slower learning in non-pregnant healthy women. Benefit for: **CHD events** (MI, sudden cardiac death, heart failure), or **stroke, Alzheimer disease** (but only among APOE ε4 carriers), Increased risk: **subclinical neurobehavioral abnormalities**.	Inconclusive: No risk or benefit for **CHD death, all cause mortality**. Inconclusive: Low compared to High fish intake: no benefit for **blood pressure or lipids** **Increased risk** for sudden cardiac death (in those with stable angina) Benefit for **stroke** (ischaemic but not haemorrhagic)

Fish Oil Supplements and CVD

Trials:

CVD - Transferring the observational studies and their mostly positive stance on Omega 3 and CVD into clinical application and trials has largely been a failure (von Schacky, 2015). If there was a significant benefit, we would of seen it by now – so many trials. A meta-analysis of studies using long term use of Omega 3 fish oil supplements was also found to increase risk of atrial fibrillation (Gencer, 2021).

2018 Cochrane most extensive systematic review (112K people, 79 RCTs): (Abdelhamid, 2018)

- ❑Increasing long-chain omega 3 (EPA/DHA) while some benefit for Triglycerides, ↓TG, ↓ HDL, little or no difference to risk of cardiovascular events, coronary heart deaths, CHD events, stroke or heart irregularities.
- ❑No meaningful effect for reducing death for any cause.
- ❑ Some very slight benefit to consuming ALA for CHD mortality(from 1.1% to1.0%), arrhythmia(from 3.3% to 2.6%), and low-quality evidence that increasing ALA may reduce risk of CVD events (4.8%to 4.7%).

Authors conclusions: *There is evidence that taking omega-3 capsules does not reduce heart disease, stroke or death or for CV death/mortality when increasing EPA/DHA. There is little evidence of effects of eating fish.*

Several other reviews with similar outcomes – ***AHA Science Advisory, 2017***

Fish Oil/Fish Supplements and CVD

Risks
CVD –

Patients with Angina - The study (DART-2) also looked at increasing fish intake in men with stable angina, followed for 3-9 years. Results suggested no effect from increased fish intake for **all cause mortality**, and instead for those sub randomized and advised to consume fish oil supplements instead of fish was associated with a significant increase in **sudden cardiac death** (Burr, 2007).

Patients with Atrial Fibrillation - Prescription Lovaza fish oil actually **increased** AF and flutter in those with AF in a double blind placebo controlled 6 month trial (Kowey, 2010), and in another, despite not reaching statistical significance could be a concern (Macchia, 2013) . A meta-analysis of studies using long term Omega 3 fish oil supplements was found to increase risk of atrial fibrillation (Gencer, 2021). Framingham Hlth Study found 6 times increased risk for AF in those consuming dark fish ie. Salmon, mackerel, sardines >4/week (Shen, 2011)

Everyone : FDA notes increased bleeding times with high EPA/DHA (fish oil) intakes and combined food/supplement should not exceed 3g/day (Lewis, 2000). No effect on heart failure incidence was seen from fish intake (Levitan, 2009) nor for mortality (except higher mortality in sub group analysis with↑ fish intake (Virtanen, 2019) while in another study a positive effect was seen for baked/broiled fish but a negative effect for fried fish (Belin, 2011).

Fish Oil Supplements – Brain

Trials:

Brain function or grey matter preservation –

Recall that prospective/cross-sectional studies showed mixed results for improvement in those with Alzheimer disease or for those with cognitive decline, or improvement in cognitive function or rate of atrophy (despite some studies looking at EPA/DHA status in blood showing positive effect on brain size and brain functioning (Tan, 2012; Ammann, 2013; McNamara,2018) while others did not (Bowman, 2012; Titova, 2013) Some suggest the reason for DHA supplements not being effective in AD is possibly the other nutrients in fish not contained in fish oil, many of which have established association with brain function (Cunnane, 2013)

One longer term trial in 'healthy' adults (6.5 month) suggested increased grey matter volume, structural integrity, and increased brain executive function (but not memory) in 'healthy adults' (overweight and consume few fish)* (Witte, 2014).

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doi:10.1093/cercor/bht163
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Long-Chain Omega-3 Fatty Acids Improve Brain Function and Structure in Older Adults

A. Veronica Witte[1,2], Lucia Kerti[1], Henrike M. Hermannstädter[1], Jochen B. Fiebach[1,3], Stephan J. Schreiber[1], Jan Philipp Schuchardt[4], Andreas Hahn[4] and Agnes Flöel[1,2,3]

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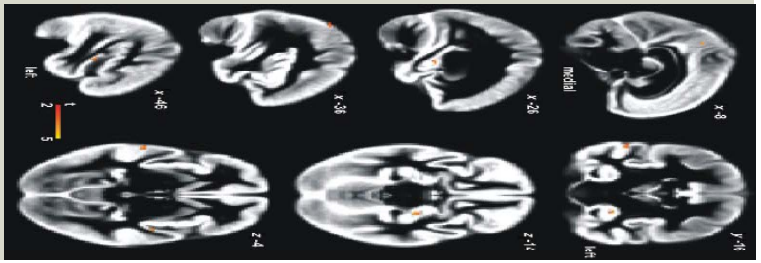
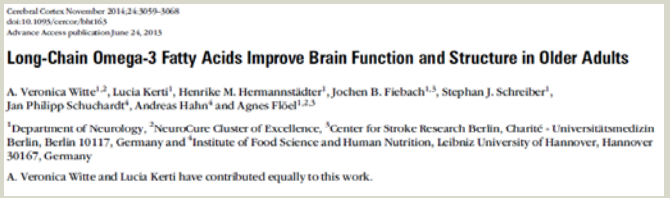


Fish Oil Supplements – Brain

Witte, 2014 Study



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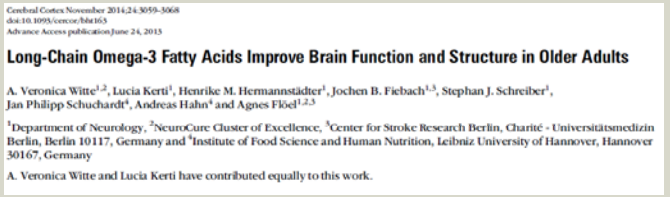
A. Veronica Witte and Lucia Kerti have contributed equally to this work.

- 1 study
- Study in Berlin. Germany has one of the highest CHD/CVD mortality in Europe, probably a very inflammatory diet. Omnivore population typically eating inflammatory standard diet. Benefits may only be seen in a population like this that has unhealthy dietary factors like animal products AND low DHA status. Animal products contain AA so as compete with EPA for DHA, the Fish oil supplements may of shown benefit partially for this reason.
- Study – Nutritional aspects: subjects had to fill out detailed nutrition protocols over periods of 7 days at baseline, after 12 weeks, and again after 26 weeks, to monitor dietary intake of fatty acids. They were instructed not to change dietary habits, for example, monthly fish consumption, throughout the intervention. Concern: no other dietary information was collected, including PUFA Omega 6 for example or amount of animal product intake, or whether any of these affected the study as this could affect true randomization. Only fish intake was monitored. While they were instructed to keep their dietary patterns it is unknown if any didn't and whether they were excluded or not. It is as if the researchers believed that only omega 3's exclusively can affect brain function/mood/grey matter size etc
- Secondly, how low was the Omega 3 status of this population prior to the study. (3/4 of intervention group had 0 to 1x/week fish intake – low). It is known that populations with low Omega 3 will show similar improvements (Peters, 2014) Is it low also because of saturated fat, cholesterol, trans fats?

Fish Oil Supplements – Brain

Witte, 2014 Study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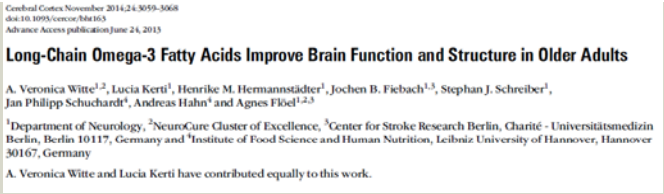
A. Veronica Witte and Lucia Kerti have contributed equally to this work.

- Study excluded normal weight individuals (BMI) <25 kg/m2. Unknown why researches wanted overweight people. Overweight people also more unhealthy diet?? Overweight people = what is status in brain?? Are they more responsive to Omega 3 supplementation? Possibly, as "Previous work has shown obesity (i.e., BMI >30) is related to deficits in brain structure in both cognitively normal older individuals and persons with MCI or AD. In fact, the hippocampus, a brain region critically important for normal memory function that is affected early in AD is exquisitely sensitive to the deleterious effects of obesity" (Raji, 2014) Central adiposity associated with cognitive decline possibly due to inflammatory release of CRP or HbA1C levels (Ntlholan, 2018) Lower Grey Matter in obese than non obese.
- Only control group showed stat.sig increase in body fat % - affect brain structure/cognition?
- Study excluded individuals who smoked >10 cigarettes/day so there could be smokers in the study who smoked up to half a pack per day. Unknown if any smokers were randomized equally, and smoking affects brain anatomy so this could be a more responsive group
- Fish oil of 2.2g/day also included 15mg of Vit E likely to reduce lipid peroxidation. Control group did not get Vit E so it is unknown what contribution Vit E had on the positive study

Fish Oil Supplements – Brain

Witte, 2014 Study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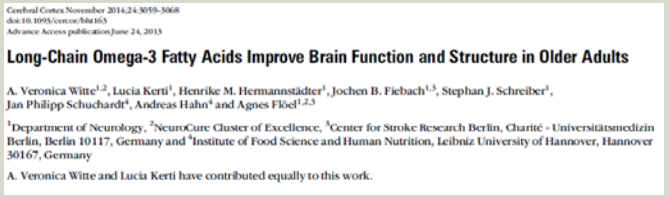
A. Veronica Witte and Lucia Kerti have contributed equally to this work.

- Control group given unknown quantity of sunflower oil to take. Sunflower oil is 62% Omega 6. Theoretically limit ALA > DHA for control group and affect n-6/n-3 ratio, may be why EPA was lower Omega 3 index p-value 0.057 Already and omnivore inflammatory diet and now added additional n-6. But what about Brain? So essentially a reduction in production of omega 3 in control group means less in brain, and less compared to free living population. This could make the intervention group results inflated? Also, was Vit E added to Sunflower?? High N-6 intake could lead to lipid peroxidation. FA. We also know that the levels of unsaturation within neuronal tissue is tightly controlled, dietary insufficiency or deficiency of n-3-FA may lead to increased concentrations of n-6 fatty acids (n-6-FA) in place of DHA (Reddan, 2019) . So in this study they received high doses of Omega 6 and if affects brain, when compared to the intervention group, could inflate intervention group results.
- Results: control group erythrocytes of peripheral blood showed significant decreases in EPA pre to post, and also for Omega 3 index. Interesting finding and as control group told to remain on whatever diet they were on, could suggest compliance may have been an issue. And unknown how this could of affected the results. The only PANAS score that was significant was in the control group who had a significant lowers score on overall positive feelings. (Development and validation of brief measures of positive and negative affect are what PANAS is) – this was not discussed

Fish Oil Supplements – Brain

Witte, 2014 Study



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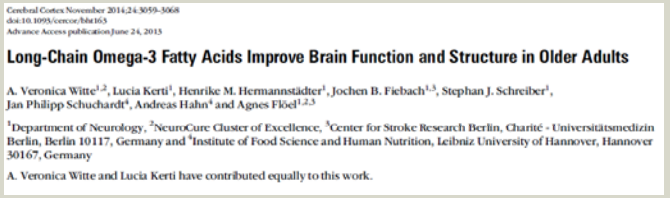
- Researchers discuss how DHA increases hippocampal brain-derived neurotrophic factor (BDNF), which promote neuronal growth and metabolism in such regions as the hippocampus, in rats, and larger hippocampal and prefrontal GM volume, memory, executive processing in humans and this study confirms this as BDNF correlated with improved executive functions after LC-n3-FA. However, both supplement and controls show stat significant increases in hippocampal brain-derived neurotrophic factor (BDNF) yet no improvement was observed for the control group in terms of these brain changes.
- Fish oil and Control group = sig. decreases in TNF- α and Interleukin-6 and ↑ BDNF and researchers mention "which may be due to potential changes in lifestyle habits such as diet or exercise in both groups " important!!!! Researchers say in discussion: Even though nutrition records and detailed questionnaires at baseline and follow-up did not actually show significant changes in lifestyle habits in our subjects, lifestyle measures were only based on self-reported information and may thus be over- or underestimations
- Results fish oil: no significance reached for memory scores, nor composite memory scores
- Fish supp group N = 40 then dropouts >> N= 33. Five of 33 or 15% said fishy burps which could of introduced bias (Significant bias as this as 15% of the intervention group).
- Physical activity was greater in the fish oil group, and PA has been shown to increase brain volume

Fish Oil Supplements – Brain

Witte, 2014 Study



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Did the study set the conditions for the invention group to benefit from DHA and set the control group up to not only be worse than usual free living conditions but via Omega 6 supplement show worse brain morphology?

Fish Oil Supplements – Brain

Trials:

Dementia or AD or Cognition - mixed or inconclusive results on cognitive performance or decline in youth and healthy adults or adults with dementia, or AD (Cederholm, 2013; Raji, 2014; Daiello, 2015; Morris, 2016; Luchtman, 2013; Abubakari , 2014; Danthiir, 2018;Phillips, 2015;Jiao, 2014) including Cochrane review (Burckhardt, 2016) or any positive effect on cognitive decline in healthy older individuals (Cochrane meta-analysis) (Sydenham, 2012; Dominguez, 2018) nor benefit in coronary patients (Geleijnse, 2012). Possible positive effect in those with very mild cognitive impairment (Daiello, 2015; de Souza Fernandes, 2015). Or APO E4 carriers (Shinto, 2024) and for memory in young healthy adults with low DHA status (episodic memory in females not males, and working memory in men, not women) (Stonehouse, 2013) but one study using algae showed worsening memory (Benton, 2013), and protective effect in those with minor memory problems for some but not for other memory domains and protective effect in those with no memory problems (Yurko-Mauro, 2015)

In the largest and one of the longest double-masked randomized clinical trial yet (National Institute of Health AREDS2 study), lasting 5 years, >3500 participants who were at risk for developing late age-related macular degeneration were enrolled in a secondary cognitive study and given cognitive function testing: fish-oil supplements had no change in cognitive function compared to placebo and failed to reduce cognitive decline (Chew, 2015).

Fish Oil Supplements – Brain

Trials:

Dementia or AD or Cognition - A long term well controlled trial in older adults with sub-optimal omega 3 fatty acid status used high dose 975 mg EPA, 650 mg DHA daily for three years, found no significant change in white matter lesion accumulation nor for neuronal integrity breakdown except those who were APOE*E4 carriers which showed benefit in neuronal integrity breakdown, but also no change in white matter lesions. As a result, this may suggest limited benefit to exogenous EPA/DHA and also suggest plasma status of these omega 3 fatty acids may not be a useful marker for brain health. (Shinto, 2024)

Memory in Youth - A total of 285 young adult females took 400 mg of (Algae) DHA, in a double-blind, placebo-controlled trial, for 50 days. After 50 days, recently acquired information was more likely to be forgotten by those who had consumed (algae oil) DHA (than the placebo). No beneficial effect on mood, cognition, or visual acuity (Benton, 2013)

Fish Oil Supplements – Brain

Summary relating to brain function:

While some studies suggest Omega 3 and brain size/morphology, there is limited evidence that supplementation improves brain disorders and despite apparently low DHA intake in AD, brain DHA levels are frequently the same compared to controls, suggesting that low DHA intake results in low plasma DHA but does not necessarily reduce brain DHA in humans, and the presumed association between lower plasma DHA and higher risk of dementia or AD is very inconsistent. (Cunnane 2013;Bos, 2016) Most studies correlate levels of DHA in the blood and tissue status is more complicated to assess, and levels in the blood may not reflect the composition in the brain/CNS (Dyall, 2015).

Study results may suffer from residual confounding, and fish may contain other nutrients influencing brain health, and may be a marker of a healthier lifestyle (Raji, 2014) especially when replacing recommendations to reduce meat intake which may show fish as being healthy but not necessarily healthy.

Observational studies suggest ALA intake, (Zamroziewicz, 2018) , low trans fats (Bowman, 2012) , low saturated fat, physical activity, not being overweight (Raji, 2014) and a combination of food groups including vegetables, fruit, nuts, whole grains (not just fish), a Mediterranean-style diet, and nutrients like vitamins B (B1, B2, B6,folate, and B12), C, Mg, D, and E, suggest better brain size/volume/cognitive measures, **B12 particularly** associated with being neuroprotective esp. hippocampal region (Medawar, 2019). Conversely, chronic life stress which is associated with ↓ grey matter volume and ↑homocysteine levels with total brain volume loss (Hooshmand, 2016; Croll, 2018; Bowman, 2012; Ruan, 2018; Luciano, 2017; Dominguez, 2018); Gianaros, 2007).

Fish Oil Supplements – Brain

Summary relating to brain function:;
Some studies did not control for some of these factors on the previous slide, including arachidonic acid (AA), which is the 2nd most prevalent PUFA in the brain and 20% of fatty acids in neuronal tissue.

•Is considered a underappreciated risk factor for cognition/AD.

•AA produces PGE2 eicosanoids which are neuro-inflammatory (and one of most abundant prostaglandins in the brain) which is why non-steroidal anti-inflammatory drugs have been shown to reduce risk for AD. (Thomas, 2016).

•PGE2 - implicated in pre-clinical development of AD (Johansson, 2015)

•In AD patients, ↑ AA incorporation occurred via PET scan compared to healthy controls (Rapoport, 2008).

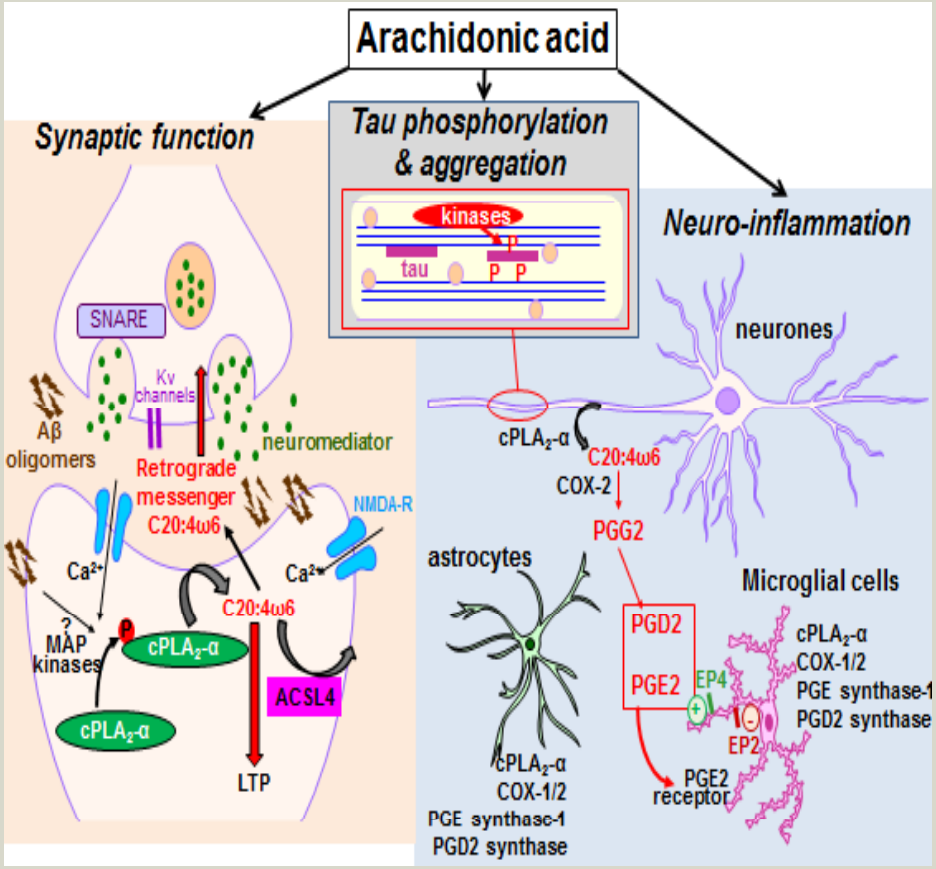


Figure 1: Pleiotropic effects of arachidonic acid in Alzheimer's disease. Thomas MH, Pelleieux S, Vitale N and Olivier JL. J Neurol Neuromedicine (2016) 1(9): 1-6

Fish Oil Supplements – Brain

Trials: Pregnancy and infant development

Studies in newborn babies suggest DHA deficiency adversely affects certain learning behaviors (Harris, 2014) . Most DHA accumulates in the brain during the perinatal period (Joffre, 2014) and while ALA converts minimally to DHA, it increases in times of need, ie. pregnancy and as an infant, and there is insufficient evidence to demonstrate maternal transfer of DHA or other long chain fatty acids from pregnant or breast feeding vegans are inadequate during this time (3rd trimester to 2 years of age).

Trials in pregnant omnivores with a DHA supplement show mixed results in terms of Central Nervous System development and evidence from RCTs does not demonstrate a clear and consistent benefit of maternal supplementation on the neurodevelopment of the offspring. (Mulder, 2014; Joffre; 2014). and there is strong inconsistency for benefit in trials supplementing with omega 3 during pregnancy and lactation in term and pre-term infants with several DHA trials showing no improvement in white matter maturation, including a 8 year long RCT and in general no neurodevelopmental benefit from supplementation when infants were followed up at three, six and nine years of age in several but not all studies (Columbo, 2019; Luchtman, 2013; McNamara, 2018; Jasani, 2017; Ogundipe, 2019). Systematic reviews and meta-analyses did not support DHA supplementation for cognitive benefits from birth up to age 25 (Garg, 2017; Emery, 2020).

Fish Oil Supplements – Brain

Trials: Pregnancy and infant development

No clear or consistent evidence for DHA supplementation in pregnant or lactating women for infants on **term infant growth**, **neurodevelopment or visual acuity, cognitive or language development, memory** even when DHA supplemented with formula in RCT's (Campoy, 2012; Qawasmi, 2012; Makrides, 2010;Newberry, 2016; Jasani, 2017; Keenan, 2016; Shulkin, 2018; Patro-Golab, 2023; Liu, 2025) no/mixed benefit for reduced risk of **gestational hypertension** or **preeclampsia**, **pre-term birth or benefit in lengthened gestation, slight benefit for early pre-term birth, but also higher risk for post-term births requiring obstetric intervention** (Makrides, 2010; Wieland, 2019;Newberry, 2016). (½ of the trials included women already at high risk or poor mother or infant outcomes from a previous preterm birth, gest diabetes, or overweight or underweight).

A Cochrane review found no benefit for omega 3 supplementation for cognition, IQ, vision, other neurodevelopment and growth outcomes, language and behavior (Middleton, 2018)

Fish Oil Supplements – Brain

Trials: Pregnancy and infant development - risks

Early childhood (girls, not boys) of women supplemented with DHA/EPA during their pregnancy showed poorer mean adaptive behavior scores and worse language scores and delayed language development compared to controls(Makrides, 2010). and several studies suggested DHA negatively affected cognitive development in term infants <2 years of age (Scott, 1998;Keim, 2018).

Some suggest a proper balance of DHA and AA is needed for optimal infant cognitive performance as too much EPA or DHA may **suppress** the benefits provided by AA via competitive inhibition. (Hadley, 2016) and cause concerns for inadequate AA in brain tissue for infants possibly leading to suboptimal neurological development (Weder, 2025).

Mulder 2014 suggest that if there is any benefit for DHA supplementation in pregnant women, DHA insufficiency among infants of women following **typical western diets** for which risk may be reduced by increasing the maternal DHA intake. (Mulder, 2014)

Fish Oil Supplements - Brain

Trials:

Depression: Results of trials looking at reductions in **depression** or depressive symptoms and use of Omega 3 fatty acids are mixed/inconclusive (Giles, 2013) do not show a consistent effect on mental status(Cederholm,2013 Luchtman 2013; Beezhold, 2010; Makrides 2010).

A Cochrane Systematic Review in 2015 on Omega 3 fatty acid supplementation and **depression** in adults found reviews and meta-analysis to be mixed, with a small to modest effect and no meaningful clinical effect on mild depressive symptoms and some possible benefit to those with **severe depression** though evidence is of low to very low quality, small sample sizes, wide confidence intervals (Appleton, 2016)
Cochrane Systematic Review for **post-partum depression** both show no effect or support for Omega 3 supplementation during pregnancy (Saccone, 2015; Miller, 2013).

Other non-Omega factors and Brain

Cognitive impairment or decline/dementia Alzheimer Disease

Improvement or reduced risk: fruit and vegetable intake, particularly blueberries and strawberries, grapes, beets (think nitrates!), lycopene, carotenoids, flavonoids, Vit. D, and some of the strongest support for vitamins B (B2 - riboflavin, B6 - pyridoxine B9 - folate, B12), mushrooms (Jiang, 2017, Moore, 2018; Flanagan, 2018; Zwilling, 2019; Krikorian, 2010; Wightman, 2015; Boespflug, 2018; Haskell-Ramsay , 2017; Miller, 2018; Palacios, 2019; Feng, 2019; Zhang, 2017; Chou, 2019) The brain is particularly susceptible to oxidation and DHA/AA are oxidizable and AD autopsies do not always show lower DHA (Fraser, 2010) but also show oxidative damage, and lower Magnesium (Dominguiez, 2018) , hence a role for antioxidants in ~~plant foods. (Dietary groups like vegans have the highest~~ intakes of Mg compared to other groups) (Schüpbach, 2017)

Aerobic exercise for 1 year increased hippocamel volume by 2% and lifelong exercise routine increased brain volume in older adults, and increased volumes also seen in children, adolescents, and cognitively impaired adults (Edwards, 2019; Jackson, 2016; Tomoto, 2021) . Both observational and short term trials suggest **meditation** increases grey matter volume (Dodich, 2019; Hernández, 2016).

Mediterranean-type diet (<u>but not fish in this diet</u>) reduced risk of brain shrinkage (Luciano, 2017) or preserved cognitive decline (McEvoy, 2019) .

Nurses' Health Study - Blueberries and strawberries may delay cognitive aging by up to 2.5 years (Devore, 2012).

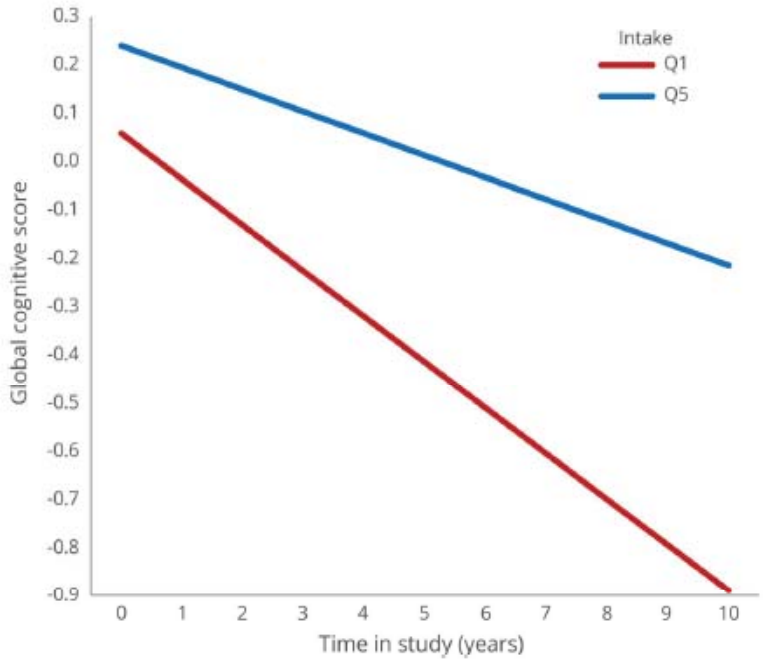
Fruit and Vegetable intake inversely and independently associated with the risk of <u>depression</u> - meta analysis of 10, 21 and 27 studies and also reduced risk for brain shrinkage(Liu, 2016; (Li, 2017; Saghafian, 2018; Croll, 2018)

Other non-Omega factors and Brain

Cognitive impairment or decline/dementia Alzheimer Disease

1.3 daily serving of leafy greens (either, kale, spinach, or even lettuce) protective against cognitive decline and those with highest compared to lowest intake had equivalent to 11 years younger cognitively, even when adjusted for seafood/fish intake (Morris, 2018). Mean 1.3 servings/day to show this result!

Figure Rate of decline in global cognitive score for the top and the lowest quintile of intake of green leafy vegetables



Rate of decline in global cognitive score for the top quintile of intake of green leafy vegetables (median 1.3 servings/d) and the lowest quintile of intake (median 0.09 servings/d) based on mixed models adjusted for age, sex, education, energy intake, participation in cognitive activities, physical activity, smoking, and alcohol consumption in 960 Rush Memory and Aging Project participants, 2004–2014.

Other non-Omega factors and Brain

Cognitive impairment or decline/dementia Alzheimer Disease

Improvement or reduced risk with dietary plans rather than individual (reductionist approach) nutrients:

In the Rotterdam Study using brain MRI, higher intakes of fruits, vegetables, grains, nuts, dairy, and lower intake of sugar beverages as part of a healthy dietary plan were all associated with larger brain volume, grey matter volume, white matter volume, and hippocampal volume, suggesting the importance of diet overall, not just fish/seafood. In this study fish was not protective for total brain, hippocampus or grey matter volumes), (Croll, 2018)

MIND diet - reduced risk for both cognitive decline and AD in elderly followed for ~15 years, and in participants with a history of stroke, slowed cognitive decline (Cherian, 2019) The MIND diet emphasizes natural plant-based foods (though some poultry) and limited intakes of animal and High saturated fat foods but uniquely specifies consumption of berries and green leafy vegetables and not emphasize fish intake greaterthan 1x/wk (Morris, 2015).

The MIND Diet

Mediterranean-DASH diet Intervention for Neurodegenerative Delay

WHAT TO EAT

Every day	• 3 servings of whole grains • 1 serving of vegetables • 1 glass of wine (5 oz)
Most days	• Leafy green vegetables (6x) • Nuts (5x)
Every other day	• Beans (3x)
Twice a week	• Poultry • Berries
Once a week	• Fish

WHAT TO LIMIT

Less than 1 T. a day	• Butter and stick margarine
Less than 5x/week	• Pastries and sweets
Less than 4x/week	• Red meat
Less than 1x/week	• Whole-fat cheese • Fried fast food

A study following young adults into adulthood for 25 years showed protective effects from both fruit and vegetable intake on cognitive function (Mao, 2019) Two studies in adults showed a plant-based diet to be protective for cognitive decline (Wu, 2019; Liu 2022)

Other non-Omega factors and Brain

Cognitive impairment or decline/dementia Alzheimer Disease

Increased risk

These 7 risk factors could result in ½ of AD cases: Smoking, Diabetes, midlife hypertension and obesity, depression, physical inactivity, cognitive inactivity (Farrer, 2001).

Recent review identified these factors in addition to Omega 3: (Edwards, 2019)

•Heart Disease (atherosclerosis major risk factor for AD (Janssen, 2014)

•Type 2 Diabetes (doubled risk for AD)

•Saturated Fat, Trans-Fat, Cholesterol, high fat diet

•Traumatic Brain injury, Epilepsy

•Late Life Depression – for onset of AD ▪ Heavy drinking

•Sleep disturbances (30% increased risk for dementia for those with <6 hours sleep during middle age or for those with short sleep duration during old age (Sabia, 2021)

Excess adipose tissue and its associated co-morbidities in middle-age, has emerged as a significant risk factor for age-related cognitive decline.(Vauzour, 2017) and obesity is related to brain structure deficits in cognitively normal, mild cognitive impairment and AD older adults (Raji, 2014) to the extent that being overweight or obese in mid-life increased risk for late-onset dementia up to 2.44 fold (Dominguez, 2018). Inflammatory CRP or IL-6 are related to microstructural integrity and white matter lesions and ↑ risk to AD as is B12 deficiency (Medawar, 2019). Low uric acid levels ↑ risk to AD (fish/omnivores ↓, vegans ↑) (Katsiki, 2013; Schmidt, 2013)

•Aluminum and Fluoride in drinking water – does response ↑ risk for Dementia (Russ, 2019)

Fish Oil Supplements - Eye

Trials:

Eyes - No effect on age related **macular degeneration** (retinal degeneration) or **visual acuity** *(even after 5 years of supplementation).* (Lawrenson, 2014; Age-Related Eye Disease Study 2 Research Group,2013; Souied, 2013)

No consistent beneficial effects on visual acuity in term infants comparing regular formula with ALA/LA to supplemented formula with DHA/AA (Jasani, 2017)

It has been suggested that increasing DHA intake could aggravate macular degeneration as it creates an oxidative byproduct that is a biomarker for macular degeneration (Swinkels, 2023)

Glaucoma – some benefit for in reducing ocular pressure for those with current or prior glaucoma (Downie, 2018) .

Dry eye syndrome mixed results with some showing benefit (Bhargava , 2013; Epitropoulos , 2016) while other have not (The Dry Eye Assessment and Management Study Research Group, 2018) .

Fish Oil Supplements - Frailty

Trials:

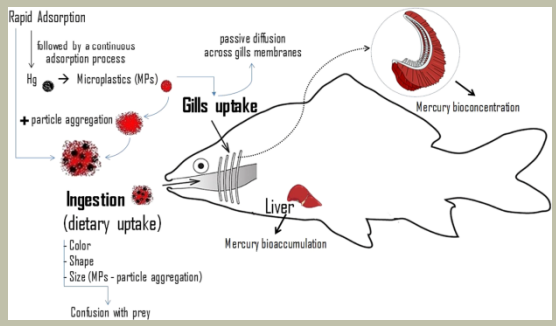
Despite **low** concentration levels of long chain Omega 3 fatty acids and risk for frailty (inflammation is related to frailty), a 5 year study with participants receiving 1g/daily for 5 years showed no effect (Orkaby, 2022).

Fish Oil Supplements - Summary

No association/no clear benefit/mixed	Benefit
Dry eye syndrome, Brain function or grey matter preservation though one longer term trial (6.5 month) suggested slowed brain shrinkage, structural integrity, and increased brain executive function in healthy adults, **Dementia** or **AD** or **Cognitive function, term infant growth**, **infant neurodevelopment or visual acuity, Depression or post-partum depression, CVD** (though favorable on some blood lipids, and 1 trial beneficial in patients with chronic heart failure, but primarily in those with ↓ EF), Increased risk for atrial fibrillation. No effect: **Age related macular degeneration** or **visual acuity** *(even after 5 years of supplementation).* **two prospective studies looking at grey matter and brain function and Omega 3 status suggest ALA is mediator, not EPA/DHA	**Glaucoma** – some benefit for in reducing ocular pressure for those with current or prior glaucoma **Pregnancy and infant development –** reduced risk of pre-term birth

Considerations beyond nutrition

- Neurotoxin (beta-N-methylamino-L-alanine) from algae blooms now found in seafood and fish, and in some fish very high concentrations – risk factor development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Lou Gehrig's disease (Amyotrophic Lateral Sclerosis (ALS).
- bioaccumulative effects of heavy metals (chromium, mercury and lead, cadmium) and other environmental toxins/pollutants (dioxins, hexachlorobezene, and polychlorinated biphenyls particularly in fatty fish.
- TMAO - Fish intake raises levels of a purported pro-atherogenic compound more than meat or eggs
- Micro-plastics found in fish fillets. Increases Hg.



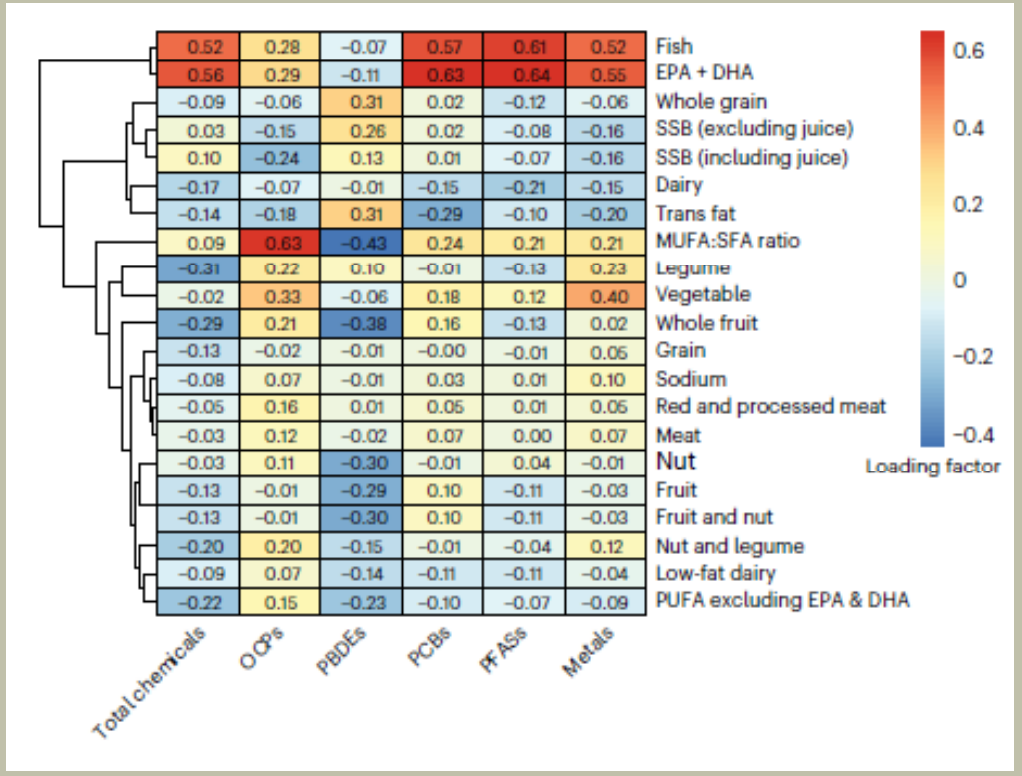
Salmon May Be the Greatest Source of Dietary Pollutants

Written By Michael Greger M.D. FACLM on August 11th, 2015

- https://nutritionfacts.org/2015/08/11/salmon-may-be-the-greatest-source-of-dietary-pollutants/

Considerations beyond nutrition

- Seafood and fish, which are the main contributors (Yu, 2024) to environmental chemicals in pregnant women consuming healthy diets like the Mediterranean and DASH diets (per- and poly-fluoroalkyl substances (PFAS), heavy metals and polychlorinated biphenyls (PCBs)) and why advisories to those who may become pregnant, caution against some species of fish as fish is the leading source of mercury exposure and is associated with cognitive dysfunction and child neurodevelopment (Grandjean, 1997; Masley, 2012; Oken, 2008;Karagas, 2012; Deroma, 2013; Barbone, 2019).



- Yu, 2024 (main loading factors for environmental chemicals)

CVD and Omega FA in Vegetarians and Vegans

- **Thrombosis**: Some observational studies which compared vegans /vegetarians and omnivores found differences or no differences in platelet function (Mezzano, 1999; Chetty, 1993; Rajaram, 2003; Sanders, 1992) and most cross-sectional studies suggest a benefit on hemostasis for vegetarians (Rajaram, 2003). Some ex-vivo studies on platelet aggregation suggest more risk in vegetarians compared to omnivores (McCarty, 2004) . Trials administering ALA or EPA/DHA in vegans or vegetarians found mixed or no difference in thrombotic factors (Rajaram, 2003; Mezzano, 2000; Conquer, 1996).
- **Lower CVD risk factors** in those following plant based diets, i.e a better lipid profile ie, lower levels of cholesterol, LDL, lower LDL oxidation, saturated fat intake; lower BP, reverse angina, and such diets are considered protective for CHD (Dinu, 2016; Bodai, 2018; Ornish, 1998; Massera, 2015; Korpela, 1999).
- Example from **EPIC Oxford Study** – 15K Vegetarians (large sample), ↓ 28% Ischemic heart disease (IHD) compared to those who eat meat or fish (Crowe, 2013). **Five prospective studies** suggested ↓ 24% for vegetarians compared to non-vegetarians for IHD mortality (Appleby, 2016). Though new analysis of EPIC-Oxford and Oxford Vegetarian Study show **no difference in mortality** (Appleby, 2016) as did the 45 and Up Study (Mihrshahi, 2017). Another Meta-analysis/systematic review found vegetarian diets reduced risk for both CHD incidence (↓28%) and mortality (↓22%) (Glenn, 2019). Most of these combined vegans and vegetarians. Vegans (male) in separate analysis showed better protection for all-cause mortality, IHD, and CVD (Le, 2014).

CVD and Omega FA in Vegetarians and Vegans

- Trials using Plant based diets reduce many things fish oil claims were used for: **angina** (McCarty, 2004), **BP** (Lindahl, 1984), reduce risk for **CV event** (McDougall, 2014), reduced systemic **inflammation and CRP** in CHD patients Vegan diet compared to AHA Diet (Shaw, 2017) and there is evidence for **reversal of CVD** (Bodai, 2018; Esselstyn, 2014).

- **Inflammation**: Some studies in vegetarians found lower levels of pro-inflammatory eicosanoids compared to omnivores, (Yu, 2014) as well as lower CRP (Haghighatdoos, 2015; Paalani, 2011) Dod, 201), and low CRP levels in vegans (Franco-de-Moraes, 2017; Fontana, 2007; Harvinder). Systematic review of plant-based diet trials also found lower CRP (Eichelmann, 2016). Three week vegan diet lowered CRP in two separate studies (Sutliffe, 2015; Bloomer, 2010) .Those with RA put on vegan diet for 1 year showed a decrease in CRP and an increase in atheroprotective antibodies (Elkan, 2008).

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

Cognitive/Mental Status: While it has been suggested that low long chain omega 3 levels are associated with mental decline, less research has been conducted in vegetarian populations who typically have lower status levels than omnivores. "Few data are available on whether inflammatory or neurologic diseases are more common in vegetarians and in vegans." (Rosell, 2005; Pistollato, 2014) and 2 large mortality studies showed no difference in death for vegetarians from neurologic diseases (AD, Parkinson) (Appleby, 2016; Orlich, 2013)

- **Cognitive:** Vegetarians and Vegans in the first Adventist Health Study showed a lower risk for developing dementia (Giem,1993) compared to meat eaters (includes poultry and fish). Meat eaters were twice as likely to have dementia and three times as likely when factoring past meat intake. These results are observed despite DHA levels in the vegetarian populations typically being considered as lower than in omnivores.

- Studies evaluating children growing up as vegans or vegetarians show no differences in cognitive development or visual acuity with no developmental differences (Sanders, 2009; Crozier, 2019)

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Cognitive/Mental Status:** A UK study (doctoral dissertation) investigating vegan men in a cohort of the EPIC study showed no evidence of cognitive impairment via scores on 13 cognitive tests and same mean IQ as assessed by National Adult Reading Test despite having low EPA/DHA status as compared to omnivores (Lloyd-Wright, 2005) . (B-12 plays an important role in neurological functioning but did not change results as there were no difference between low or normal B-12 groups).
- **DHA Supplementation**.
- A smaller trial of the above study using vegan men with normal B-12 levels but still low EPA/DHA status was conducted to determine any cognitive effect from supplementation of 200mg DHA for 12 weeks vs placebo (Lloyd-Wright, 2005) .
- Results suggested no difference in the mean IQ as assessed by National Adult Reading Test and 1 of the 13 tests was shown to be statistically significantly different due to the DHA supplementation (however, this was not considered meaningful as it would have been expected that the other memory tests would show corresponding changes) (Lloyd-Wright, 2005) .

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Cognitive/Mental Status:** One of the lead authors added that the results of all of the studies raise questions as to the utility for recommending vegans to use an EFA supplement as both vascular and cognitive functions were not significantly affected.(Sanders, 2009).

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Mood**
- The mental health status with regard to mood was investigated in healthy Seventh Day Adventist men and women who were Vegetarian or Omnivores suggesting vegetarians showed less negative emotion, anxiety, and stress measured by Depression Anxiety Stress Scale (DASS)and Profile of Mood States (POMS) questionnaires compared to Omnivores (Beezhold, 2010). This is despite the lower EPA/DHA intakes in Vegetarians compared to Omnivores in the study.

Table 3: DASS and POMS scores by diet group

	OMN		VEG		P
	Mean	± SE	Mean	± SE	value
	n = 78		n = 60		*
DASS-total[1]	17.51	1.88	8.32	0.88	0.000
DASS-D	4.81	0.69	1.67	0.28	0.000
DASS-A	4.31	0.53	1.53	0.24	0.000
DASS-S	8.40	0.92	5.12	0.52	0.024
POMS-total[2]	15.33	3.10	0.10	1.99	0.007
Tension-anxiety	6.04	3.83	3.83	0.40	0.031
Depression-dejection	8.99	0.80	4.36	4.10	0.000
Anger-hostility	7.08	6.72	4.28	0.55	0.010
Fatigue	7.59	0.66	5.03	0.47	0.021
Confusion	4.65	0.43	3.24	0.38	0.085
Vigor	19.15	0.71	20.61	0.71	0.133

* < 0.05 is significant.
1 DASS normative scores: D-5.55, A-3.56, S-9.27, total 18.38.
2 POMS normative scores, M-F: T 7.1-8.2, D 7.5-8.5, A 7.1-8.0, V 19.8-18.9, F 7.3-8.7, C 5.6-5.8, total 14.8-20.3.

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Mood**
- Same researchers assessed mood in another study (not in Adventists) in Vegans and Omnivores, using the Depression Anxiety Stress Scale (DASS) suggesting lower anxiety in vegan males and better mood and less stress in vegan females compared to omnivores. Vegans reported higher intakes of plant based omega 3 foods than omnivores (Beezhold, 2014) .

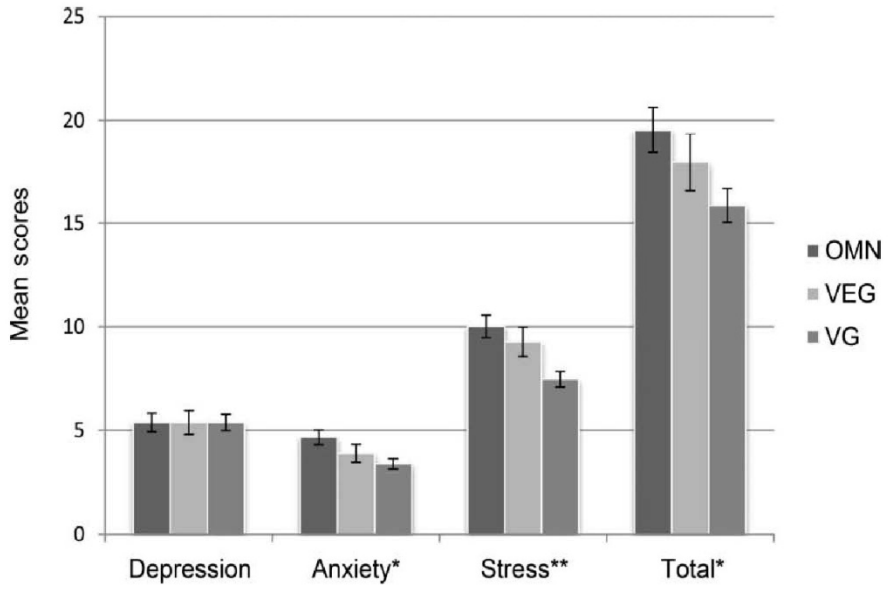


Figure 1 DASS-21 scores by diet group. *Indicates a significant difference at $p < 0.05$; **indicates a significant difference at $p < 0.01$. All significant differences are between omnivores and vegans groups.

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Mood**
- The same researchers also performed a small RCT in omnivores assigning to either an omnivore, fish, or vegetarian diet for two weeks. No changes were seen in the omnivore or fish groups (both had EPA/DHA) but the vegetarian group (which had no EPA or DHA) showed several improvements in mood scores assessed by Depression Anxiety Stress Scale (DASS), and Profile of Mood States (POMS) (Beezhold, 2012) .

Table 1 Dietary fatty acids at baseline and after the 2-wk diet intervention for participants randomized to omnivorous, fish, or vegetarian diets[a]

	Omnivorous diet		Fish diet		Vegetarian diet		
	Baseline	Week 2	Baseline	Week 2	Baseline	Week 2	P
α linolenic, g	0.37 (0.68)	0.44 (0.79)	0.79 (0.89)	0.28 (0.81)	0.58 (0.70)	0.38 (0.50)	0.874
Eicosa-pentaenoic, g	0.06 (0.10)	0.09 (0.12)	0.10 (0.13)	0.23 (0.26)[b]	0.06 (0.10)	0.00 (0.00)[bc]	.001
Docosa-hexaenoic, g	0.12 (0.15)	0.12 (0.17)	0.19 (0.25)	0.36 (0.37)[b]	0.09 (0.13)	0.00 (0.00)[bc]	.001
Total n-3, g	0.69 (0.88)	0.61 (0.85)	1.10 (0.74)	1.11 (1.48)	0.73 (0.60)	0.39 (0.50)	.065
Linolenic, g	4.29 (4.49)	3.54 (4.48)	6.49 (6.85)	5.53 (7.49)	4.63 (4.08)	4.69 (4.72)	.790
Arachidonic, g	0.12 (0.12)	0.08 (0.12)	0.14 (0.07)	0.08 (0.11)	0.10 (0.06)	0.00 (0.00)[bc]	.001
Total n-6, g	5.63 (3.78)	4.21 (4.49)	6.77 (6.95)	5.71 (7.11)	5.03 (4.64)	4.70 (5.05)	.821
Saturated, g	10.44 (7.92)	9.69 (10.22)	13.15 (9.86)	7.56 (8.72)	14.66 (12.36)	8.44 (9.99)	.173
Total fatty acids, g	29.78 (13.79)	30.12 (25.73)	39.52 (34.8)	30.64 (31.59)	38.40 (28.45)	22.86 (23.86)	.278
n-6/n-3*	7.32 (5.21)	7.50 (5.67)	6.76 (5.63)	3.99 (6.21)	7.88 (2.12)	14.55 (10.60)[bc]	.001

- A study in Iran suggested better mood in those who adhered to a lacto-ovo vegetarian diet compared to a traditional or Western diet (Hosseinzadeh, 2016). Those given a vegan diet for about 3 weeks reported a reduction in anxiety and stress as measure via Anxiety and Depression Scale and Perceived Stress Scale tests(Link, 2009) .

Cognitive/Mental Status and in those following Vegetarian or Vegan diets

- **Mood**
- The 18 wk GEICO trial in T2DM or overweight subjects using a vegan diet suggested improvements in all measures, depression, anxiety, fatigue, and emotional well-being (Agarwal, 2015).
- Meta-analysis of vegetarian studies are mixed for risk for depression compared to omnivores (Askari, 2020; Iguacel, 2021) .
- Other studies using a vegetarian diet: in T2DM subjects suggested improvement in quality of life and depression scores (Kahleova, 2013) two others showed less risk for depression in vegetarians compared to omnivores (Shen, 2021;Jin, 2019), while another study did not (Baines, 2007) and another study in those with rheumatoid arthritis reported improvement in psychological distress including depression and anxiety subscores (Kjeldsen-Kragh, 1994), while another study in obese women did not show changes in mental well-being using a lacto-vegetarian diet (Karlsson, 1994).
- Some studies with negative results may be because depression actually occurred prior to adopting a vegetarian diet , or the study did not access dietary intake (Karlsson, 1994; Baines, 2007) , nor assess Vitamin B-12 status.

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Mood**
- Some European /Australian studies conflict with US studies though some results were attenuated when controlling for confounders leading authors to suggest that an association with depression and vegetarians diets were due to residual confounding/reverse causality(Matta, 2018; Hibbeln, 2018; Northstone, 2018)
- The Austrian Health Interview Survey suggested vegetarians show greater anxiety or depression than omnivores(Burkert, 2014) . Such results from this study and others may be due to not assessing mood by psychometric tests or diagnosis but rather self-report. Vegetarians in the study were made up from a combination of 3 groups (vegan, lacto-ovo, lact-ovo who ate fish) which could also make interpretations difficult.(Burkert, 2014). Another study in Europe suggested vegans showed no difference in mental health or medication intake compared to omnivores (Wirnitzer, 2018).
- Other studies with similar results may be due to either one line item self report , or failure to similarly match for socio-demographic characteristics, or unclear definition of “vegetarian” (German study asked about absence of meat intake but didn’t account for poultry intake), or several study authors suggest that depression actually occurred prior to adopting a vegetarian diet (Michalak, 2012; Baines, 2007) .
- Some may choose a vegetarian diet out of existing health concerns adding bias to results and some who choose vegan diets may do so for awareness of misery with animal agriculture/ethics which are depressing to say the least. “Vystopia”

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Intra Partum or Post Partum Depression**
- Omnivore studies or reviews find no consistent association with omega 3 and intra or post partum depression nor any benefit from supplementation (Chong, 2015; Parker, 2015; 89. Saccone, 2016; Miller, 2013).
- Very few studies in vegetarians. Unknown if lower EPA/DHA status in vegetarian/vegan pregnant women has any significant effect on PPD though vegan pregnant women have less PPD (Pistollato, 2015).
- One retrospective study in women found Post Partum Depression (by self-report) was greater in those who were vegetarian (Hogg-Kollars, 2011) but several methodological concerns: → self report, very small sample size of vegetarians, non-random sample, result also found in those who consumed the most oily fish, prevalence for PPD in Austria is 8-10% but in this study 21%.

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

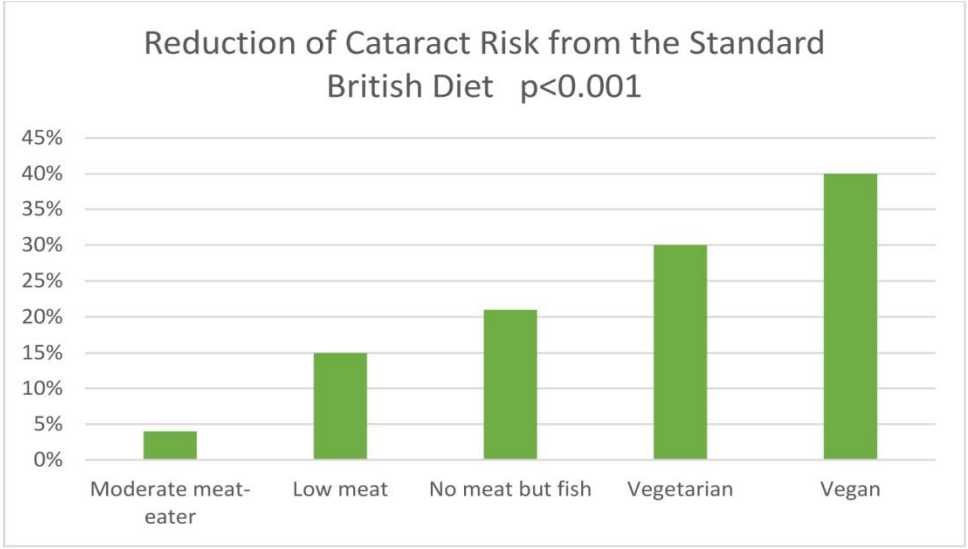
- **Pregnancy/Breast Milk/Infants:**
- Lower DHA levels in umbilical cord blood with vegetarian pregnancies (Reddy, 1994), somewhat lower DHA in breast milk of vegetarians/vegans, though one study found no difference compared to omnivores (Karcz, 2023; Perrin, 2019) and as term and preterm infants can make DHA from ALA, data is still inconclusive on DHA levels transferred to the fetus and infant, though one study found no difference (Sanders, 1999; Sanders, 2009). Infants have greater ability to convert ALA to DHA than adults. Vegetarian women with low ALA during pregnancy (third trimester where fetus needs are intensified) compared to non vegetarians did not differ in plasma EPA/DHA suggesting a compensatory effect to ensure that overall long chain PUFA of the neonate are not compromised (Joshi, 2019) .
- Vegetarian/Vegan diets during pregnancy is not associated with poorer neurocognitive development or cognitive performance (Crozier, 2019; Sebastiani , 2019; Mulder, 2014).
- Note that lower blood levels of DHA may not equate with levels in CNS/brain/retina. More research is needed in this area as children raised as vegans or vegetarians do not demonstrate any differences in mental or neuro-development or who were born from vegetarian mothers. (Sanders, 2009; Mulder, 2014)
- Need to focus on not just one nutrient and overall dietary influences, such as processed foods, however B-12 is an exception

Cognitive/Mental Status and Omega FA in Vegetarians and Vegans

- **Pregnancy/Breast Milk/Infants:**
- Vegetarian and vegan mothers are more likely to breast feed for at least 6 months compared to omnivores and, while DHA levels in breast milk are generally lower (or equal) (Finley, 1985), the levels are still higher than what is seen in un-supplemented formulas (Sanders, 2009). Plant-based diets with high intakes of fruits and vegetables during pregnancy may ↓ the risks for several diseases in infants (Pistollato, 2015);healthy vegetarian pregnancies do not ↑ risk for pre-term birth and plant-based diets may ↓ it (Grieger, 2014). Mixed or protective for low-birth weight (Sebastiani, 2019; Tan, 2019) Vegan pregnant women: lower rates of C-section, preeclampsia, neonatal and maternal mortality, and no difference in negative outcomes/complications (Pistollato, 2015);
- What we do know: balanced plant-based diets rich in fibers and low in fat are considered to be protective against poor pregnancy outcomes such as preeclampsia, gestational diabetes, and preterm delivery and updated evidence highlights that well-balanced vegetarian and vegan diets should be considered safe for the mother's health and for offspring during pregnancy and lactation (Sebastiani, 2019)
- If mothers who are malnourished or low BMI or *B*12 could impair fetal development leading to physical and cognitive delays (Sebastiani, 2019). Despite the data on importance of healthy diet during pregnancy, many don't change diet during pregnancy or fully utilize lactation (Sebastiani, 2019)

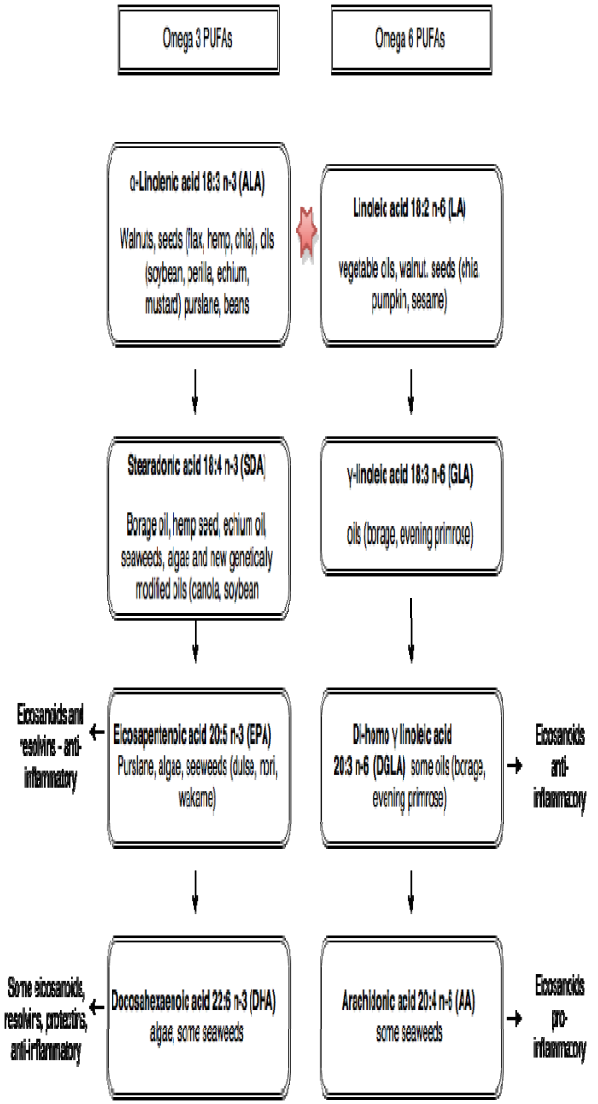
Eye and Omega FA in Vegetarians and Vegans

- **Eye: Cataracts and Macular Degeneration (leading causes of blindness)**
- Cataracts – lower risk for both vegans and vegetarians compared to meat or fish eaters (Appleby, 2016) though ALA increased age-related opacity in lens of eye (Lu, 2007)
- Autofluorescence (lipofuscin accumulation in retina which can lead to vision problems in older age - lower levels in vegetarians (Kommana, 2015)
- Vegans or vegetarians do not demonstrate any differences in visual or mental development. (Sanders, 2009)
- Macular Degeneration – studies suggest elements of plant-based diet reduced risk (Segasothy, 1999; Hever, 2016; Chapman, 2019)



Vegetarian/Vegan intake data re: Omega 3 and 6

- **Omega 3 Intakes**
- **α-Linolenic acid** meets adequate intakes and is generally higher in vegans/vegetarians though some studies show less or equal levels compared to omnivores. (Beezhold, 2010; Rosell, 2005; Welch, 2010; Fokkema, 2000; Kornsteiner, 2008; Phinney, 1990;Sanders, 1978; Lee 2000; Melchert, 1987).
- **Eicosapentaenoic acid (EPA)** and **Docosahexaenoic acid (DHA)** in most studies is typically lower in vegans/vegetarians, sometimes several fold lower than in omnivores or fish eaters (Li, 1999; Yu, 2014; Sanders, 1978; Lee, 2000; Agren, 1995;Fokkema, 2000; Salvador, 2019) (though several studies showed no significant difference) (Kornsteiner, 2008; Morgan-Bathke, 2019).
- **Omega 6 Intakes**
- **Linoleic acid** intake is generally higher in vegans/vegetarians though some studies show less or equal levels compared to omnivores (Beezhold, 2010; Yu, 2014; Rosell,, 2005; Welch, 2010; Fokkema, 2000; Kornsteiner, 2008; Phinney,1990; Lee, 2000; Agren, 1995; Melchert, 1987).
- **Arachidonic acid** intake is from animal products so vegans would have none and some for vegetarians.



Vegetarian/Vegan data re: ALA, EPA, DHA, AA status of levels in body

- **Blood status level -- Omega 3**
- Generally higher ALA, lower EPA and DHA and AA than omnivores (sometimes extremely low) but not in all cases, particularly in some newer studies:
- Recent study in the US in 40 vegans and 78 omnivores looking at fatty acid levels in blood found vegans to have *higher* EPA and ALA, and non-significantly lower DHA and LA than the omnivores and no difference in the Omega-3 index (Sarter, 2015).
- Large study in the UK (EPIC-Norfolk cohort) suggested that despite groups like non fish eating omnivores and vegans/vegetarians having less EPA and DHA intake than fish eaters**,** their overall status in the blood is higher that would be expected (Welch, 2010). Overall status for women, ↑ DHA, DPA, Total long chain Omega 3 than both meat eaters or fish eaters. Vegans = 5
- So while dietary intake of EPA and DHA may vary greatly between fish eaters and vegetarians and vegans, the differences in plasma levels were much smaller than what would be expected by dietary intake.
- The authors mentioned that conversion rates from ALA to longer chain fatty acids in vegetarians/vegans may be greater than earlier small scale studies suggested (Welch, 2010).

Vegetarian/Vegan data re: ALA, EPA, DHA, AA status of levels in body

- **Blood status level -- Omega 3 Welch, 2010**

TABLE 5
Characteristics, dietary intakes, and circulating plasma phospholipid n−3 polyunsaturated fatty acids (PUFAs) and plasma linoleic acid in the substudy in 4902 men and women aged 39–78 y with plasma measures of n−3 PUFAs who were not fish-oil-supplement consumers[1]

			Non-fish-eaters			
	All	Fish-eaters	Meat-eaters	Vegetarians	Vegans	P^2
Women						
n	2256	1891	309	51	5	
Age (y)	62.3 ± 8.8	62.4 ± 8.7	61.8 ± 9.3	60.1 ± 9.2	48.4 ± 5.0	0.002
Weight (kg)	68.8 ± 11.9	68.8 ± 11.8	69.1 ± 12.7	66.1 ± 11.5	69.4 ± 9.5	0.53
Height (cm)	160.4 ± 6.2	160.4 ± 6.2	160.1 ± 6.1	160.7 ± 6.6	164.3 ± 6.3	0.91
BMI (kg/m^2)	26.8 ± 4.4	26.7 ± 4.4	27.0 ± 4.7	256 ± 4.1	25.9 ± 4.7	0.70
Current smokers [% (*n*)]	11.7 ± 263	11.5 ± 217	12.3 ± 38	15.7 ± 8	0 ± 0	0.65
Diet (g/d)						
Total n−3 PUFAs	1.18 ± 0.46	1.24 ± 0.46	0.89 ± 0.34	0.87 ± 0.39	0.72 ± 0.33	<0.001
α-Linolenic acid	0.97 ± 0.33	0.99 ± 0.32	0.86 ± 0.33	0.86 ± 0.39	0.71 ± 0.33	<0.001
Eicosapentaenoic acid	0.09 ± 0.12	0.1 ± 0.13	0.02 ± 0.01	0.01 ± 0.01	0.002 ± 0.004	<0.001
Docosahexaenoic acid	0.13 ± 0.17	0.15 ± 0.18	0.01 ± 0.01	0.002 ± 0.007	0 ± 0	<0.001
Linoleic acid	9.18 ± 3.86	9.33 ± 3.73	8.25 ± 3.94	9.02 ± 5.81	10.89 ± 10.86	<0.001
Plasma (μmol/L)						
α-Linolenic acid	12.5 ± 6.3	12.4 ± 6.1	13.1 ± 7.3	12.3 ± 4.8	13.71 ± 8.10	0.22
Eicosapentaenoic acid	63.4 ± 43.0	64.7 ± 43.4	57.1 ± 38.4	55.1 ± 52.5	50.0 ± 29.4	0.001
Docosapentaenoic acid	72.3 ± 30.4	71.8 ± 29.6	74.7 ± 34.2	75.0 ± 32.2	90.6 ± 54.0	0.056
Docosahexaenoic acid	266.0 ± 113.8	271.2 ± 113.1	241.3 ± 109.6	223.5 ± 137.8	286.4 ± 211.7	<0.001
Total long-chain n−3 PUFAs	401.7 ± 170.2	407.7 ± 169.3	373.1 ± 166.2	353.5 ± 191.5	426.8 ± 284.0	<0.001
Linoleic acid	1244.0 ± 334.3	1236.9 ± 328.4	1271.2 ± 373.9	1325.9 ± 278.6	1406 ± 162.1	<0.001

Vegetarian/Vegan data re: ALA, EPA, DHA, AA status of levels in body

- Adventist Health Study – (in adipose – usually marker of diet intake) vegans ↑ ALA, total *ω-3* and LA, ↓ DHA (.12 compared to.18) and ↓ AA, and similar EPA, compared to non-or semi-vegetarians (Miles, 2019). Despite no direct source of DHA, vegans had 12% of total fatty acids as DHA. Another study showed same EPA and non-significant DHA levels compared to omnivores (Morgan-Bathke, 2019). Adipose represents PUFA intake 1-2 years and endogenously in adults is believed to store 20-50g of DHA and 60-70g in whole body fat (Venø, 2019; Luxwolda, 2014)
- Another study suggested low plasma concentrations of EPA and DHA in vegans and vegetarians but stable endogenous produced quantities of both after 20 years of following a vegan diet (Rosell, 2005).
- And another found no significant difference for EPA or DHA levels between vegetarians and omnivores in the 4 different serum fractions investigated (Phinney, 1990) possibly because omnivores may have had low ALA intake (Fokkema, 2000).

- **Status level in body -- Omega 6**
- Linolenic Acid – generally higher than in omnivores
- Arachidonic acid – similar (Rosell, 2005; Melchert, 1987) generally lower vs. omnivores (Fokkema, 2000; Phinney, 1990; Kornsteiner, 2008; Lee, 2000;Actis, 2005; Miles, 2019; Weder, 2025).
- Conclusions - not all studies are in agreement with respect to ALA, LA, EPA, DHA in vegans/vegetarians, though most studies – low EPA/DHA compared to omnivores, though several studies show equal or higher status

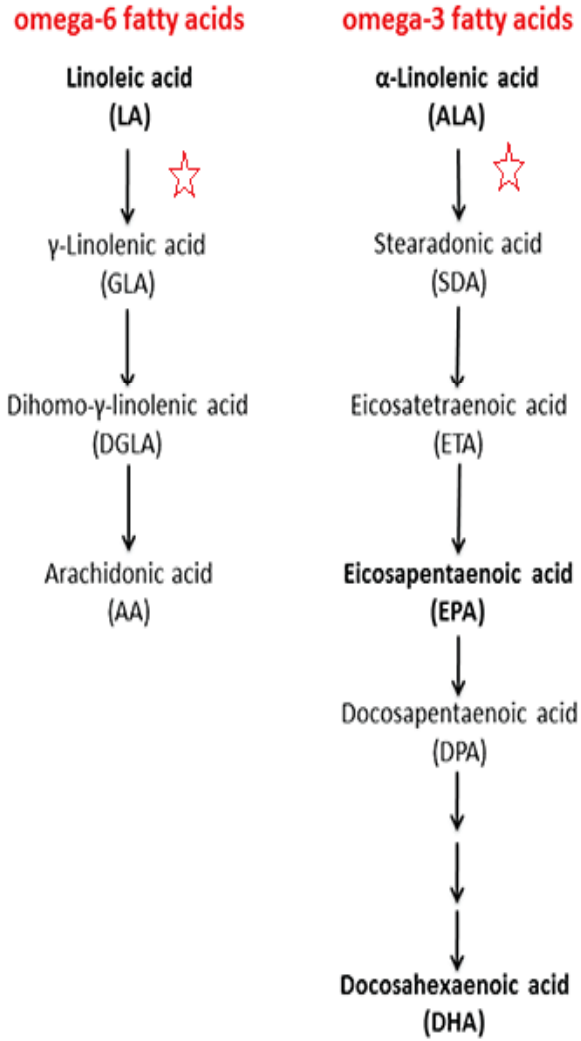
Vegetarian/Vegan trials using supplementation

- **ALA**
- Studies in vegetarians giving supplemental ALA mostly show increases in EPA, but not DHA but one found 33% ↑ DHA after 6wks (Rosell, 2005; Sanders, 1981;Ghafoorunissa, 1992; Greupner, 2018).
- A study in lacto-ovo-vegetarians using standard eggs, omega 3 enriched eggs or walnuts, found that those eating walnuts had increased ALA along with reductions in triglycerides, total cholesterol and Apo B, while those eating omega 3 enriched eggs had increased EPA and DHA, Apo B and total cholesterol and reduced triglycerides (walnuts were better & significant at lowering triglycerides (Burns-Whitmore, 2014) .
- **Algae –DHA, or EPA/DHA**
- increases in DHA as well as EPA (retro conversion) and decreases in AA (EPA compete with AA for Eicosanoid production). Some but not all studies showed increases in LDL Cholesterol which is a causal factor for atherosclerotic CVD (Sanders, 2009; Bernstein, 2012; Geppert, 2006) LDL increases also seen with fish oil (Jacobson, 2012)
- A study longer in duration in 40 vegans who were given a DHA/EPA algae supplement for 3 months showed increases in EPA, DHA, LA, and decreases in AA (LDL Cholesterol not reported) (Sarter, 2015) .
- Interestingly, healthy Omnivores given a DHA/DPA algae supplement showed increases in pro-inflammatory AA (Sanders, 2006) .

Conversion Rate

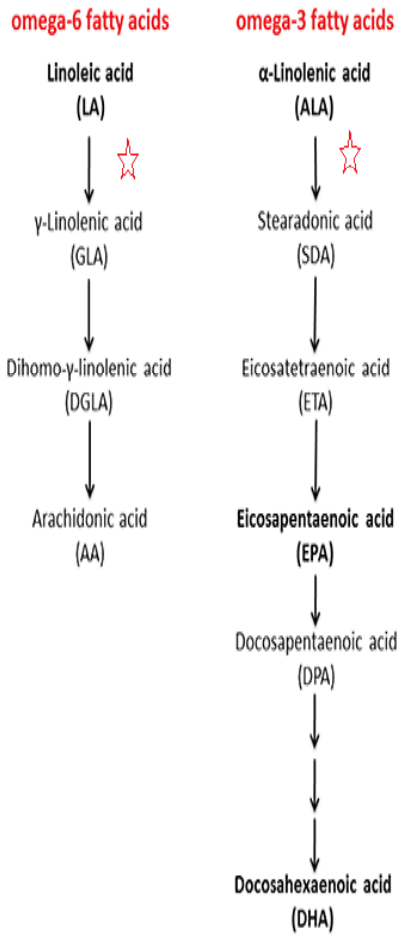
- **In Omnivores**
- The rate of conversion from ALA to longer chain EPA and DHA is limited.
- **ALA to EPA - .1% to up to 21%** (avg **8%♂, 21% ♀**) (Brenna, 2009; Baker, 2016; Petrović-Oggiano, 2020; Burdge, 2004)
- **ALA to DHA anywhere from undetectable to up to 9%** (Geppert, 2005; Burdge, 2005)**.**
- **Infants have greater ability for ALA to DHA than adults** (Baker, 2016)

- Looking more specifically at gender:
- **Men**: ALA to EPA **~ 8%** and conversion to DHA **~ <0.1% to 4%** (Williams, 2006)
- **Women**: one research group suggested rates of up to **9%** to DHA (Williams, 2006)
- Conversion rate **LA to DGLA** 1.5% and DGLA is main contributor to **AA** (Pawlosky, 2006; Demmelmair, 1999).
- Conversion rate **LA to AA ~.2 to 2.7% or even less** (Rett, 2011; Hadley, 2016; Pawlosky, 2006; Weder, 2025) **~1.8%** of LA is used for other fatty acids (Pawlosky, 2006)



Conversion Rate

- **What affects conversion rates?**
- Omega 3 and 6 competition. Most research suggests ↑ LA will ↓ ALA conversion rate & vice versa despite ALA being the preferred substrate for Δ 6 desaturase enzyme (Joshi, 2019; Burdge 2005; Hibbeln,2006; Cleland, 1992; Wood, 2014; Gibson, 2011; Gu, 2024; Gerster, 1998; Wien, 2010; Drobner 2023).



In Vegetarians/Vegans

- Literature has framed the slow conversion rates as a potential problem for vegetarians/vegans because of lower synthesis of EPA/DHA.
- Some researchers have suggested vegans/vegetarians double the recommended adequate intake of ALA when no other EPA/DHA source is used (Saunders, 2013) and to avoid high LA intake(Sanders, 1999) .
- The limited conversion rate of omega 3 fatty acids has resulted in many recommendations for vegetarians to increase not only ALA but also increase EPA/DHA via an algae supplement.
- There is some other evidence to suggest the conversion rates are greater in vegetarians/vegans but this is yet to be confirmed (Welch, 2010; Vannice, 2014) . Epic/Norfolk study, non fish eaters had 22% greater conversion rates than fish eaters (Welch, 2008)

Conversion Rate

Reasons for varied conversion rates-

Other factors affecting conversion rates include:

- ALA conversion rates may be lower because DHA levels are sufficient in tissues (most studies show ALA ↑ EPA (Plourde, 2007; Baker, 2016)
- Genes and Genotype variability(Minihane, 2016; Kothapalli, 2016) ie. Δ6desaturase gene (FADS2)
- Different analytical tests being used for fatty acid determination/concentration, (von Schacky, 2015)
- Composition and type of the diet (lipogenesis from alcohol/glucose rich diet/high carb diet – produces Palmitic acid which competes with ALA and LA for desaturation ↓ EPA/DHA (Park, 2016), saturated fat, trans-fats (Carlson,1997; Das, 2006; Mustonen, 2023)
- Supplement usage, BMI, caffeine intake, age or stage of lifecycle (especially elderly), genetics, medical conditions such as diabetes, metabolic syndrome, chronically inflamed states, hypertension, or fat mal-absorption, glucocorticoids (prescribed and natural)
- Lack of vitamin and mineral cofactors – B12 and other B vitamins, zinc, magnesium, calcium, niacin, vitamin C (Saunders, 2013; Carlson,1997; Das, 2006; Mustonen, 2023; Weder, 2025)
- Tobacco use

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- Most studies show ALA > EPA (5%) and as body can further EPA > DHA it may take what it needs and may not need additional DHA hence conversion is less.
- Many co-factors that were previously mentioned affect conversion rate, but have these been controlled for in studies?
- One study showed ALA supplementation had no change in DHA after 3 months, but ↑21% after 10 months (Ezaki, 1999). More time needed in studies?
- Rate of conversion in studies is often not classified by gender despite studies showing wide variation in conversion rates based on gender.
- Recent research by Domenichiello (2015) suggested that *conversion of ALA to DHA is underestimated when using current tracer studies to estimate synthesis of ALA to DHA* and that studies in animals either fed ALA only diets or diets with DHA produced the same DHA concentration in the brain (Domenichiello, 2015) .

  Idea is that ALA supplementation with a tracer is absorbed into tissues and adipose and does not reach the liver where it would be processed and then affect plasma levels.
- Additionally, elevated Omega 6 Docosapentaenoic acid (DPA 22:5n-6) is considered to be a marker for Omega 3 deficiency in human brains which can result in reduced DHA levels in the brain (Sinclair, 2022). Studies looking at vegans showed no difference in DPA levels compared to Omnivores (Welch, 2010).

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- The UK (EPIC-Norfolk cohort) mentions that despite vegans/vegetarians having less EPA and DHA levels than fish eaters*, their overall long chain PUFA status in the blood is higher that would be expected and in females vegan plasma phospholipids contained slightly more ALA*, *about the same EPA as meat eaters, and vegans had greater DHA than any of the other groups, while for males, vegans had more ALA and EPA and less DHA than fish or meat eaters* (Welch, 2010) .

- There may be a valid biochemical reason for slow conversion. For example, as omega 3 are anti-inflammatory, slow rates could be a way to ensure that body stays in balance with regard to inflammation and anti-inflammation. Could too much omega 3 suppress immune function and lead to disease? Concern has been expressed for EPA/DHA supplements upsetting the balance with AA, and EPA or DHA as the latter may suppress the benefits provided by AA via competitive inhibition (Hadley, 2016) and cause concerns for inadequate AA in brain tissue for infants possibly leading to suboptimal neurological development (Weder, 2025).

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- Most of ALA/ LA gets β-oxidized for energy and the rest gets converted or stored for both Omega 3 and 6 fatty acids. This may be exactly what the body designed and wants and hence not flawed.

- Adults are estimated to store 20-50g of DHA and 60-70g in whole body fat and estimates are that the brain DHA uptake rate is 3.8 mg/day suggesting that adult human adipose contains enough DHA to supply the brain for 14–36 years. (Domenichiello, 2015)

- EPA/DHA – highly unsaturated, prone to oxidative degradation. Body doesn't want too much of this circulating throughout body? Could affect LDL oxidation (Cameron-Smith , 2015; Finnegan, 2003; Hishikawa, 2020). Mostly not covered is also the fact that Fish Oil supplements also contain oxidized lipids (plays a central role in atherogenesis) and in many cases exceeding set levels (Mason, 2017)
- Dr. Kim Williams - seafood #1 source of micro/nano plastics. 453% increase in heart attack, stroke and death(Marfella, 2024) … stopped taking algae supplement and believes we do not need to get omega 3's from the ocean

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

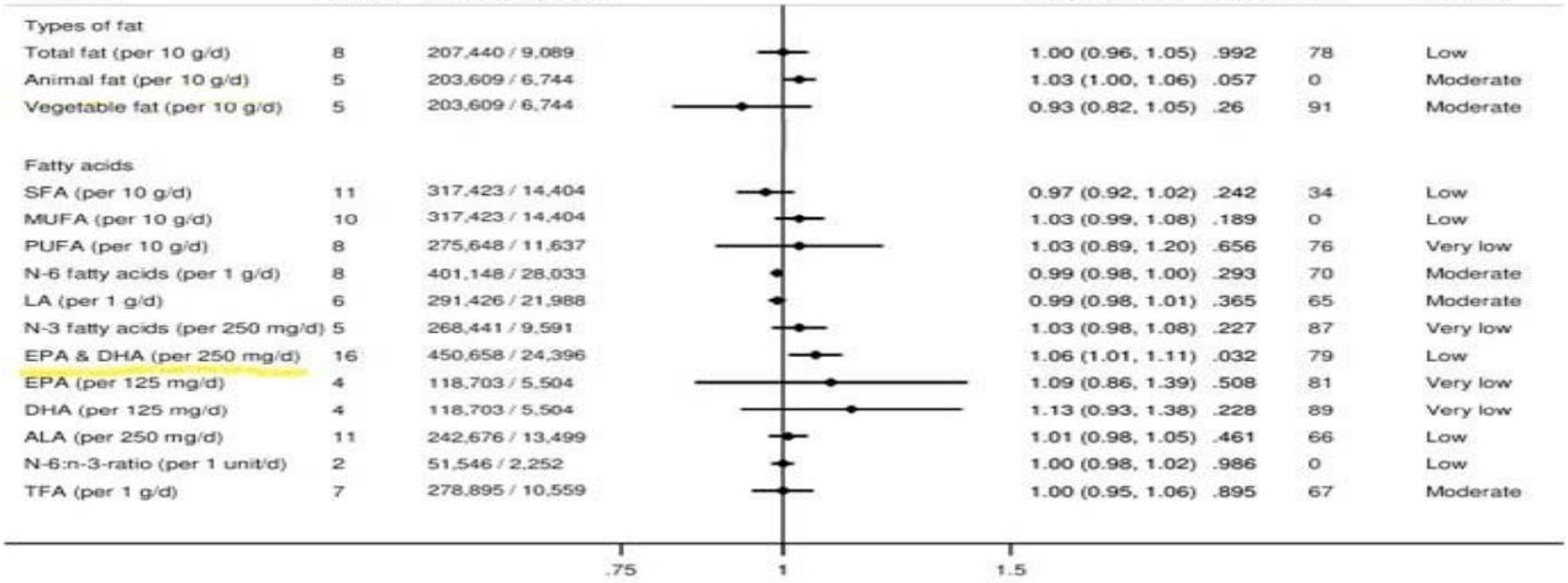
- **Opposing viewpoints**
- Many recommend we increase Omega 3 (EPA/DHA) because of the low conversion rate from ALA > EPA/DHA. Since the conversion rate of Omega 6 is even less than Omega 3, we certainly wouldn't follow the logic of therefore needing to consume Omega 6 AA! Nature doesn't decide which pathway (3 or 6) is considered healthy and which one is not. They are both essential and needed. Both DHA and AA play important separate roles in body functioning including brain. Bibus, 2015 notes that studies that describe only Omega 3 amounts and omit data on (competing) Omega 6 fail to provide to the scientific community the important evidence related to the balance between them which will produce biologically significant eicosanoid actions.

- Could too much have other negative effects? For example, the military is assessing whether there is an increase in bleeding during injury with certain doses of omega 3(Hamazaki, 2014) , and some studies suggest prolonged bleeding time in populations with high levels of fish oil/fish intake, and immunosuppression with DHA supplements and the institute of medicine advises caution if taking supplements (Lichtenstein, 2005); Dyerberg, 1979; Food and Nutrition Board, 2002).

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- dose–response meta-analysis of 23 prospective observational studies found an association between combined intakes of EPA and DHA and type 2 diabetes. Conversely, total intakes of Omega 6 or Linoleic Acid were found to be slightly protective(Neuenschwander, 2020).

Exposure	No of cohorts	No of participants / cases	SRR Random effects (95% CI)	p-value	I-squared (%)	Certainty of evidence
Types of fat						
Total fat (per 10 g/d)	8	207,440 / 9,089	1.00 (0.96, 1.05)	.992	78	Low
Animal fat (per 10 g/d)	5	203,609 / 6,744	1.03 (1.00, 1.06)	.057	0	Moderate
Vegetable fat (per 10 g/d)	5	203,609 / 6,744	0.93 (0.82, 1.05)	.26	91	Moderate
Fatty acids						
SFA (per 10 g/d)	11	317,423 / 14,404	0.97 (0.92, 1.02)	.242	34	Low
MUFA (per 10 g/d)	10	317,423 / 14,404	1.03 (0.99, 1.08)	.189	0	Low
PUFA (per 10 g/d)	8	275,648 / 11,637	1.03 (0.89, 1.20)	.656	76	Very low
N-6 fatty acids (per 1 g/d)	8	401,148 / 28,033	0.99 (0.98, 1.00)	.293	70	Moderate
LA (per 1 g/d)	6	291,426 / 21,988	0.99 (0.98, 1.01)	.365	65	Moderate
N-3 fatty acids (per 250 mg/d)	5	268,441 / 9,591	1.03 (0.98, 1.08)	.227	87	Very low
EPA & DHA (per 250 mg/d)	16	450,658 / 24,396	1.06 (1.01, 1.11)	.032	79	Low
EPA (per 125 mg/d)	4	118,703 / 5,504	1.09 (0.86, 1.39)	.508	81	Very low
DHA (per 125 mg/d)	4	118,703 / 5,504	1.13 (0.93, 1.38)	.228	89	Very low
ALA (per 250 mg/d)	11	242,676 / 13,499	1.01 (0.98, 1.05)	.461	66	Low
N-6:n-3-ratio (per 1 unit/d)	2	51,546 / 2,252	1.00 (0.98, 1.02)	.986	0	Low
TFA (per 1 g/d)	7	278,895 / 10,559	1.00 (0.95, 1.06)	.895	67	Moderate



SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; n-6 fatty acids: omega-6 fatty acids; LA: linoleic acid; n-3 fatty acids: omega-3 fatty acids; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; ALA: alpha-linolenic acid; TFA: *trans*-fatty acids

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- The body's processes to ensure homeostasis is well known for other nutrients. Our bodies may perform compensatory measures when intakes are low to ensure sufficient amounts for vital processes.
- The body takes measures to increase conversion when needed i.e for offspring: One example: Females have enhanced conversion of αLNA > EPA and EPA > DHA during early reproductive years or during pregnancy, and conversion decreases with increasing age (Burdge, 2005; Williams, 2006; Harris, 2013; Childs, 2014)
- There is also the *brain plasticity hypothesis* which suggests the brain has the ability to adapt and that there may be no adverse consequences to small reductions in DHA (McCann, 2005)
- Examples include:
  - More absorption of calcium in intestine when habitual intakes are low to ensure adequate serum calcium. Vegetarian diets appear to pose no greater risk for hip or other bone fracture when controlling for calcium intake, and several studies show similar rates of bone loss and clinically insignificant differences in bone density in vegetarians/vegans
  - Low heme-iron intake in vegans/vegetarians has not resulted in any differences in iron deficiency anemia compared to omnivores. (may ↓ Diabetes) (McElduff, 2016)
  - Vegetarians generally show less protein intake than omnivores though have adequate protein.

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- If levels are of EPA/DHA are chronically low in plant-based diets, and/or there are greater intakes of Omega 6, we would expect to see an increased in inflammatory mediated disease in plant-based followers i.e CVD, diabetes, rheumatoid arthritis, asthma, systemic lupus erythematosus, multiple sclerosis, dementia, as well as other conditions like visual acuity, macular degeneration and dry eye syndrome (Welch, 2010; Miljanovic, 2005). Retinal neurodegeneration is associated with brain neurodegeneration and smaller gray-matter and white-matter and brain volume (Mutlu, 2017; Ong, 2015).
- Adults and children fed a total parenteral nutrition formula with no ALA showed deficiency symptoms: visual dysfunction suggesting decreased availability of DHA to be incorporated into neural membranes (Burdge, 2005), and sensory neuropathy, all of which were resolved when ALA was given (Holman, 1992)
- Some research suggested that conversion of ALA to DHA may actually occur in the brain itself as opposed to primarily in the liver, making blood level assessments possibly subjective. A study in infants suggested DHA status in red blood cells only explained about ¼ **of the variance** in overall brain growth (Lauritzen, 2001)
- As DHA is located in some of the highest levels in the retina, brain, do we see any issues in those with low intakes???

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- We do know that vegetarians/vegans have:

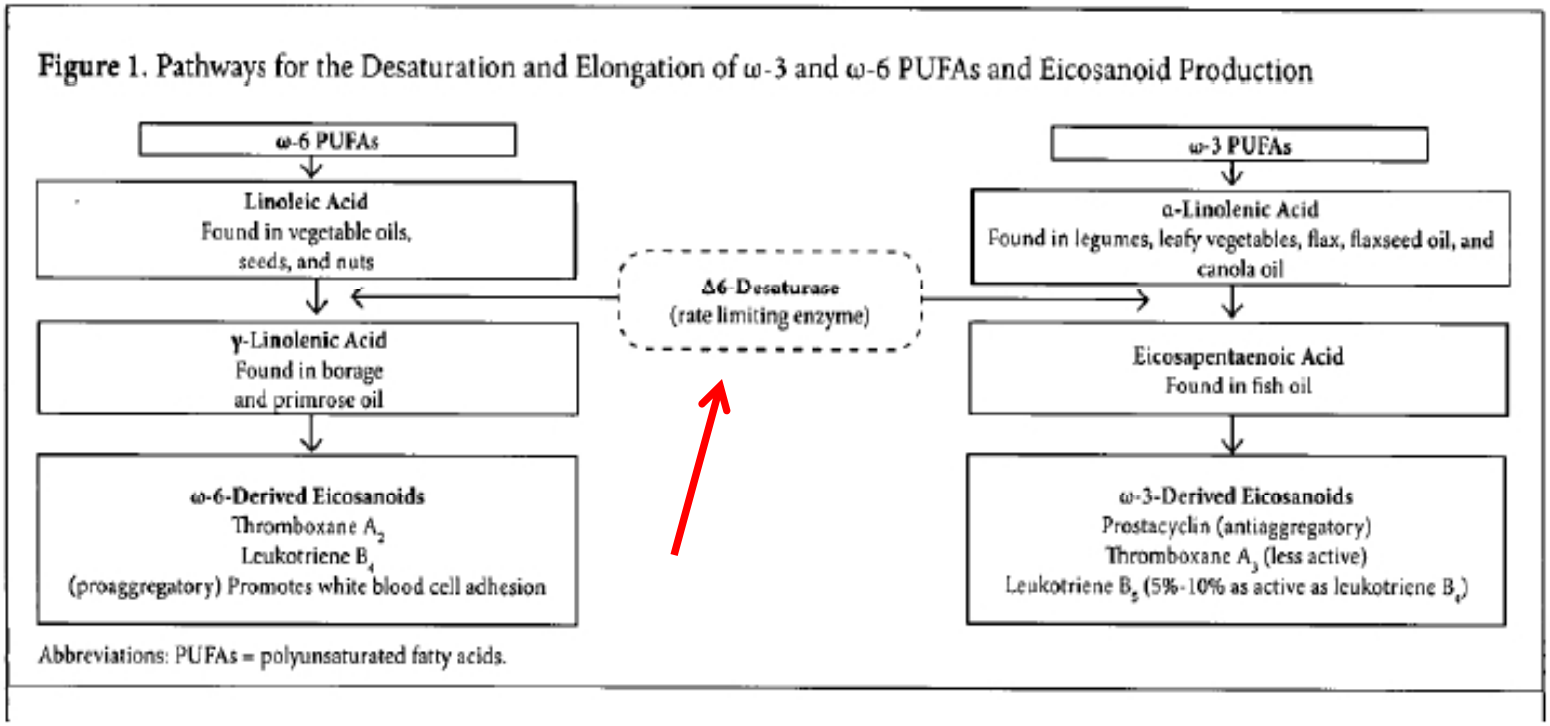
1. Some of the highest disease fighting biomarkers (Miles, 2019)
2. Some of the best risk reductions for fatal and non-fatal heart disease compared to omnivores as well as those whose animal product consumption has a significant amount of fish (Crowe, 2013).
3. Compared to omnivores as well as fish eaters, vegans are at lower risk for cataracts than any other dietary group, a 30% reduction compared to fish eaters (Appleby, 2016).
4. Compared to omnivores, vegetarians have less risk for dementia (Giem, 1993) and no difference on cognitive tests (Lloyd-Wright, 2005), less anxiety and better mood scores in both vegans and vegetarians (Beezhold, 2010; Beezhold, 2014; Link, 2009), appropriately planned vegetarian and vegan diets are safe during pregnancy (Piccoli, 2015; Sanders, 1994), promote normal growth of infants and young children (Key, 2006; Radak, 2018; Sanders, 1994), and vegetarian and vegan children do not appear to experience any difference of impairment for visual or mental development (Melina, 2016).
5. Vegans have lower Palmitic acid which competes with ALA and LA for desaturation ↓ EPA/DHA (Rosell, 2005; Miles, 2019).

Controversy over conversion rate - whether vegetarian/vegans need more Omega-3

- **Opposing viewpoints**
- The end products of Omega 3 fatty acids include Oxylipins: Eicosanoids/Resolvins/Protectins, prostaglandins, thromboxanes: powerful and potent, short lived chemicals involved in platelet aggregation, inflammatory processes like tissue injury, neuroprotective activity, and vasoconstriction.
- If levels are of EPA/DHA are chronically low in plant-based diets, and/or there are greater intakes of Omega 6, we would expect to see issues in these processes. As Omega 6 mediates the inflammation process via eicosanoid end products, and Omega 3 end products counter that, we would expect to see issues in vegetarians/vegans involving inflammation.
- Some studies in vegetarians found lower levels of pro-inflammatory eicosanoids compared to omnivores,(Yu. 2014) as well as lower CRP (Haghighatdoost, 2015; Paalani, 2011) , and low CRP levels in vegans (Franco-de-Moraes, 2017; Fontana, 2007). Systematic reviews of plant-based diet trials also found lower CRP (Eichelmann, 2016) . Three week long vegan diet lifestyle intervention lowered CRP in all types of diets reported(Sutliffe, 2015),and also 8 wk trial in CAD patients (Shaw, 2017). Those with RA put on vegan diet for 1 year showed a decrease in CRP and an increase in atheroprotective antibodies (Elkan, 2008) .

Ratio of Omega 6 to Omega 3

- The relationship between the omega 3 and omega 6 pathways are linked in that they both compete for the same enzyme used when converting fatty acids into longer chain fatty acids and incorporating these longer chain fatty acids into cell membranes.



Ratio of Omega 6 to Omega 3

- When diets have a high ratio of LA to ALA, this suppresses some ability of ALA to convert to EPA and in some studies to DHA (Wood, 2015, Emken, 1994; Wien, 2010). Most studies suggest that ↓ LA and maintaining ALA ↑ = EPA/DHA or ↑ ALA and ↓ LA = ↑ EPA/DHA
- The general belief is that an imbalance of Omega 6 to 3 can hinder omega 3 production and be pro-inflammatory. Much of this belief has centered around the production of AA and its pro-inflammatory eicosanoids.
- It has been suggested that maintaining a proper ratio between n-6 and n-3 is important for health maintenance and could reduce risks for inflammatory diseases such as CHD and, to a lesser extent, possibly diabetes, asthma, dementia , and dry eye syndrome (Welch, 2010; Miljanovic, 2005) however most studies have not shown an increase in risk related to the ratio.

Ratio of n-6 to n-3

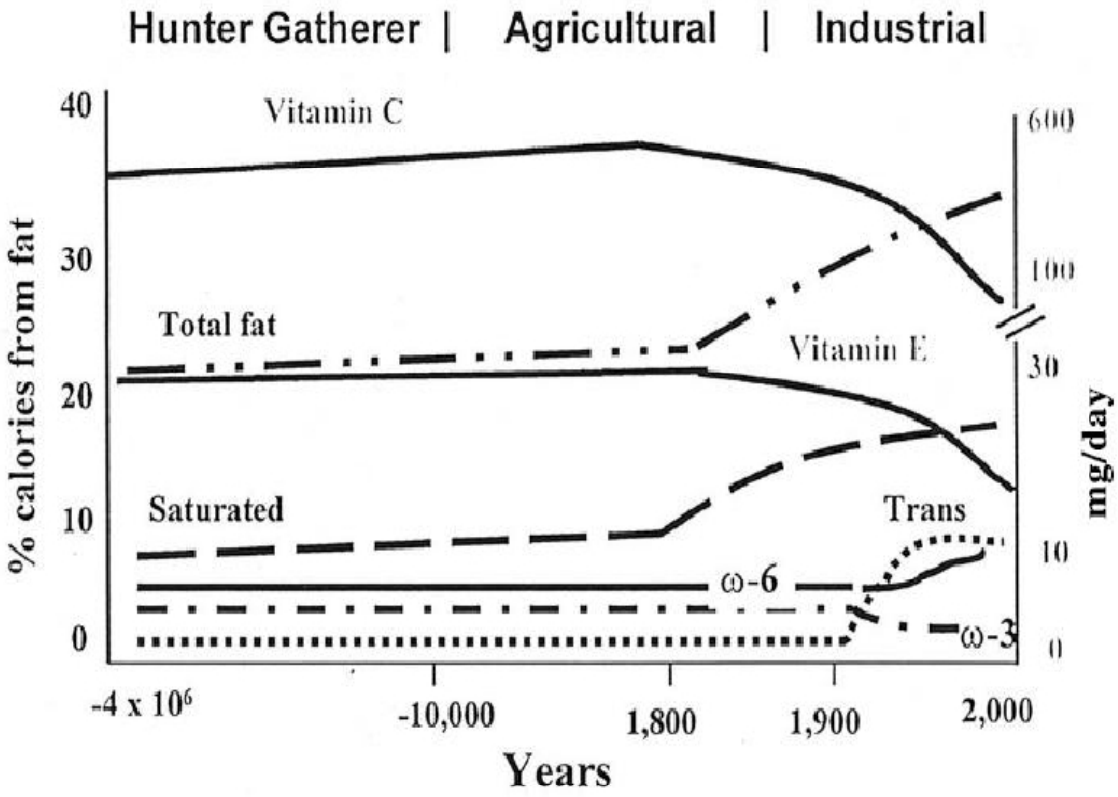
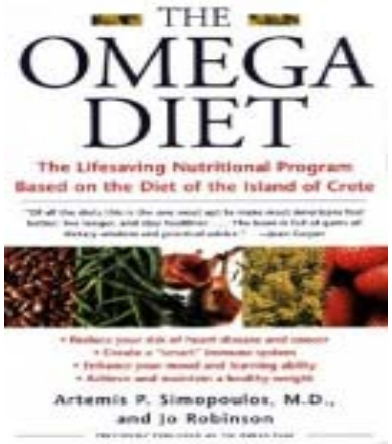


Fig. 1. Hypothetical scheme of fat, fatty acid (ω6, ω3, *trans* and total) intake (as percentage of calories from fat) and intake of vitamins E and C (mg/d). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years [75].

- Figure 1 of (Simopoulos 2002) - Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother. 2002 Oct;56(8):365-79.

Ratio of Omega 6 to Omega 3



- The Western diet can be as high as 25:1 (Robinson, 2013).

  Vegan and vegetarian intake studies suggest greater ratios than in omnivores.

  Vegan females 13-17: 1

  Vegan males 8-17: 1

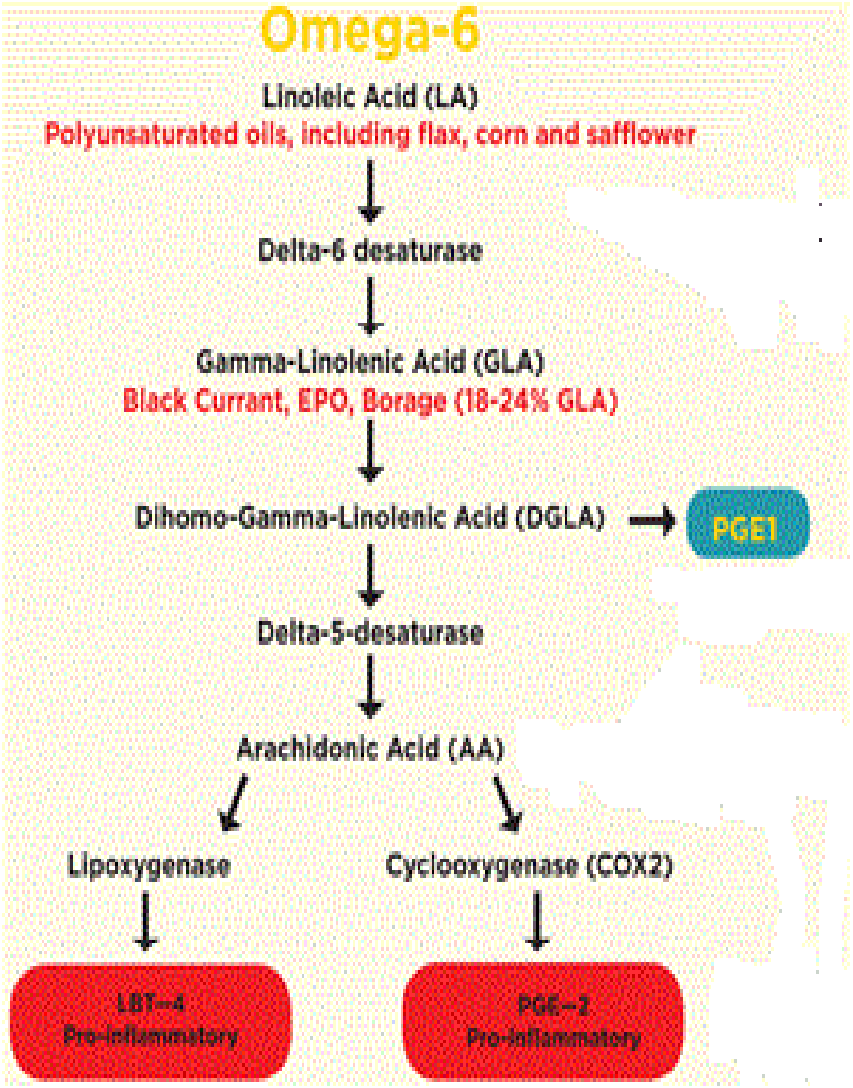
  Vegan mixed gender averages of 9-10:1

  Vegetarians 12 :1 (Li, 1999; Yu, 2014; Fokkema, 2000; Kornsteiner, 2008; Simopoulos, 2002) .

Some scientists propose a ratio for vegetarians in the area 2–4: 1 (Simopoulos, 2006) .

Controversy over Ratio – and whether to make a case for less Omega 6 ?

- The concern about the ratio imbalance may have been before we knew conversion rates of LA to AA.
- While the ratio of omega 6 to 3 is often mentioned in the context of negatively affecting omega 3 production, some studies contradict this. Studies suggest *LA does not convert appreciably to AA* (which are believed to be pro-inflammatory), and some suggest the ratio to be less important than maintaining high levels of both in the diet. "*The ratio of n-6 to n-3 is unlikely to impart meaningful information over and above assessment of the individual fatty acids alone* (Simopoulos, 2008).
- Conversion of DHLA → AA is limited as well ~1.5% (Roshanai, 1984; Wang, 2012) .



Controversy over Ratio – and whether to make a case for less Omega 6 ?

- A recent systematic review of clinical trials did not find support to claim that LA promotes inflammation (Fritsche, 2015) or increases mortality, CVD mortality or CHD events and may help reduce myocardial infarction (Marklund, 2019; Hooper, 2018) Fritsche (2015) asserted that high fat meals may have more to do with inflammation via the gut microbiome as they create more Lipopolysaccharide (LPS) an endotoxin that may increase inflammatory response. He lastly contends that concept of LA being inflammatory was based on animal and cell culture models and the belief that it appreciably converts to AA, which is not the case. Its conversion rate (0.3 – 0.6%) is *typically less* than for Omega 3 conversion rates. Additionally, DGLA to AA is limited as well (Roshanai , 1984) .

The Science of Fatty Acids and Inflammation[1–3]

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ABSTRACT

Inflammation is believed to play a central role in many of the chronic diseases that characterize modern society. In the past decade, our understanding of how dietary fats affect our immune system and subsequently our inflammatory status has grown considerably. There are compelling data showing that high-fat meals promote endotoxin [e.g., lipopolysaccharide (LPS)] translocation into the bloodstream, stimulating innate immune cells and leading to a transient postprandial inflammatory response. The nature of this effect is influenced by the amount and type of fat consumed. The role of various dietary constituents, including fats, on gut microflora and subsequent health outcomes in the host is another exciting and novel area of inquiry. The impact of specific fatty acids on inflammation may be central to how dietary fats affect health. Three key fatty acid–inflammation interactions are briefly described. First, the evidence suggests that saturated fatty acids induce inflammation in part by mimicking the actions of LPS. Second, the often-repeated claim that dietary linoleic acid promotes inflammation was not supported in a recent systematic review of the evidence. Third, an explanation is offered for why omega-3 (n–3) polyunsaturated fatty acids are so much less anti-inflammatory in humans than in mice. The article closes with a cautionary tale from the genomic literature that illustrates why extrapolating the results from inflammation studies in mice to humans is problematic. *Adv Nutr* 2015;6:293S–301S.

Controversy over Ratio – and whether to make a case for less Omega 6 ?

- The FAO report on Fats and Fatty Acids in Nutrition concluded: "Based on the evidence and conceptual limitation, *there is no rationale for a specific recommendation for omega-6 to 3 ratio, or LA to ALA ratio, if intakes of n-6 and n-3 fatty acids lie within the recommendation established in this report*" (LA 2.5% and ALA .5% energy" (FAO, 2010) . .
- Farvid (2015) noted in a systematic review on LA and CHD, "Despite theoretical concern about the potential pro-inflammatory and thrombogenic properties of omega-6 polyunsaturated fats, evidence from human studies to support a positive association between intakes of these fatty acids and biomarkers of inflammation or risk of cardiovascular disease or cancer is limited." A review paper that summarized 15 randomized controlled trials of dietary n-6 PUFAs (mainly LA), reported that none of the studies showed elevation of pro-inflammatory markers in healthy adult population(Johnson, 2012) , which make sense as little LA is converted to AA (Rett, 2011).Other research supports Omega-6 and ↓ chronic disease (Asnicar, 2021).
- And from the US multi-center Cardiovascular Health Study "…*the ratio of omega-6 to omega-3 is not particularly meaningful because both types of fatty acids are essential and confer health benefits and there is little evidence that the ratio per se is related to health outcomes*." (Wu, 2015).

Controversy over Ratio – and whether to make a case for less Omega 6 ?

- **Lowering LA and effect on Omega 3**
- McLennan et al., (2015) suggest that omega 6 does not adversely effect omega 3 actions in the body and point to total mortality and CVD mortality being lower with high intakes of both omega 3 and 6.
- A 4 wk study in omnivores in which subjects reduced LA intake from 4.6% to 2% total energy, showed increases in EPA and DHA and no Δ in AA in plasma phospholipids and no Δ in EPA/DHA/AA in erythrocyte phospholipids suggesting no influence on inflammatory pathways related to AA. Authors noted changes in EPA/DHA in this study were not as significant as compared to when supplementing ALA (Wood, 2014).

A low omega-6 polyunsaturated fatty acid (n-6 PUFA) diet increases omega-3 (n-3) long chain PUFA status in plasma phospholipids in humans ☆

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Controversy over Ratio – high ALA?

- **Too much ALA affecting LA?** ALA has higher affinity for the Δ6 than LA (Phinney, 1990)
- It has been shown that strong suppression of omega 6 metabolism can occur by having less than 2% of the total calories coming from omega 3 (Wang, 2012) (AI recommendations are .6-1.2%).
- Both Omega 3 and 6 Produce Anti-inflammatory metabolites. We can no longer say Omega 3 are Anti-inflammatory and Omega 6 is Inflammatory.
- LA converts to GLA then DGLA (dihomo-γ-linolenic acid). Very little converts to AA therefore reducing production of inflammatory metabolites (prostaglandins, leukotrienes and platelet activating factor) (Wang;2012) .
- DGLA also produces several anti-inflammatory and anti-proliferative metabolites itself and are associated with anti-tumor activity (Xu, 2014) .
- Wood 2015 suggests that too much ALA may affect DHA synthesis as there are 2 delta 6 desaturase enzymes (ALA > EPA, and EPA > DHA) and too much ALA may use the first enzyme and be rate-limiting to the second one. Other research suggests that trials giving high ALA may displace DHA in membrane phospholipids which could provide a rationale to not focus so heavily on increasing ALA (Hussein, 2005)

Controversy over Ratio – and whether to make a case for less Omega 6 ?

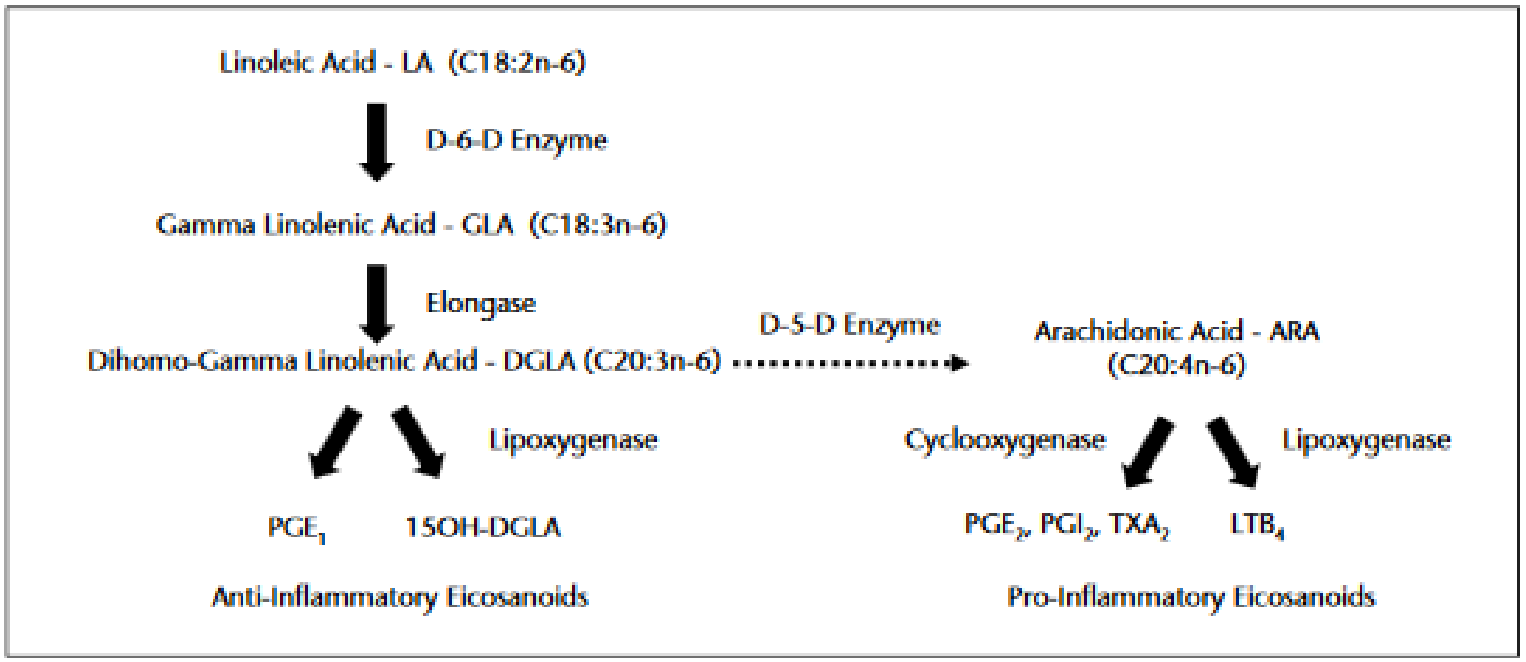


Figure 1. *The metabolic pathway of n6 fatty acids and its consequent formation of eicosanoids in humans. The conversion of LA to GLA by delta-6-desaturase is the rate limiting step towards the production the anti-inflammatory eicosanoids.*

It is now known that the earlier view of n-6 PUFAs and their derivatives being generally pro-inflammatory and, thus, harmful was an oversimplification (Mustonen, 2023).

Controversy over Ratio – and whether to make a case for less Omega 6 ?

- **Importance to Vegans/Vegetarians**: may suggest a need to keep reasonable levels of both Alpha-linolenic Acid (ALA) and Linoleic Acid (LA) but only if research suggests lower EPA/DHA are problematic; and cast doubt on the notion that Omega 6's cause disease. Some studies show ↓ LA = ↑ DHA, and ↑ ALA = ↑ EPA, but not DHA (but unknown if body converts to DHA as needed).
- Further reading:

Farvid et a. **Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies**. Circulation. 2014 Oct 28;130(18):1568-78

McLennan PL, et al. **Weighing Up Fish and Omega-3 PUFA Advice with Accurate, Balanced Scales: Stringent Controls and Measures Required for Clinical Trials**. Heart Lung Circ. 2015 Aug;24(8):740-3.

Wood KE, Mantzioris E, Gibson RA, Ramsden CE, Muhlhausler BS. **The effect of modifying dietary LA and ALA intakes on omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) status in human adults: a systematic review and commentary**. Prostaglandins Leukot Essent Fatty Acids. 2015 Apr;95:47-55

Wang X, Lin H, Gu Y. **Multiple roles of dihomo-γ-linolenic acid against proliferation diseases**. Lipids Health Dis. 2012 Feb 14;11:25.

Controversy on low DHA EPA in vegan and vegetarians

- Most studies cite lower DHA/EPA status in vegetarians/vegans as problematic. The following quotes oppose this view:
- Harris (2014), in a recent review of the topic, contended that "*cardiovascular risk markers and cardiovascular events appear to be significantly reduced in vegetarians compared with those in omnivores*" and there is an *absence of data to show that the risk reduction could be even greater with additional omega 3"* (Harris, 2014) .

- Sanders (2014) concluded: "*Current evidence is insufficient to warrant advising vegans and vegetarians to supplement their diets with EPA or DHA for CVD prevention*."(Sanders, 2014).

- "The importance of the lower plasma concentrations of DHA seen in vegetarians and in vegans than in omnivores is not known, and plasma concentrations do not necessarily reflect tissue concentrations, conversion of Omega 3 is affected by many things" (Rosell, 2005)
- Burns-Whitmore (2019) review "it is prudent not to suggest that VGNs take EPA and/or DHA supplements unless needed."

Controversy on low DHA EPA in vegan and vegetarians

- Saunders (2013) in a review with Brenda Davis, RD suggested "There is no convincing evidence that vegetarians or vegans experience adverse effects as a result of a low dietary intake of EPA and DHA."(Saunders, 2013).

- Barcelo-Coblijn (2009) suggested that "the brain has the capacity to nearly meet its daily needs for DHA through the conversion of plasma-derived ALA." (Barceló-Coblijn, 2009) . And theorize that at intakes of 1.2g/ALA per day, would produce 2.4–3.6 mg of DHA per day in the brain, along with other sources result in 5–8 mg of DHA per day produced by the brain and would exceed adult brain usage estimated at 4.6mg DHA per day.
- In relation to ALA, elderly scored better for cognitive fluid intelligence via performance tests and larger left frontoparietal cortices but not for EPA/DHA leading authors to conclude "dietary consumption of precursor n-3 PUFAs may support neuronal health through the unique neuroprotective benefits of ALA and its immediate downstream products". (Zamroziewicz, 2017)

- Sarter (2015) from a recent US vegan/omnivore study: "…at present, there is no direct evidence that raising the omega-3 (intakes) would confer additional health benefits over and above their already-protective vegan diet."(Sarter, 2015).

Controversy on low DHA EPA in vegan and vegetarians

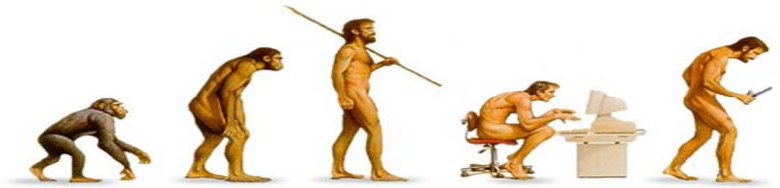
- **Vegans** might be at a distinct advantage (with possible exception to ↑ LA intakes). Less Omega long chain fatty acids may be needed than other diets as they do not consume preformed inflammatory Omega 6 AA found only in animal products which may affect cognitive function. AA and EPA compete for incorporation and so theoretically vegans should be able to convert EPA to DHA more efficiently due to less or no AA from the diet.
- Vegans also typically have lower intakes of saturated fat, cholesterol, and less hypertension, obesity and heart disease all associated with increased risk for cognitive disorders or AD. As well as more fruit and vegetable/antioxidant protection. Vegans have ↓ uric acid levels than omnivores/fish (↑ levels = ↑ AD/Parkinson's (Schmidt, 2013; Katsiki, 2013).
- Hussein states "The fact that DHA can be formed from ALA, albeit at a very low rate,but cannot be increased by increased dietary ALA suggests that DHA concentrations, at least in circulating phospholipid pools, are regulated to satisfy a relatively low metabolic demand that can be satisfied by the relatively low levels observed in vegans with no dietary DHA intake and with erythrocyte DHA levels lower than EPA." (Hussein, 2005)
- Conversely, the population that may benefit the most from ingesting EPA/DHA may be omnivores who also obtain significant inflammatory AA in their diets and long chain Omega 3 can compete with AA to produce less inflammatory molecules; as well as those following SAD diet high in processed food and oil and whom may have a very unbalanced Omega 3/6 ratio.

Controversy on low DHA EPA in vegan and vegetarians

- Further reading:
- Sanders TA. **Plant compared with marine n–3 fatty acid effects on cardiovascular risk factors and outcomes: what is the verdict?** Am J Clin Nutr 2014;100 (suppl):453S–8S.
- Harris WS. **Achieving optimal n-3 fatty acid status: the vegetarian's challenge... or not**. Am J Clin Nutr. 2014 Jul;100 Suppl 1:449S-52S. doi: 10.3945/ajcn.113.071324. Epub 2014 Jun 4.
- Saunders AV, Davis BC, Garg ML. **Omega-3 polyunsaturated fatty acids and vegetarian diets**. Med J Aust. 2013 Aug 19;199(4 Suppl):S22-6
- Gwendolyn Barceló-Coblijn, Eric J. Murphy . **Alpha-linolenic acid and its conversion to longer chain n3 fatty acids: Benefits for human health and a role in maintaining tissue n3 fatty acid levels**. Progress in Lipid Research 48 (2009) 355–374.
- Cunnane SC, et al. **Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: Can we reconcile the evidence?** Prostaglandins Leukot Essent Fatty Acids. 2013 Jan;88(1):61-70.
- Barceló-Coblijn G, Murphy EJ. **Alpha-linolenic acid and its conversion to longer chain n-3 fatty acids: benefits for human health and a role in maintaining tissue n-3 fatty acid levels**. Prog Lipid Res. 2009 Nov;48(6):355-74

Controversy on low DHA EPA in vegan and vegetarians – evolutionary perspective

- "Aquatic Theory": Were those living away from coastal areas developing abnormally with respect to brain size?
- Carlson (2007) Dept of Anthropology @ Emory-- "preformed DHA has only been identified to an appreciable extent within aquatic resources (marine and freshwater), leading to **speculation that hominin encephalization (amount of brain mass related to total body mass) is linked specifically to access and consumption of aquatic resources**. The key premise of this perspective is that biosynthesis of DHA from ALA is not only inefficient but also insufficient for the growth and maturation demands of an encephalized brain."(Carlson, 2007)
- "However, this assumption is not well-supported, and much evidence instead suggests that consumption of ALA, available in a wider variety of sources within a number of terrestrial ecosystems, is sufficient for normal brain development and maintenance in modern humans and presumably our ancestors." (Carlson, 2007)



Controversy on low DHA EPA in vegan and vegetarians – evolutionary perspective

- Langdon (2006) (Anthropology/Biology)- also reviewed whether an aquatic-based diet is necessary for brain evolution and functional development and remarked, “both the maternal and infant bodies have mechanisms to store and buffer the supply of DHA, so that functional deficits are generally resolved without compensatory diets” (Langdon, 2006) .
- “**There is no evidence that human diets based on terrestrial food chains with traditional nursing practices fail to provide adequate levels of DHA or other n-3 fatty acids**. Consequently, the hypothesis that DHA has been a limiting resource in human brain evolution must be considered to be unsupported.” (Langdon, 2006)
- Instead other factors may be responsible

for increased brain size (changes to the ecosystem, pressure from selection, language, socialization,the ability to make tools, artistic talents, domesticating fire,hunting in groups, eating meat/**carbs**, gene mutations) (Majou, 2018;Hardy, 2015)

- Barcelo-Coblijn, 2009 state: “In other words, can a terrestrial animal (humans) that is an omnivore truly require dietary DHA in order to have optimal physiological performance despite the true rarity of DHA in the world’s food web, but a web where ALA exists in abundance” These anthropologists say no.

Omega 3 and 6 considerations for plant based diets

- These considerations may be useful in discussing with your health care professional:
- There is increasing evidence to support that vegan and vegetarian omega 3 status does not pose a health risk either from lower intakes, slower conversion rates, or reasonable ratios of 6 to 3.
- Not unreasonable (prudent?) to ensure getting some omega 3 sources, i.e., walnuts, flax, others. Handful of walnuts will meet your ALA daily recommended requirements. ALA in beans, squash, leafy greens, seeds, and nuts.

  Will help improve higher omega 6 to 3 ratio seen in vegetarians/vegans if this is a concern and or if certain disease states/conditions that may require more omega 3 intake are present in individuals (ie. Diabetes)/Smoking and may help increase DHA by ↓ LA.
- Algae supplement for those who want to match DHA intakes recommended by some health professionals but is associated with atrial fibrillation (dementia), and 3 studies showed increases in LDL Cholesterol which could affect CHD Risk (Sanders, 2009), and one meta-analysis did and another found a trend for a slight increased risk for prostate cancer for EPA/DHA as did other studies when assessed via blood concentration levels of DPA/EPA/DHA (from fish/oil) (Crowe, 2014; Alexander, 2015; Brasky, 2013).

  And supplementation may increase bleeding times and suppress immune function as previously mentioned.

Omega 3 and 6 considerations for plant based diets

- Need for an "**oil change**"?
- Though oils like canola, walnut, flax, and hemp oil can be recommended sources of EFA, consider more whole food choices instead of refined oils, e.g., walnuts, ground flax, purslane, chia, hemp, seaweeds, etc., which contain other nutrients and health promoting properties as compared to just their refined oils. It takes a lot of whole foods to produce oils and nutrients and fiber are lost.
- Limit seed oils and tropical oils like palm and coconut (Sat. fat)
- Genetic predisposition for low conversion of ALA: considerer Stearidonic acid sources like hemp which bypass the enzyme and make EPA.
- Trans Fats – may limit EFA conversion levels – should become less prevalent in foods due to shifting policy (June 2014 FDA major action to limit, completely removed by 2020)
- Consider fortified products.
- If using margarine type oil spreads/mayo, consider brands like *Earth Balance Omega 3* (ALA, EPA, DHA) or *Butter 2.0 Melt* and Vegenaise mayo.

α-Linolenic acid - Omega 3 sources - more than just walnuts, flax and chia seeds

Source	Serving Size	kcal	ALA	LA	Ratio LA/ALA	% of Adequate Intake (AI) for ALA: 1.1 to 1.6 g,
Nuts and Seeds						
English walnuts	1 oz, 28.35g, 7 walnuts	185	2.57g	10.8g	4.2	160-233%
Black walnuts	1 oz, 28.35g, 7 walnuts	175	.76g	9.57g	12.6	48-69%
Chia seed ground (Spectrum)	1 tbsp, 6g	30	1.1g	.35g	.318	69-100%
Flax seed, (Now)	1 tbsp, 10.5g	50	2.0g	.6g	.30	125-181%
Hemp seed hulled	1 tbsp, 10g	55	.86	2.75	3.2	54-78%
Pecans	1 oz, 28.35g, 91/2 pecans	196	.28g	5.8g	20.7	18-25%
Butternuts	1 oz, 28.35g	174	2.47g	9.56g	3.87	154-224%
Pumpkin seeds roasted	1 oz, 28.35g	126	.02g	2.48g	124	1-1.8%
Sesame seeds	1 tbsp, 9g	52	.03g	1.92g	64	2-3%

α-Linolenic acid - Omega 3 – Sources

Source	Serving Size	kcal	ALA	LA	Ratio LA/ALA	% of Adequate Intake (AI) for ALA: 1.1 to 1.6 g,
Oils						
Sacha Inchi oil	1 tbsp	130	6.5	4.4	.67	406-590%
Walnut oil	1 tbsp, 13.6g	120	1.41g	7.19g	5.1	88-128%
Flax oil (linseed)	1 tbsp, 13.6g	120	7.26g	1.95g	.27	453-660%
Hemp oil[1]	1 tbsp, 13.6g		3g	7.6g	2.5	187-272%
Canola oil	1 tbsp, 14g	124	1.28g	2.61g	2	80-116%
Perilla oil[2]	1 tbsp, 13.6g	122	6.92g	1.91g	.28	432-629%
Soybean oil	1 tbsp, 13.6g	120	.92g	6.9g	7.5	58-84%
Mustard oil	1 tbsp, 14g	124	.83g	1.63g	1.96	52-75%
Earth Balance® Buttery Spread[3]	1 tbsp, 11g	100	.44g	1.86g	4.2	28-40%
Vegenaise – original[4]	1 tbsp, 14g	90	.85g	1.74g	2.04	53-77%

α-Linolenic acid - Omega 3 – Sources

Source	Serving Size	kcal	ALA	LA	Ratio LA/ALA	% of Adequate Intake (AI) for ALA: 1.1 to 1.6 g,
Other						
Raspberries	1 cup, 123g	64	.155g	.306g	1.97	10-14%
Strawberries	1 cup, 166g sliced	53	.108	.149	1.37	7-10%
Green peas	1 cup, 145g	117	.05g	.22g	4.4	3-5%
Kiwi	1 whole 69g	42	.03g	.17g	5.7	2-3%
Tofu	1/2c, 126g	88	.23	2g	8.7	14-21%
Soybeans, roasted	.5 cup, 46.5g	210	.67g	5g	7.46	42-61%
Mungo beans (black lentil)	.5 cup, 103.5g	353	1.03g	.075g	.07	64-94%
Navy beans	½ cup, 104g	350	.56	.35	.63	37-54%
Kidney beans	½ cup, 92g	310	.33g	.21g	.64	20-30%
Lima beans, Lg	½ cup, 89g	301	.085g	.191g	2.2	5-8%

α-Linolenic acid - Omega 3 – Sources

Source	Serving Size	kcal	ALA	LA	Ratio LA/ALA	% of Adequate Intake (AI) for ALA: 1.1 to 1.6 g,
Acorn Winter Squash	1 cup, 140g	56	.036	.022	.61	2-3%
Oats	1/3 cup, 51g	200	.057g	1.25g	22	4-5%
Quinoa	1 cup, cooked	222	.157	1.8	11	10-14%
Purslane[4]	2 cups, 86g	18	.34g	.076g	.22	21-31%
Spinach	2 cups, 60g	14	.08g	.016g	.2	5-7%
Kale	2 cups chopped 32g	16	.058g	.044g	.76	4-5%
Spirulina	2 tbsp, 14g	41	.12	.18	1.5	8-11%

All foods uncooked. Nmbers derived from USDA National Nutrient Database Release 27 unless otherwise noted. [1]Rodriguez-Leyva, 2010; [2]http://item.rakuten.co.jp/magimaguu/004-21 and Asif, 2011 Company correspondance[3], [4]Uddin, 2014,

Long Chain Essential Fatty Acids (**EPA/DHA**) – Sources

Source	Amount	ALA	LA	EPA	DHA
Purslane[4]	2 cups, 86g	.34g	.076g	.86mg	trace
Wakame[5]	½ cup, dried			15mg	
Nori[5]	2 sheets, roasted			21.6mg	
Algae supplements-various[6]	Per soft-jel			72-130mg	120-350mg
Enriched Omega 3 egg[7]	1 Large, 50g	.47g	2.77g	<0.02g	.24g

[5]Sanchez-Machado, 2004, [6]Brands: Ovega, Deva, Amala, Life's DHA, Be Whole, [7]West, 2014

α-Linolenic acid – Sample meal without walnuts, chia, flax or algae, or significant oil or fortified foods

- **Breakfast**

  Oatmeal – 1 ½ cups cooked .063g
  ½ cup red raspberries .0775g
  1 slice wheat bread .045g
  margarine – none
  1 cup soymilk .19g

- **Lunch**

  Salad –
  Spinach 2 cups raw .082g
  Broccoli 1 cup raw .057g
  Cauliflower ½ cup cooked .104g
  Tomato 1 cup chopped .005g
  ½ cup pumpkin seeds .033g
  Avocado pureed ½ c .128g
  Italian salad dressing 1 Tbsp .211g
  Vegetarian baked beans 1 cup .13g

- **Dinner**

  1 cup cooked Kale .438g
  1 cup cooked kidney beans .375g
  1 cup cooked brown rice .022g
  1 1/2 cup cooked yam .018
  1 oz pretzels .08g
  1 cup blueberries .086g

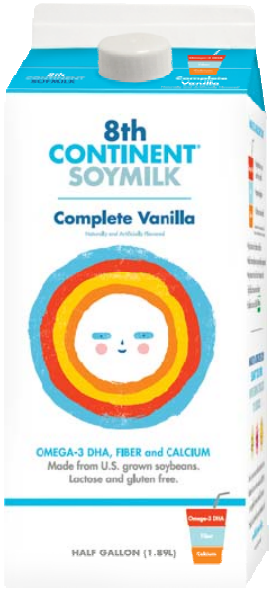
- **Adequate Intakes**

  Males 1.6g/day
  Females 1.1g/day

- **Total for sample meal** 2.15g

Short Chain and Long Chain Essential Fatty Acids – Sources- Omega 3 - Fortified

- Fortified products on market (Functional Foods).
- Many on market responding to omega 3 interest and research. Soymilks, energy bars, margarines, yogurts, oils.



Short Chain and Long Chain Essential Fatty Acids – Sources- Omega 3

- Some misinformation on sources. Avocadoes are touted as a excellent sources of Omega 3 fatty acids. However, a standard size portion of 50g (1/3 of a medium avocado) offers about 3 ½ % of needs, and conversely a significant source of Omega 6 fatty acids (about 15 times more).

Testing? Necessary?

- How will I know if I am deficient or low in intake? Essential fatty acid deficiency for either omega 3 or 6 is rare and most health practitioners do not test for it, and has been observed in very few clinical situations. LA deficiency is characterized by scaly dermatitis, increased susceptibility to infection, and poor growth (Sanders, 1999) infertility, growth retardation (Lauritzen, 2001), and ALA deficiency possibly may cause neuropathy, blurred vision, fatigue, depression, Schizophrenia, allergies, rheumatoid arthritis and inflammatory and cardiovascular conditions (Holman, 1982; Nicolle, 2010) . Essential fatty acid deficiency can result in Hepatic steatosis (fatty liver), abnormal liver function, ↑ Mead acid, hematologic disturbances (Jeppesen, 1998;Gramlich, 2015)
- Serum or plasma phospholipids/ Longer term status can be tested via red blood cell RBC and researchers often use the Omega 3 index using RBC's which OmegaQuant sells and provides some observational studies to suggest many are deficient in EPA/DHA.
- Note that what is most important is what tissue levels are, and blood may not reflect or even be misinterpreted as being deficient in EPA/DHA, so testing in my opinion is not useful unless there is a genetic disposition for fatty acid synthesis. A study in infants suggested DHA status in red blood cells only explained about ¼ of the variance in overall brain growth (Lauritzen, 2001).

Slide Future directions

- More research needed on omega-6/3 ratio and effect on specific diseases both looking at risk or benefit.
- More research using the gold standard (adipose) for dietary marker of fatty acids rather blood/serum
- More research specifically in vegetarians/vegans who follow appropriately planned whole foods based minimally processed diets, to consider if the health benefits from this diet (already known to be anti-inflammatory) could be expanded further when modifying omega-6 and omega-3 intakes.
- A trial or prospective study comparing an appropriately planned whole foods based minimally processed vegan diet to a fish based diet on several disease outcomes. (many studies compare meat based diets to those consuming higher intakes of fish – inflating fish benefits). Many studies in vegetarians/vegans don't control for healthfulness of these diets (some may be junk food veggies)
- More research to evaluate the general idea that omega 6 are inflammatory and contribute to disease. Also Arachidonic Acid status and worse brain health.
- More research needed during the period of brain growth and maturation (last trimester until adult age), and particularly after 2 years of age, to evaluate levels of DHA and assess health status and long term health status. (very few studies in this area)
- More research needed to determine what impacts additional DHA intakes may have on cognition and dementia and long term brain health.
- gut microbiota (bifidobacteria) and influence on fatty acid composition (DHA) in liver and tissues, brain (human studies needed). Gut dysbiosis > Insulin Res > inflammation >AD

Summary

- While the science sorts out whether these intakes pose any risk in vegetarians and vegans, we already know the data from large published studies suggest both groups share protection from:

  CVD (~ 1/3 less in some but not all studies (note influence of processed unhealthy foods that can be part of plant-based diet), some cancers, less cardio-metabolic risk factors and disease states (diabetes, stroke hypertension, kidney disease). Vegan oil free diet can halt and reverse heart disease (Esselstyn, 2014).

  A few studies suggest better mood, less anxiety/depression. Whether even greater benefits could be seen with increased omega 3 intakes remains unproven.

- The proper whole foods plant-based diet is critical

  Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults

- less-healthy plant foods (juices/sweetened beverages, refined grains, potatoes/fries, sweets) and animal foods: ↑ CHD Risk

- healthful plant-based foods (whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee): ↓ CHD Risk

Satija A, et al. Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. J Am Coll Cardiol. 2017 Jul 25;70(4):411-422. [Nurses Hlth Study, Hlth Prof Follow up Study]

Summary

- Vegetarians and vegans typically have lower levels of intake of EPA and DHA and typically higher intakes of omega 6 Linoleic acid compared to omnivores but available scientific data suggests this not to be a risk. Omega 6 LA does not convert appreciably to the pro inflammatory AA as once believed, and intermediates like DHGLA are actually anti-inflammatory.
- It is still unknown how to correctly interpret the limited conversion rates of omega 3 (ALA → EPA/DHA). Both omega 3 and omega 6 pathways show conversion rates that are a fraction of intake and there may be valid biological reasons for this and furthermore would suggest evolution has not erred or flawed in how these essential fatty acids are converted to longer chain products.
- New evidence has called into question the importance of the omega 6 to 3 ratio, including the view that omega 6 fatty acids (Linoleic acid) are unhealthful in high amounts, but ↓ LA can ↑ EPA (DHA?) in some studies. Could large intake of ALA offset Omega 6 conversion?
- Increasing EPA (Omega 3) may be more important of a consideration for Omnivores (than for vegans) as they consume Arachidonic Acid (Omega 6 – meat/dairy) and both compete, (EPA*AA) while Vegans consume no AA and convert very little LA to AA may therefore have less of a need to supplement. Omnivores: more obese, processed food, meat made from Omega 6 grains, high oil, less exercise?, more disease states like diabetes? SAD Diet so poor and inflammatory that DHA may have more benefit than non-inflammatory WFPBD.

Summary

- We have seen a rush to promote fish oil supplements which now have been called into question. Fish intake and supplements are not fully supported for CVD with few exceptions and no consistent benefit for brain (except for 1 study), eye function; some add risk. This should give us some pause as we continue to assess the true required level and importance of Long Chain omega 3 FA like EPA and DHA for health maintenance and optimal health for vegans and vegetarians.
- And…. whether or not omega 3 FA from supplements are required or recommended. While it should cause no harm to increase plant sources of Omega 3, research is still unclear for deriving additional health benefits or if humans are required to consume seafood or algae or marine mammals like seal/whale high in EPA/DHA.
- What may be equally or more important is minimizing known hazards liked processed foods, high fat meals, high glucose meals, certain fats like saturated fats and trans fats, as well as conditions like diabetes, metabolic syndrome, hypertension being overweight, all that impede the Omega 3 pathways.
- We live in a culture with some of the most inexpensive, highly accessible unhealthy processed food environments (a lot of which can be classified as vegan) and most of our energy should be on ensuring we follow as closely as possible a WFPBD.
- More prospective studies of vegans/vegetarians looking at EPA/DHA and followed to assess specific disease outcomes will help determine whether current levels need to be increased or are adequate.

Essential Fatty Acids: Recommendations for Plant Based Diets – Do vegans and vegetarians require a DHA supplement?

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