

Omega-3 Fatty Acids

Nutrition Masters Course

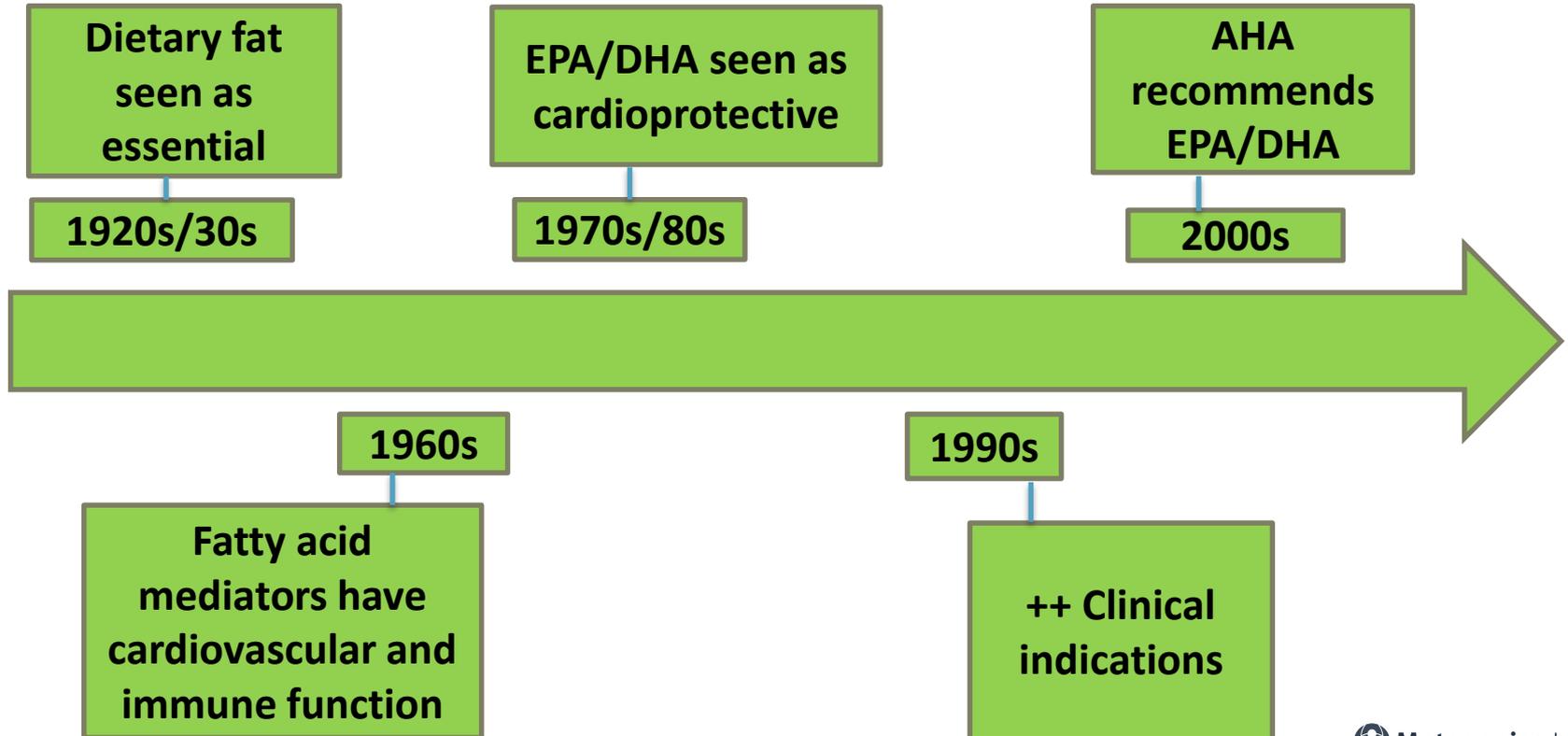
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Learning Objectives

- What are polyunsaturated fatty acids?
- Difference between omega-3 and omega-6 fatty acids
- Why are omega-3 fatty acids important?
- Disease prevention and treatment with omega-3 fatty acids
- Quality and safety of fish oils

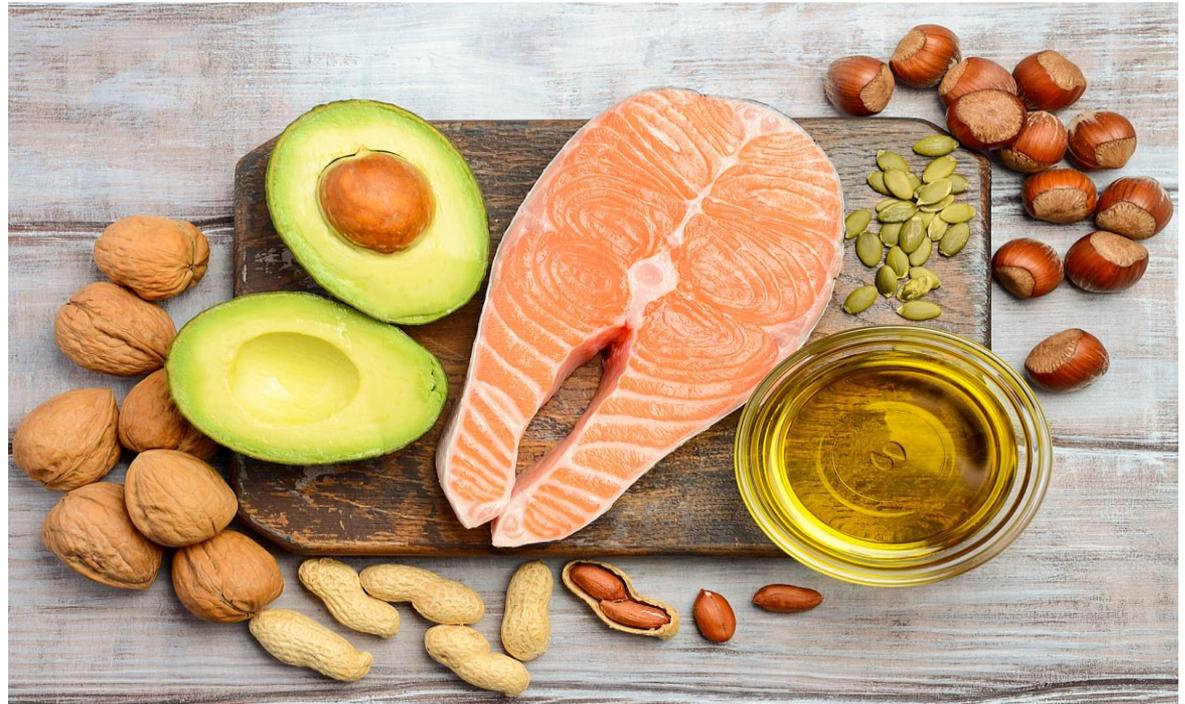
Essential Fatty Acids Timeline



Omega-3 Fatty Acids: Sources

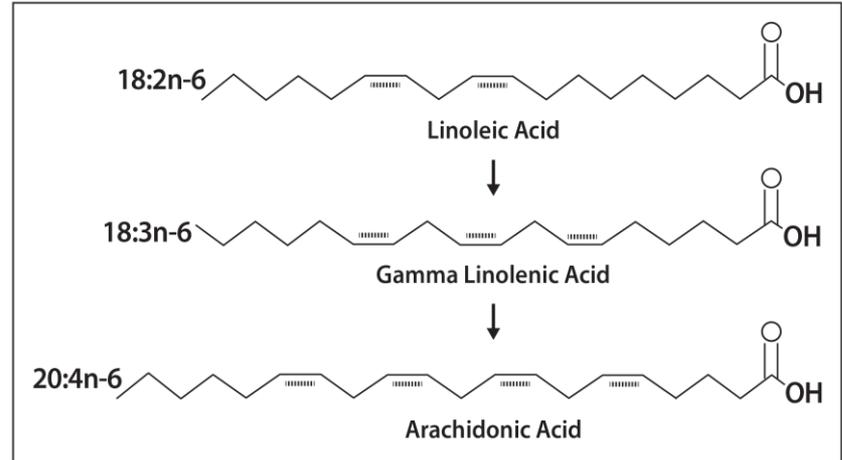
- ALA
 - Flaxseed oil
 - Algal oil
 - Canola oil
 - Soybean oil
 - Hemp oil
- EPA
 - Salmon, tuna, trout (oily fish)
 - Algal oil
 - Krill oil
- DHA
 - Salmon, tuna, trout (oily fish)
 - Algal oil
 - Krill oil

Fatty acids are found in the diet in triglyceride form



Omega-6 Fatty Acids

- Three important omega-6s:
 - Linoleic acid (LA)
 - Gamma-linolenic acid (GLA)
 - Arachidonic acid (AA)
- LA is an essential fatty acid. Essential nutrients that cannot be synthesized in the body must be obtained from the diet.



Omega-6 Fatty Acids: Dietary Sources

- Linoleic acid
 - Safflower oil
 - Sunflower oil
 - Corn oil
 - Soybean oil
- Gamma-linolenic acid
 - Evening primrose oil
 - Black current oil
 - Borage oil
- Arachidonic acid
 - Meat
 - Eggs
 - Dairy products

Fatty acids are found in the diet in triglyceride form



Why Are EPA and DHA Considered Conditionally Essential?

- Essential nutrients cannot be made in the body
- Technically, EPA and DHA can be made in the body, using the essential fatty acid ALA as a precursor
- This conversion of ALA to EPA and DHA is affected by:
 - Gender
 - Genetics
 - Age
- Conversion is low—only ~5-10% of ALA are converted to EPA and DHA. Therefore EPA and DHA are considered **conditionally essential**

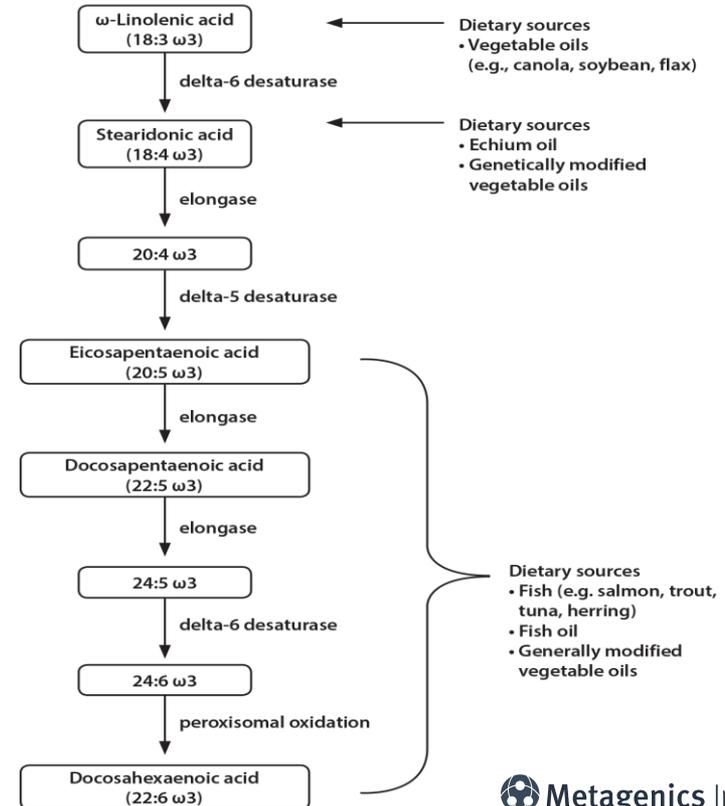


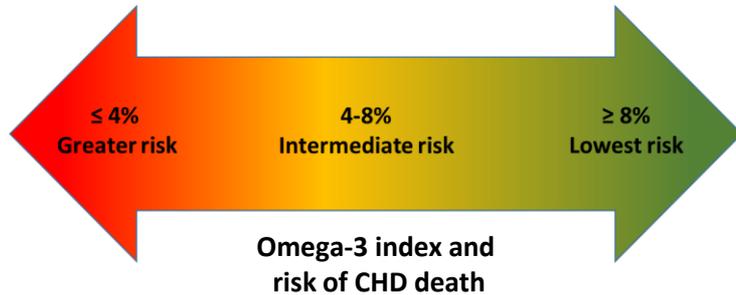
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Omega-3 Fatty Acids: Deficiency

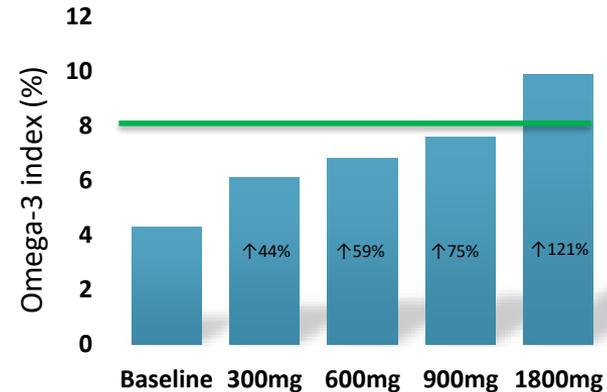
- True omega-3 fatty acid deficiency is rare but can occur in patients with:
 - Chronic fat malabsorption
 - Cystic fibrosis
 - TPN infusion containing fat-free, glucose-amino acid mixtures
- Deficiency can result from:
 - Low dietary intake
 - Severe malabsorption
 - Increased physical requirements such as growth
- Clinical signs:
 - Dry scaly rash
 - Decreased growth in infants and children
 - Increased susceptibility to infection
 - Poor wound healing
 - Renal toxicity
- Plasma eicosatrienoic acid (mead acid):arachidonic acid ratio > 0.2 -indicative of EFA deficiency

Measuring EPA and DHA Status Using the Omega-3 Index

Defined as the amount of EPA+DPA in red blood cell (RBC) membranes; expressed as the % of total RBC membrane fatty acids¹



EPA+DHA dose dependently increases omega-3 index in healthy adults (n=115)²



Following supplementation for 5 months with EPA+DHA (300-1800mg/day), see ↑ increase in omega-3 index from baseline

1. Image adapted from: Harris WS. *Am J Clin Nutr.* 2008;87(6):1997S-2002S.

2. Image adapted from: Flock MR et al. *J Am Heart Assoc.* 2013;2(6):e000513.

Omega-3 Index: World Map

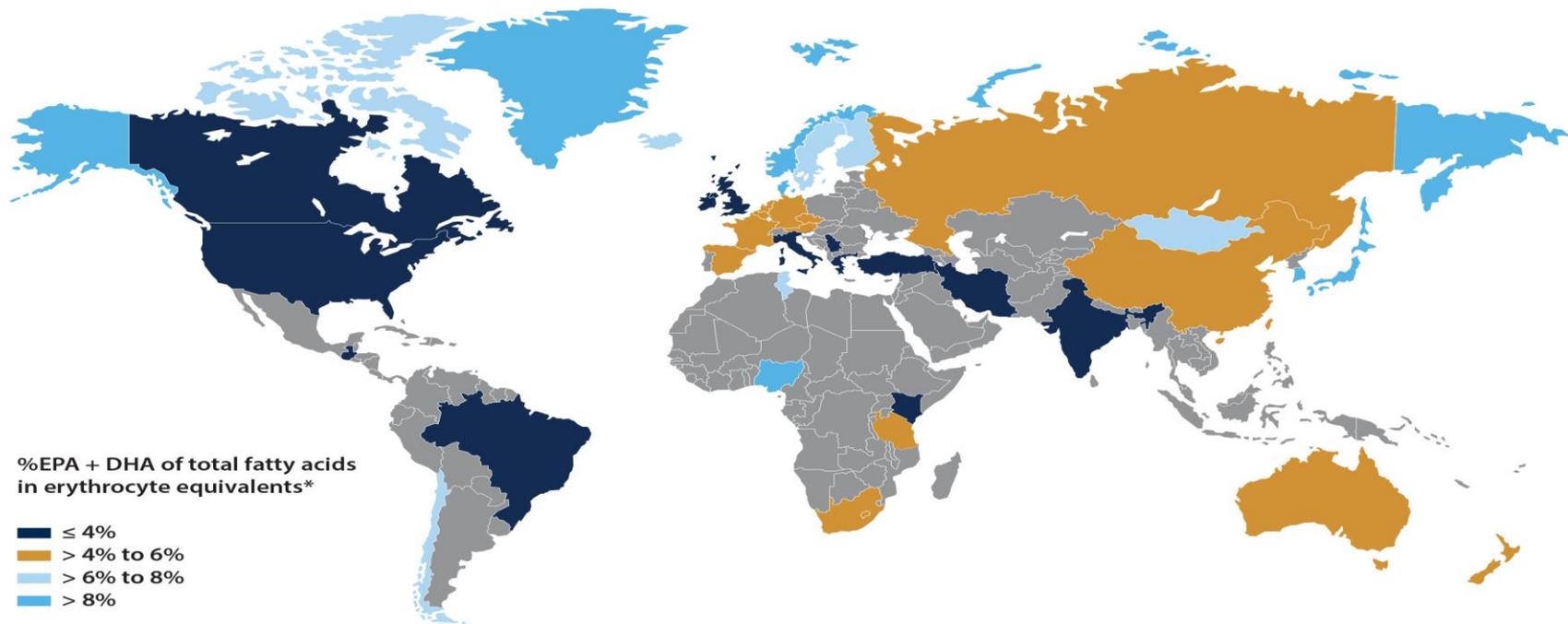


Image adapted from: Stark KD et al. *Progress in Lipid Research*. 2016;63:132-152.

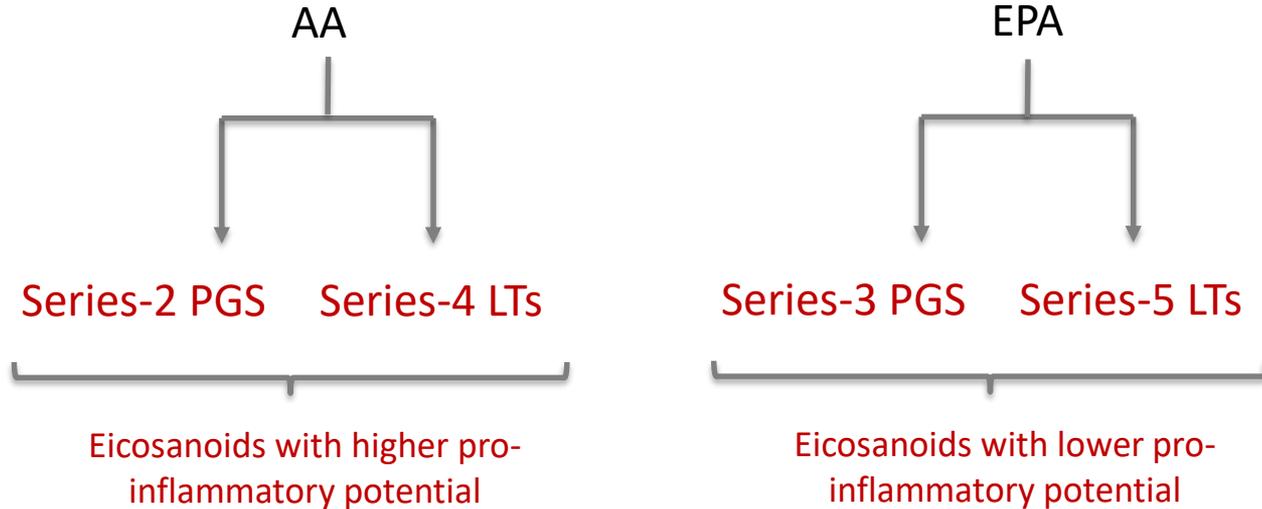
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Omega-3 and 6 Fatty Acids: Dietary Status/Nutrient Gap

- ALA is very sensitive to destruction by light, oxygen, and heat
- >95% of the population consumes less omega-3s than the recommended amount
 - Median daily intake of EPA+DHA is 110mg/day
 - Only 6.2% of US adults report taking fish oil supplements
- Paleolithic nutrition studies indicate a lower saturated and Trans fat diet, along with equal ratio of omega-6:omega-3 fatty acids (1-2:1)
- Current intake of omega-6:omega-3 fatty acids ratio is (20:1); emerging data indicates a ratio as low as 2:1 may be optimal

1. Kaur N et al. *J Food Sci Technol.* 2014;51(10):2289-2303.
2. Yashodhara BM et al. *Postgrad Med J.* 2009;85:84-90.
3. Strijbosch R et al. *Metabolism.* 2008;57(5):698-707.
4. Richter CK et al. *Lipids.* 2017;52(11):917-927.

Omega-6 and Omega-3: Balance between AA and EPA



Prostaglandins (PGs) and leukotrienes (LTs) promote inflammation initiation

AA: arachidonic acid (omega-6)

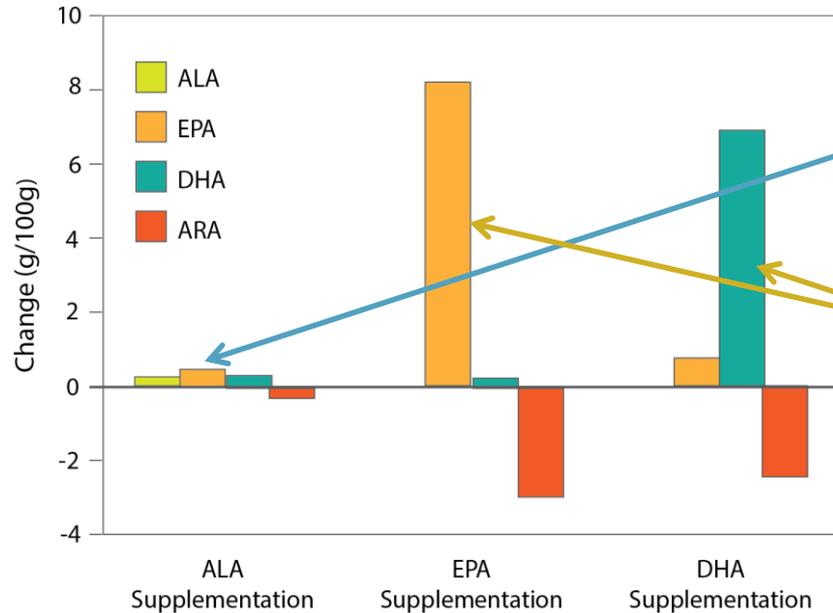
EPA: eicosapentaenoic acid (omega-3)

Omega-3 Fatty Acid: Recommended Intake

- Adequate intake (AI) for omega-3 fatty acids (ALA) established by the Institute of Medicine (IOM) is 1.6g/day for adult males and 1.1-1.4g/day for adult females; omega-6 is 14-17g/day for adult males and 11-13g/day for adult females
- 2015-2020 Dietary Guidelines for Americans recommend eating ≥ 8 oz/week of seafood
 - Provides ~250mg/day combination of EPA+DHA
- Benefits of fish intake and cardiovascular disease
 - ~250mg/day EPA/DHA was associated with a reduced risk of coronary death by 36%
 - 17% decrease in total mortality in the general population
 - Sufficient amount for primary prevention

1. Food and Nutrition Board, Institute of Medicine. Dietary fats: total fats and fatty acids. Washington, D.C.: National Academies Press; 2002:422-541.
2. [Dietary guidelines for Americans. https://health.gov/dietaryguidelines/2015/guidelines/chapter-1/a-closer-look-inside-healthy-eating-patterns/#callout-seafood](https://health.gov/dietaryguidelines/2015/guidelines/chapter-1/a-closer-look-inside-healthy-eating-patterns/#callout-seafood). Accessed March 29, 2018.
3. Mozaffarian D et al. *JAMA*. 2006;296:1885-1899.

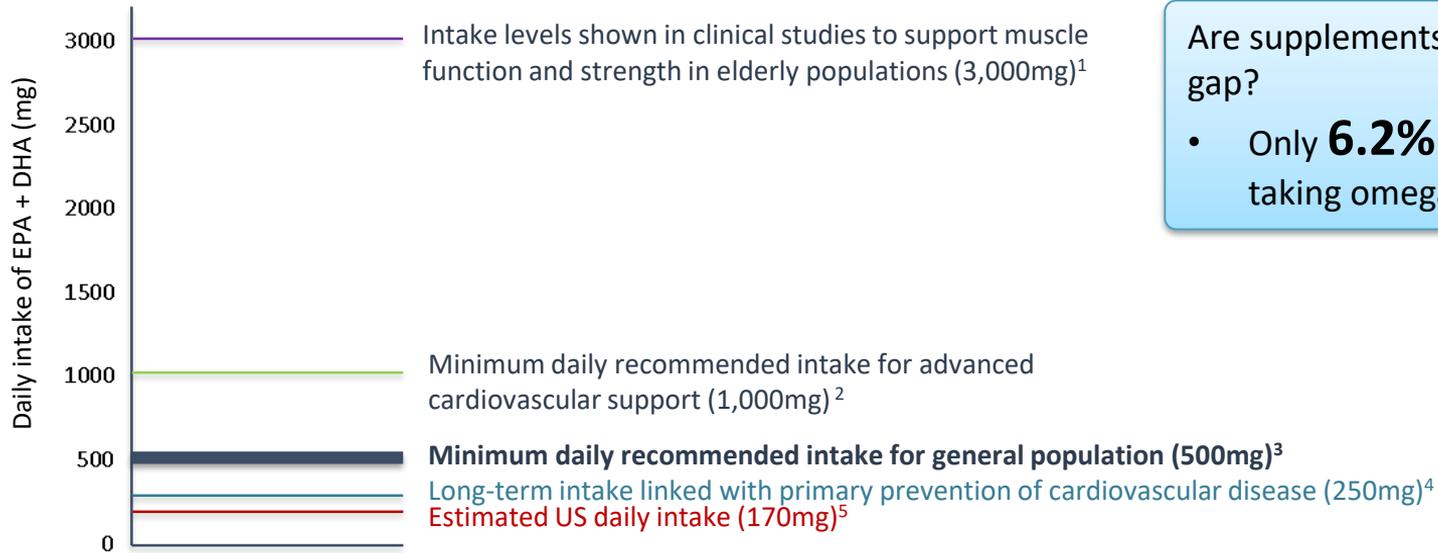
Way to Improve EPA and DHA Status



Giving ALA leads to very modest increase in EPA and DHA

Giving EPA or DHA directly is much more effective at increasing their concentration in plasma and decreasing AA, an omega-6 fatty acid

EPA-DHA Nutrient Gap: Recommended vs. Reality

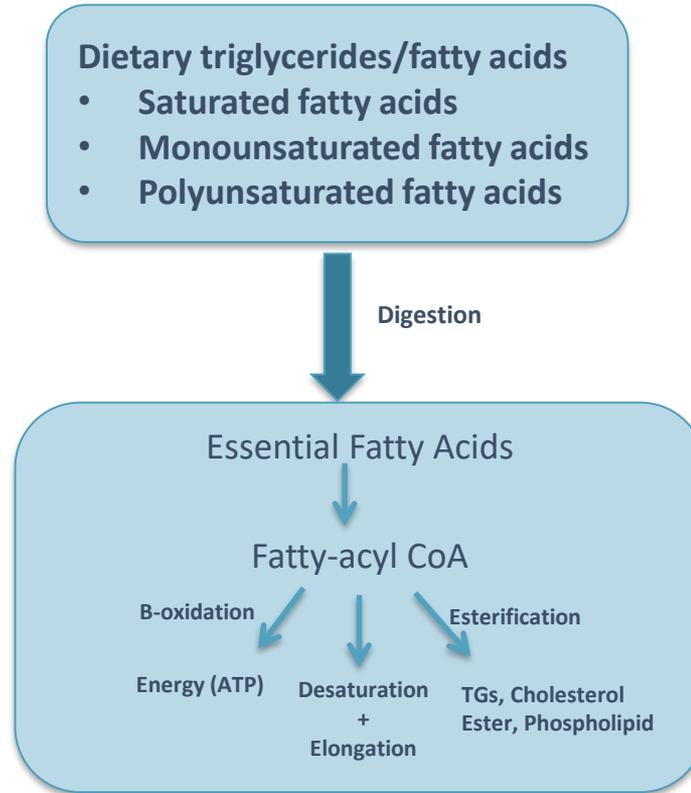


Are supplements closing this nutrient gap?

- Only **6.2%** of US adults report taking omega-3 supplements⁵

- 1) Smith GI et al. *Am J Clin Nutr.* 2015;102(1):115-122.
- 2) Siscovick DS et al. *Circulation.* 2017;135(15):e867-e884.
- 3) Vannice G et al. *J Acad Nutr Diet.* 2014;114(1):136-153.
- 4) Mozaffarian D et al. *JAMA.* 2006;296:1885-1899.
- 5) Richter CK et al. *Lipids.* 2017;52(11):917-927.

Metabolism of Essential Fatty Acids



Omega-3 Fatty Acid: Biological Activities

- Cell membrane structure and function
- Vision
- Nervous system
- Synthesis of lipid mediators
- Regulation of gene expression

Omega-3 Fatty Acid: Membrane Structure and Function

- Omega-3 and 6 fatty acids are important structural components of cell membranes
- Affect cell membrane properties
 - Fluidity
 - Flexibility
 - Permeability
 - Activity of membrane-bound enzymes
- Cell membranes accumulate more omega-3s than what is consumed in the diet

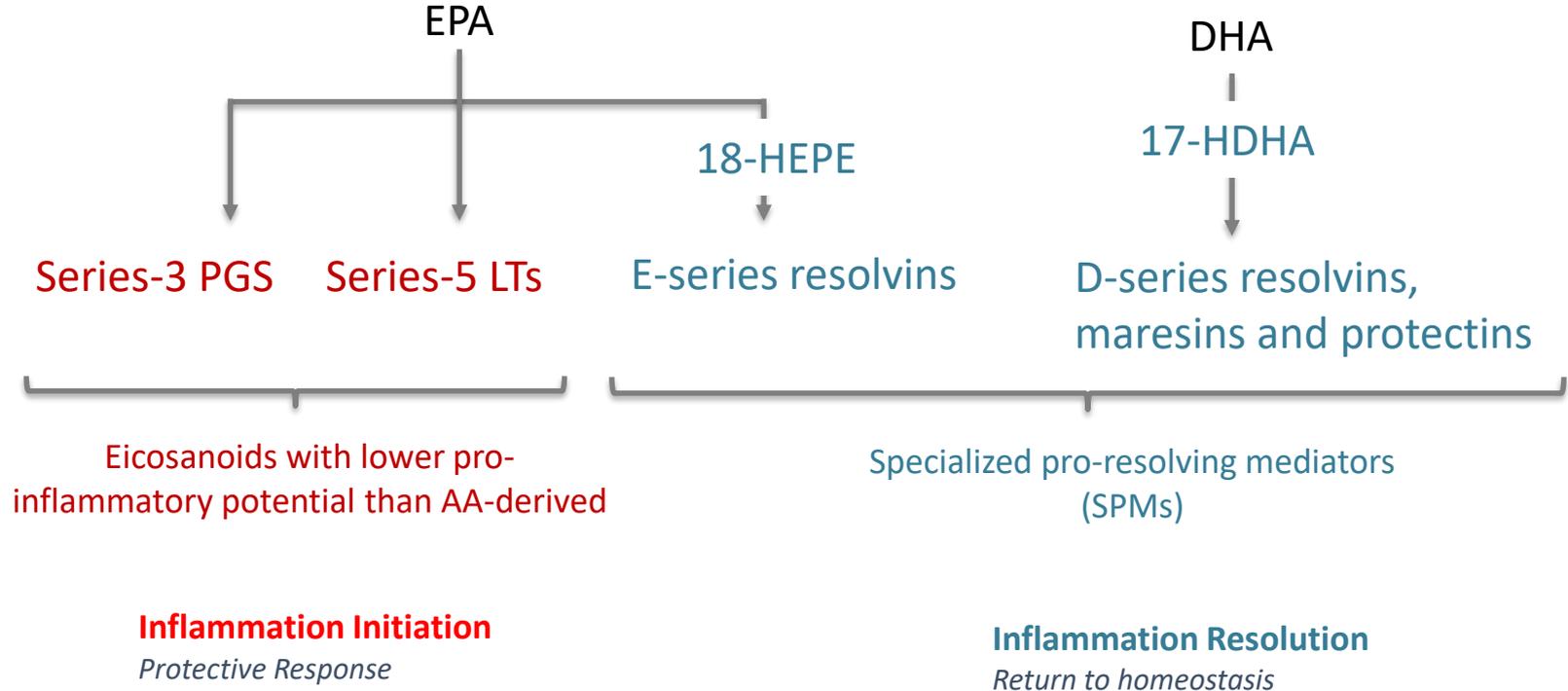
Omega-3 Fatty Acid: Vision

- DHA found at high concentrations in the eye
- Recognized as a physiologically essential nutrient for the brain and retina
- High levels of DHA deposited during the last trimester of pregnancy and the first 2 months of infancy
- DHA is needed for the optimal functioning and regeneration of rhodopsin
- Animal studies have found deficits in the retinal structure and visual activity development with omega-3 deficiency

Omega-3 Fatty Acid: Nervous System

- The gray matter of the brain has been found to have high concentrations of DHA and AA
- Suboptimal levels of DHA in the brain due to insufficient omega-3 intakes have been found to result in impaired learning ability

Omega-3 Fatty Acids: Pathways of Lipid Mediator Biosynthesis



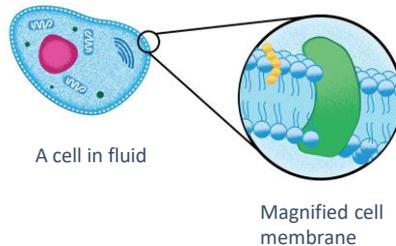
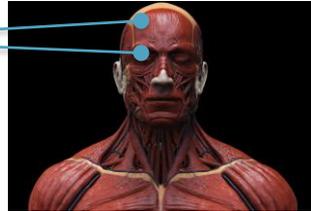
Omega-3 Fatty Acid: Regulation of Gene Expression

- Several *in-vitro* and *in-vivo* studies indicate that omega-3 and 6 fatty acids modulate the expression of number of genes involved in:
 - Fatty acid metabolism
 - Inflammation
- Omega-3s regulate transcription factors inside the nucleus of a cell
 - Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)
 - Sterol regulatory element binding protein 1 (SREBP-1)
- Omega-3s suppress NF-kB, thus inhibiting production of inflammatory cytokines
- Omega-3s suppress SREBP-1, thus decreasing the expression of enzymes involved in lipid synthesis

Omega-3 Fatty Acid: Mechanisms of Action

Structural and cell membrane function

- For example, brain gray matter is enriched with DHA and suboptimal levels linked with impaired learning ability
- DHA also enriched in the eye and required for optimal functioning and regeneration of rhodopsin
- Omega-3 and 6 fatty acids are important structural components of cell membranes
- Affect cell membrane properties
 - Fluidity
 - Flexibility
 - Permeability
 - Activity of membrane-bound enzymes



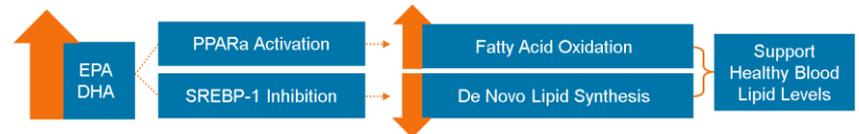
Lipid mediators in inflammation initiation and resolution

EPA
 ↓
 Less potent pro-inflammatory eicosanoids
 e.g. 3-series PGs

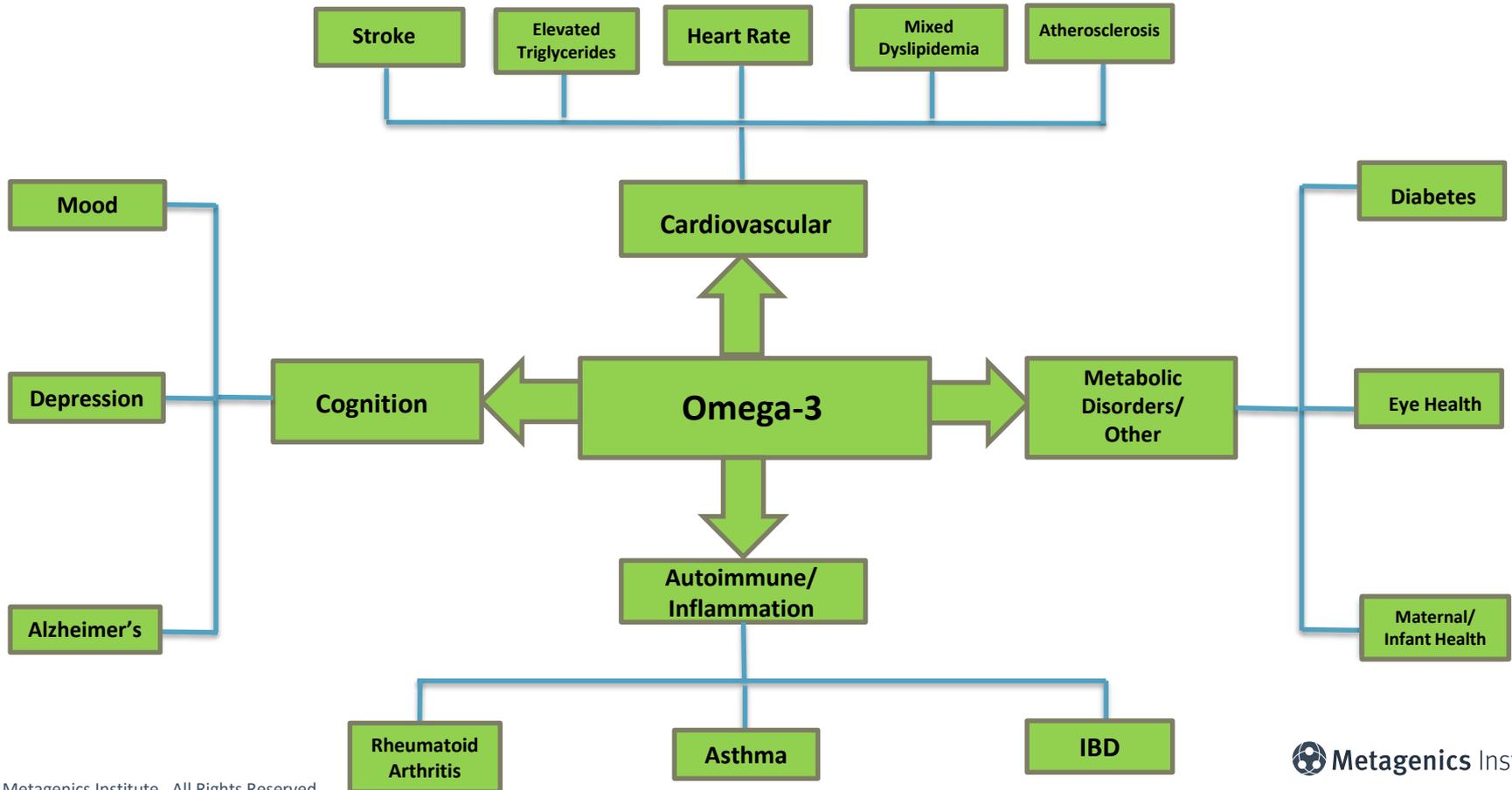
Specialized Pro-resolving Mediators biosynthesis

EPA	DHA
↓	↓
18-HEPE	17-HDHA
↓	↓
E-series Resolvins	D-series Resolvins

Cell signaling pathways



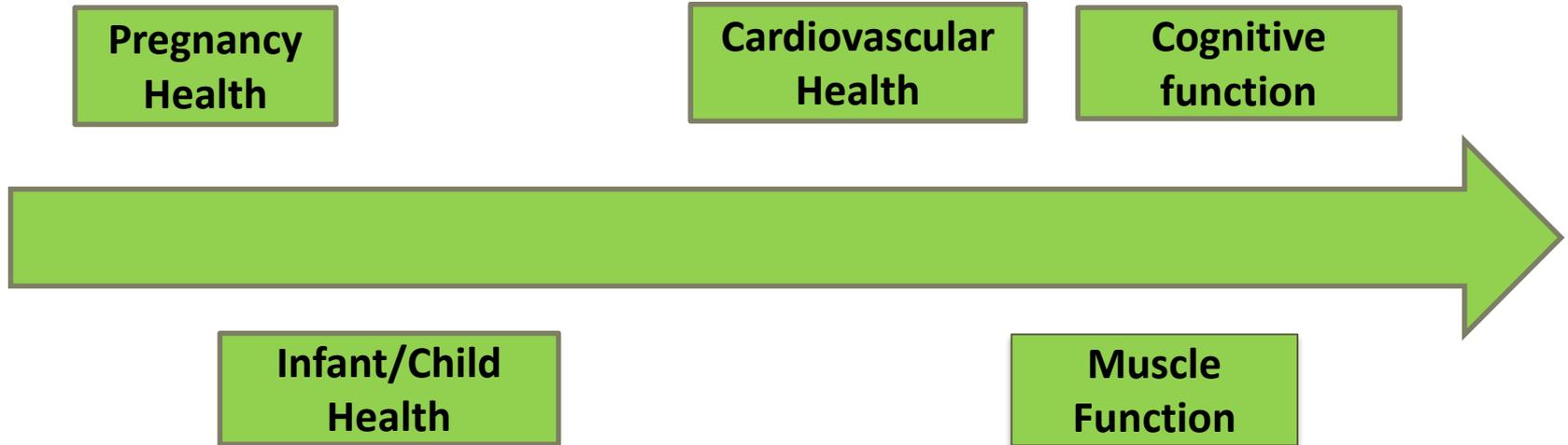
Omega-3 Fatty Acids: Conditions with Ongoing Research



Omega-3 Fatty Acids: Disease Prevention/Treatment

- Pregnancy health
- Infant health
 - Visual development
 - Neurological development
- Children's health
- Reducing asthma risk in children
- Primary prevention of cardiovascular disease
- Maintenance of cognitive function
- Muscle function in aging
- Coronary heart disease
- Plasma triglycerides
- Heart rate
- Rheumatoid arthritis
- Cognitive decline
- Alzheimer's disease
- Depression

Omega-3 Fatty Acids: Benefits Across the Lifespan



Omega-3 Fatty Acid: Pregnancy Health



- Numerous benefits associated with omega-3 consumption during pregnancy
 - Fetal/neonatal development
 - Preterm birth
 - Depression during pregnancy
- The Food and Drug Administration (FDA) and the American College of Obstetricians and Gynecologists (ACOG) recommend limiting seafood consumption to 12 oz/week to limit fetal exposure to neurotoxins (mercury)
 - Provides ~200mg DHA/day
- Institute of Medicine (IOM) recommendations: 650mg/day EPA+DHA; at least 300mg/day from DHA

1. Coletta JM et al. *Rev Obstet Gynecol*. 2010;3(4):163-171.
2. Nordgren TM et al. *Nutrients*. 2017;197(9):doi:10.3390/nu9030197.
3. Greenberg JA et al. *Med Reviews*. 2008;1(4):162-169.

Pregnancy-Research Summary

- Overall, results from several RCTs in pregnant women supplemented with omega-3s demonstrate no decrease in the incidence of GDM, PIH, or preeclampsia
- Noted that omega-3s increased gestation length
 - A meta-analysis of 6 RCTs in women (n=1278) with low-risk pregnancies supplemented with omega-3s resulted in an increase length of pregnancy by 1.6 days

Pregnancy—Key Takeaways

- Increased omega-3 intake should start at the onset of pregnancy and may also benefit those who are considering becoming pregnant
- With mercury toxicity concerns; limit fish/seafood intake to two 6-ounce servings per week
- Increased needs for omega-3s can be met through diet and supplementation
- Current data suggest supplementation with omega-3s during pregnancy can result in longer gestation, but no other effects on pregnancy outcomes such as protection against GDM, PIH, or pre-eclampsia were noted

Omega-3 Fatty Acid: Infant Health



- Last trimester of pregnancy critical for DHA accumulation in the brain and retina
 - Preterm infants are vulnerable to adverse effects of insufficient DHA on eye and brain health
 - Adequate DHA cannot be synthesized from ALA, may lead to decline in plasma and cellular DHA levels
- Human milk contains DHA+ALA and EPA
- IOM recommendations: 0.5g/day from birth-12 months

Infant Health—Research Summary

- A meta-analysis of 12 RCTs (n=1802 infants) testing formula supplemented with omega-3s at one month of age vs. no supplementation found no effect of omega-3 supplementation on infant cognition measured at one year of age
 - No significant effect of preterm vs. term infant status on omega-3 supplementation on cognition
 - The possibility of omega-3 supplementation on later cognitive development and specific aspects such as attention, mood, and information processing still remains
- Another meta-analysis of 16 RCTs (n=1949 infants) testing formula supplemented with omega-3s at one month of age vs. no supplementation found a beneficial effect on the visual acuity of the infant assessed at different stages of development (2, 4, 12 months)

1. Qawasmi A et al. *Pediatrics*. 2012;129(6):1141-1149.
2. Qawasmi A et al. *Pediatrics*. 2013;131(1):e262-272.

Infant Health—Key Takeaways

- EPA/DHA are an integral structural component of the cell membranes of the retina and central nervous system
- Infant formula is the predominant source of energy and nutrition requirements for many infants for the first 12 months of life
- Infants with diets deficient in PUFAs have been shown to have low levels of DHA and AA in plasma and RBC membranes
- Current data suggest supplementation with omega-3s of infant formulas may improve the visual acuity of infants for up to 12 months

Omega 3-Fatty Acids: Children's Health

- DHA regarded as a fundamental nutrient for children's growth and development
- DHA plays a key role in the formation and function of the CNS and retina
- RCT involving 183 children 7-9 years old were provided 892mg DHA/week for 6 months to assess omega-3 effect on cognition
 - After 6 months, omega-3 supplemented children performed better on the Hopkins Verbal Learning Test battery (HVLT), a reading test, and a spelling test
- Other observational and RCTs have also noted improvements in learning and behavior with children supplemented with DHA



Omega-3 Fatty Acids: Asthma



Asthma fact sheet

- Asthma is a serious disease causing wheezing, difficulty breathing, and coughing
- Over a lifetime, asthma can cause permanent lung damage
- Approximately 6 million children in the US ages 0-17 years have asthma—1 in 12
- Over half of all children with asthma had 1 or more attacks in 2016
- Every year, 1 in 6 children with asthma visit the Emergency Department with about 1 in 20 children with asthma hospitalized for asthma

Omega-3 Fatty Acids: Asthma

Objective: to assess the effect of supplementation with fish oil during pregnancy on the risk of persistent wheeze and asthma in children

Design:

- RCT supplementing pregnant women (n=736) in their third trimester with fish oil (containing 1.32g EPA and 0.89g DHA/day) or placebo
- The women and children were followed for 3 years and formed the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort

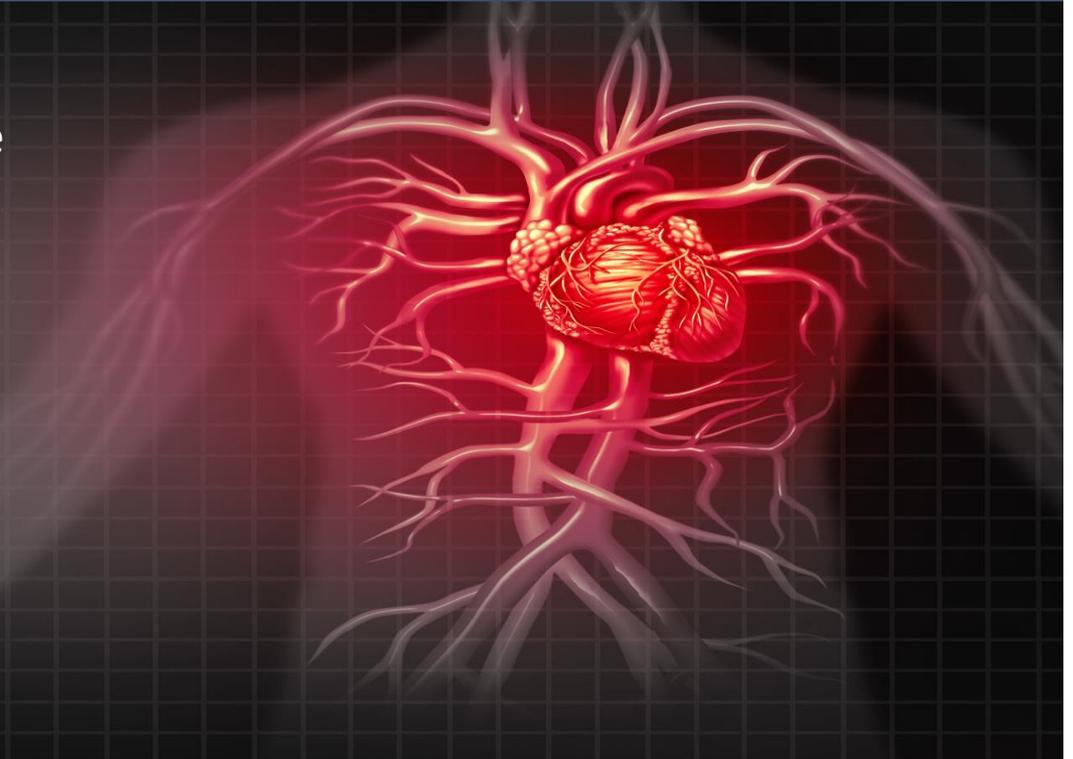
Results:

- Significantly reduced risk of persistent wheeze or asthma in the fish oil group compared to control—16.9% versus 23.7% in the control group corresponding to a relative reduction of 30.7%
- Reduction was strongest in the children of women whose blood levels of EPA and DHA were in the lowest third of the trial population at the start of supplementation

Conclusion: Supplementation with n-3 LCPUFA in the third trimester of pregnancy reduced the risk of persistent wheeze or asthma and infections of the lower respiratory tract in children by approximately 30%. These findings provide further rationale for monitoring EPA and DHA status and recommending EPA and DHA intake during pregnancy.

Omega-3 Fatty Acid: Coronary Heart Disease

- 28.4 million adults are diagnosed with heart disease
- ~633,000 people die of heart disease in the US every year
- Heart disease is **the leading cause of death** for both men and women in the US



Omega-3 Fatty Acids: Primary CVD Prevention

Objective: Determine the link between intake of fish or fish oil containing EPA and DHA and cardiovascular risk

Design:

RCTs and large prospective studies (n=23) investigating the impact of fish and fish oil intake on relative risk of coronary heart disease death and sudden death

Results:

- Modest consumption of fish (1-2 servings/wk), especially higher EPA and DHA varieties, reduces risk of coronary death by 36% and total mortality by 17%
- Intake of 250-500mg/d of EPA and DHA appears sufficient for primary prevention

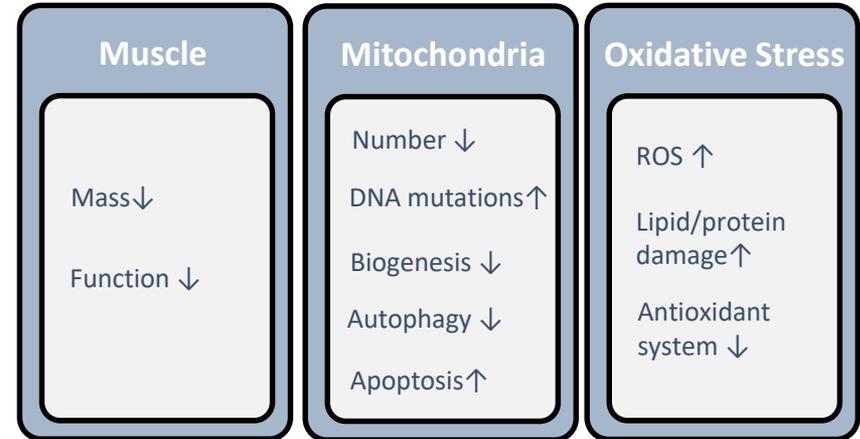
Conclusion: Long-term intake of EPA and DHA sources reduces the risk of developing cardiovascular disease and is recommended for primary prevention.

Omega-3 Fatty Acid: Muscle Function in Aging

Muscle function in aging facts

- The prevalence of reduced (weak and intermediate) muscle strength increases with age
- Muscle weakness is linked to impaired mobility and mortality in older persons and can impact activities of daily life such as rising from a chair or reducing gait speed, which can impact independence and quality of life
- Based on handgrip strength assessment, approximately:
 - 5% of adults aged 60+ have weak muscle strength and 13% have intermediate muscle strength

Skeletal muscle changes with aging



Omega-3 Fatty Acids: Muscle Function in Aging

Objective: To evaluate the impact of EPA + DHA-rich fish oil on age-related associated loss of muscle mass and function

Design:

- RCT of 4g/d fish oil (1.86g EPA, 1.5g DHA, n=29) vs. placebo (corn oil, n=15) in healthy men and women aged 60-85 years
- Participants took 2 capsules in the morning and 2 in the evening daily for 6 months

Results:

Compared with the control group, the fish oil group experienced significant increases in the following:

- Thigh muscle volume
- Handgrip strength
- 1-RM muscle strength

Conclusion: These findings support the suggestion that EPA and DHA help counteract anabolic resistance associated with aging and show that supplementation can slow the normal decline in muscle mass and function in older adults and so can be considered a therapeutic approach for preventing sarcopenia and maintaining physical independence in older adults.

Omega-3 Fatty Acids: Maintenance of Cognitive Function

Objective: To assess the association among fish, polyunsaturated fats, and omega-3 fatty acid intake on risk of cognitive decline

Design:

- Meta-analysis of 21 observational studies (n=181,580) and 4,438 cases of mild to severe cognitive decline that were identified during follow-up period (2.1 to 21 years)

Results:

- 1 serving/wk increment of fish was associated with lower risks of dementia and AD
- 100mg/day increment of DHA was associated with lower risks of dementia and AD
- EPA intake was not associated with significantly reduced risk

Conclusion: Long-term consumption of fish and DHA is associated with reduced risk for developing Alzheimer's disease and dementia. A clear dose-response relationship has not been identified, and further work is needed to make recommendations on optimal intakes to prevent cognitive decline over time.

Summary: Omega-3 Fatty Acid Recommendations

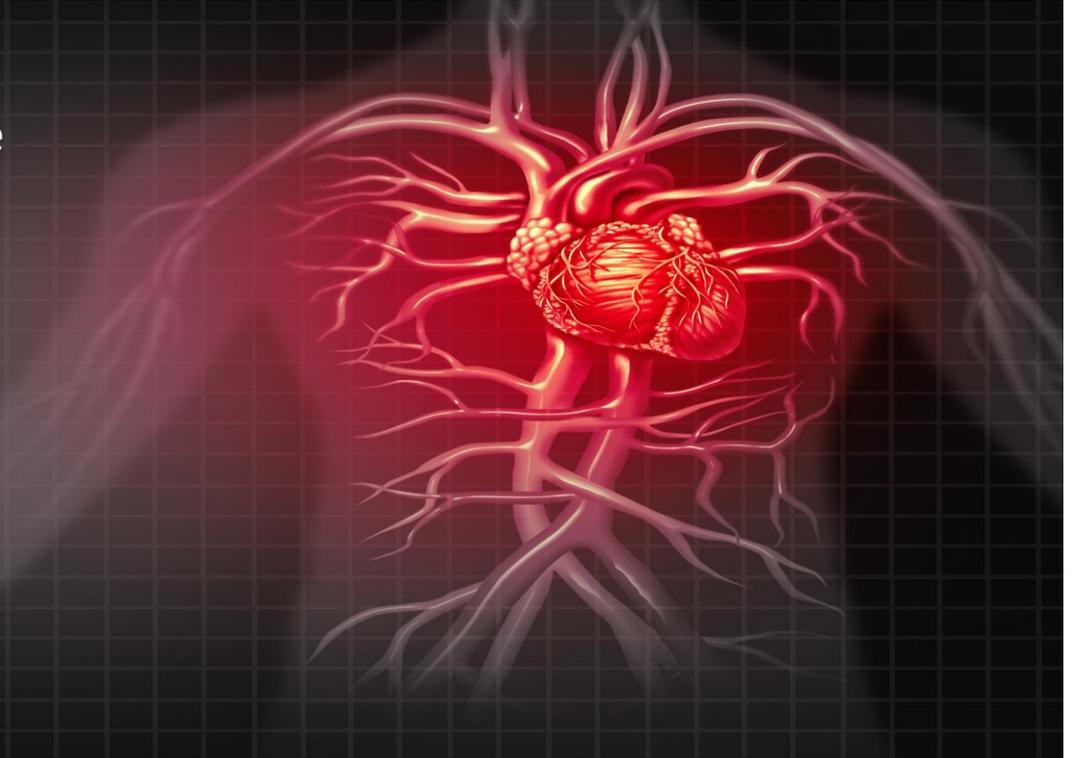
Health Category	Recommendation
Pregnancy	650mg–2000mg/day EPA+DHA; at least 300mg/day from DHA
Infant health	500mg/day from birth–12 months
Primary prevention of cardiovascular disease	Long-term intake of at least 250mg/day
Maintenance of cognitive function	Daily consumption of DHA of at least 100mg/day
Muscle function in aging	~4g/day EPA+DHA

Omega-3 Fatty Acids: Disease Prevention/Treatment

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- Coronary heart disease
- Plasma triglycerides
- Heart rate
- Rheumatoid arthritis
- Cognitive decline
- Alzheimer's disease
- Depression

Omega-3 Fatty Acid: Coronary Heart Disease

- 28.4 million adults are diagnosed with heart disease
- ~633,000 people die of heart disease in the US every year
- Heart disease is **the leading cause of death** for both men and women in the US



Coronary Heart Disease—Economic Burden

- Prevalence of US adults age 55+ with CHD expected to rise 13% between 2013 and 2020
 - 17.3 million (2013)
 - 19.5 million (2020)
- ~137,000 CHD-related medical events can be avoided each year with omega-3 supplements at preventative levels (1,000mg/day)
- 6.9% reduction in relative risk of having a CHD-related medical event if omega-3 supplemented at preventative level
- Potential savings:
 - \$2.1 billion (avoided expenditures with supplementation)
 - \$485 million (net savings after cost of supplements)
 - \$349 million (savings yet to be realized if targeted population takes omega-3s at preventative levels)

<https://www.crnusa.org/sites/default/files/pdfs-hccs/03-CRNFHCCS-CHD%2BOmega-3sandBVitamins-SP.pdf>. Accessed April 24, 2018.

Omega-3 Fatty Acids: American Heart Association Guidelines

Population/condition	Recommendations
Patients without history of cardiovascular disease (CVD)	Consume oily fish 2 or more times/week (~500mg/day)
Patients with a history of coronary heart disease (CHD)	Consume 1g daily of EPA+DHA, preferably from oily fish Fish oil supplements may be used with physician recommendation
Patients with elevated triglyceride levels	Consume 2-4g daily of EPA+DHA as capsules with physician recommendation

1. Backes JM et al. *Hosp Pharm*. 2014;49(10):907-912.
2. Surette MC. *CMAJ*. 2008;178(2):177-180.

Omega-3 Fatty Acids: Cardiovascular Disease

Objective: To analyze omega-3 fatty acid intake in the prevention of cardiovascular-related events in people with high cardiovascular risk factors

Design:

- Meta-analysis of 21 RCTs and clinical trials
- Over 50,000 participants; randomized to either omega-3 supplements or enriched in diet vs. placebo for ≥ 6 months
- Primary outcome: cardiovascular event of any kind
- Secondary outcomes: all-cause mortality, cardiac death, and coronary events

Results:

- An overall 10% decrease in risk of suffering a cardiovascular event of any kind
- 9% decrease in risk of cardiac death
- 18% decrease of fatal and nonfatal coronary events
- Trend toward lower total mortality in those with high omega-3 intake

Conclusion: These results support the AHA recommendations for the intake of omega-3 fatty acids in the prevention of cardiovascular disease, especially in those with high cardiovascular risk factors.

Omega-3 Fatty Acids: Heart Rate

Objective: Determine the impact of EPA and DHA supplementation on heart rate and differentiate between the effects of EPA and DHA

Design:

Meta-analysis of 51 RCTs including ~3000 subjects investigating the impact of EPA and DHA on heart rate (HR)

Results:

- Compared to placebo, n-3 PUFA supplementation mildly but significantly reduced HR
- Studies that supplemented with EPA and DHA separately showed that DHA (~3g per day) was responsible for the effects on heart rate reduction

Conclusion: This study provides clinical evidence that omega-3 supplementation can impact heart rate. Specifically, DHA and not EPA supplementation appears to be driving this effect.

Omega-3 Fatty Acids: Vascular Function

Objective: To investigate the impact of EPA and DHA on vascular function

Design:

- Double-blind RCT in overweight men with mild hyperlipidemia (n=59) randomized to receive either 4g/d of EPA, 4g/d of DHA, or olive oil placebo for 6 weeks
- Forearm blood flow (FBF) was measured after the intervention in all 3 groups

Results:

- Relative to placebo, DHA, but not EPA, supplementation significantly improved FBF in response to acetylcholine infusion ($p=0.040$) and co-infusion of acetylcholine with L-NMMA ($p=0.040$)
- DHA significantly enhanced dilatory responses to sodium nitroprusside ($p<0.0001$) and attenuated constrictor responses to norepinephrine ($p=0.017$)

Conclusion: Relative to placebo, DHA, but not EPA, enhances vasodilator mechanisms and attenuates constrictor responses in the forearm microcirculation

Omega-3 Fatty Acids: Serum Triglycerides



- Triglycerides are the main type of dietary fat and the most common type of lipid in the body
- Hypertriglyceridemia (>150mg/dL) affects ~25% of the US population
 - Associated with increased CVD risk
 - Progression of atherosclerosis due to ↑ in VLDL particles
- Severe hypertriglyceridemia (>500mg/dL) a risk factor for pancreatitis
- 3.4g/day (pharmaceutical dose) of omega-3s has been shown to reduce plasma TGs by 25-50% after one month of treatment
- The effect is dose dependent with clinical reductions occurring at 2g/day of omega-3s

EPA and DHA Dose-Dependently Reduce Plasma Triglycerides

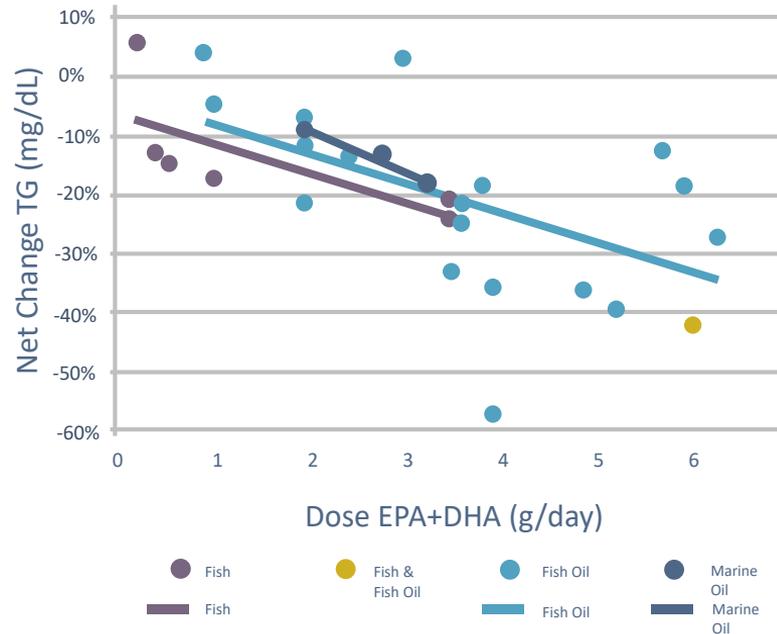


Image adapted from: Balk E et al. AHRQ Evidence report/technology assessment. 2004;(93):1-6.

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EPA and DHA Have Differing Effects on Plasma Lipids

- Findings from clinical studies comparing EPA and DHA:
 - Compared to EPA, DHA leads to increases in total, HDL, and LDL cholesterol¹
 - DHA supplementation significantly increased plasma LDL-C

	EPA Summary	DHA Summary
LDL cholesterol	On average ↓ 1.76mg/dL	On average ↑ 7.23mg/dL*
*statistically significant; results from a meta-analysis of EPA or DHA only supplementation studies ²		

- Compared to placebo, DHA increased apo-B significantly compared to control, an effect not seen in the EPA group²

1) Allaire J et al. *Am J Clin Nutr.* 2016;104:280-287.

2) Wei MY et al. *Current Atherosclerosis Reports.* 2011;13:474-483.

EPA and DHA Have Differing Effects on Plasma Lipids

Men and women
(n=154)

randomization →

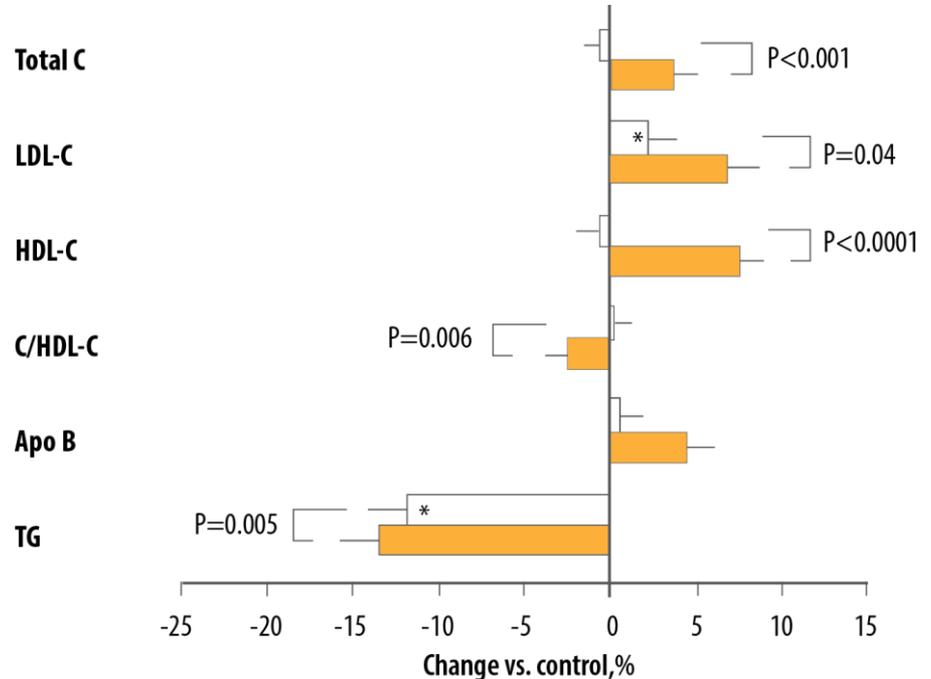
Cross-over design

EPA (2.7g/day)

DHA (2.7g/day)

Placebo (2.7g/day)

- 10-week treatments in random order
- Separated by 9-week wash-out period



National Lipid Association Recommendations for Dyslipidemia Management

Treatments that may increase LDL-C

Long-chain omega-3 fatty acids containing DHA

- Although not all clinical studies demonstrate this difference in EPA and DHA, the National Lipid Association calls out the impact of DHA on LDL-C, including in its recommendations for patient-centered management of dyslipidemia¹

Omega-3 Fatty Acids: Diabetes and Cardiovascular Risk

- Global burden of DM increased from 30 million in 1985 to 382 million as of 2014
- The International Diabetes Federation (IDF) estimates about 1 in 10 people worldwide will have DM by 2035
- CVD is the most prevalent cause of morbidity and mortality in patients with DM
- Common CVD risk factors in patients with DM are:
 - Obesity
 - Hypertension
 - **Dyslipidemia**
- Possible mechanism for developing dyslipidemia in DM:
 - Insulin-resistant adipose cell release
 - ↑ amount of free-fatty acids (FFA)
 - FFA promote TG production



Omega-3 Fatty Acids: Plasma Lipids in Patients with Diabetes

Objective: To assess the effects of omega-3 supplementation on cardiovascular outcomes (MI, sudden cardiac death), lipids and glycemic levels in people with type 2 diabetes (T2D)

Design:

- Meta-analysis of 23 RCTs involving 1075 T2D patients
- Average treatment duration was 9 weeks
- Average dose of omega-3 supplement was 3.5g/day

Results:

- No trials identified primary CVD outcomes of MI or sudden cardiac death
- Statistically significant reductions were seen in the following parameters:
 - TG levels ↓ 8.1mg/dL
 - VLDL-C levels ↓ 1.26mg/dL
 - LDL-C levels ↑ 1.98mg/dL
- No significant changes were seen in TC, HDL-C, HbA1c, fasting glucose, insulin, or body weight

Conclusion: These findings suggest that omega-3s at dosages 3.5g/day lowers TG and VLDL-C but can also modestly increase LDL-C. These findings provide further evidence for recommending increased intake of EPA/DHA in patients with diabetes, especially those with elevated TG levels.

Serum Triglycerides—Key Takeaways

- EPA and DHA dose-dependently reduce plasma triglycerides
- 2-4g/day EPA+DHA is recommended for plasma triglyceride reduction
- EPA and DHA have different effects on overall lipid profile, with some studies showing that DHA increases total, HDL, and LDL cholesterol as well as apo-B
- The National Lipid Association has recognized these results and states that in patients with severe hypertriglyceridemia, omega-3 supplements containing DHA may increase LDL-C

1. Balk E et al. AHRQ Evidence report/technology assessment. 2004;(93):1-6.
2. Allaire J et al. *Am J Clin Nutr.* 2016;104:280-287.
3. Wei MY et al. *Current Atherosclerosis Reports.* 2011;13:474-483.
4. Jacobsen TA et al. *J Clin Lipidol.* 2015;9(2):129-169.

Omega-3 Fatty Acids: Non-Alcoholic Fatty Liver Disease (NAFLD)

Objective: To determine the impact of omega-3 supplementation on liver fat and markers of liver function in patients with NAFLD

Design:

- Systematic review and meta-analysis of RCTs supplementing with EPA+DHA in patients with NAFLD
- 9 eligible studies were identified including 355 individuals

Results:

- Supplementation significantly reduced liver fat
- Supplementation also significantly reduced circulating AST levels

Conclusion: This study highlights the potential for omega-3 fatty acid supplements containing EPA and DHA in the management of NAFLD, showing reduction in liver fat and improvement in a test (AST) for liver function. Studies used doses ranging from 0.8–13.7g/day (median dose 4g/day), and further work is required to identify the optimal dose for this patient group.

Omega-3 Fatty Acids: Age-Related Macular Degeneration (AMD)

- Major cause of vision loss among older adults
- 1.75 million Americans have AMD
- Research suggests EPA/DHA may have cytoprotective effects in the retina; may help prevent the development or progression of AMD
- Results from observational studies suggest people who consume higher amounts of fatty fish have a lower risk of developing AMD



1. <https://nei.nih.gov/eyedata/pbd4>. Accessed May 12, 2018.
2. <https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/>. Accessed May 13, 2018.

Omega-3 Fatty Acids: Age-Related Macular Degeneration

Objective: To evaluate the efficacy of DHA+EPA supplements in preventing age-related macular degeneration (AMD)

Design:

- RCT (n=263) aged ≥ 55 -85 years with early lesions of AMD
- Treatment group participants received 840mg/day of DHA + 270mg/day of EPA for 3 years
- Primary outcomes: time to occurrence of choroidal neovascularization (CNV) in the study eye

Results:

- Time to occurrence of CNV was not statistically significant in the treatment vs. placebo groups
- DPA+EPA increased significantly in red blood cell membranes (RBCM) in the treatment group
- Patients achieving highest tertile of DHA+EPA in the RBCM had significantly lower risk of developing CNV

Conclusion: These findings suggest that DHA+EPA supplementation of ~ 1 g/day significantly reduced the incidence of CNV in those patients that consistently achieved a high DHA+EPA index over 3 years.

Omega-3 Fatty Acids: Alzheimer's Disease

Alzheimer's disease fact sheet:

- Alzheimer's disease is a type of dementia
- It is an irreversible, progressive condition
- It is estimated to affect 5.4 million Americans
- It is the 6th leading cause of death among adults in the US
- It is the 5th leading cause of death for those aged 65+
- The incidence increases with age, and symptoms typically do not appear until after age 60 in 90% of cases
- The causes are not fully understood but are believed to include a combination of genetic, environmental, and lifestyle factors



Omega-3 Fatty Acids: Alzheimer's Disease

Objective: To determine the effect of EPA+DHA supplementation on cognitive function in patients with Alzheimer's disease (AD)

Design:

- RCT in patients with AD (n=174) randomized to receive either 1.72g DHA+0.6g EPA/d or placebo for 6 months; after 6 months, both groups were supplemented with EPA+DHA (as above)
- Baseline and post-supplementation changes in plasma omega-3 fatty acids and cognitive performance (assessed by ADAS-cog and MMSE scores) were tested

Results:

- Preservation of cognitive functioning, assessed by ADAS-cog or its subitems (but not MMSE) scores, was significantly associated with increasing plasma omega-3 levels over time
- Greater changes in plasma DHA (marker of DHA status) was associated with slower rate of cognitive decline as measured by ADAS-cog scores

Conclusion: A significant association was found between changes in ADAS-cog scores and increased DHA plasma levels after 6 months of treatment, suggestive of a positive effect on cognitive functioning.

Omega-3 Fatty Acids: Mild Cognitive Decline

Objective: To determine the effect of DHA supplementation on cognitive function and hippocampal atrophy in elderly subjects with mild cognitive impairment (MCI)

Design:

- RCT (n=240) aged ≥ 65 years
- Treatment group participants received 2g/day DHA supplements for 12 months
- Global and specific subdomains of cognitive function and hippocampal volume measured at baseline, 6 months, and 12 months

Results:

- 219 participants completed the 12-month trial
- Statistically significant improvements seen in:
 - Full-scale intelligence quotient
 - Information
 - Digit span
 - Volumes of total, left, right hippocampus

Conclusion: These findings suggest that DHA supplementation of 2g/day in adults with MCI can significantly improve cognitive function and slow the progression of hippocampal atrophy.

Omega-3 Fatty Acids: Rheumatoid Arthritis

- An autoimmune disorder affecting over 1.3 million Americans
- 3rd most common type of arthritis behind osteoarthritis and gout
- Symptoms are triggered when antibodies attack the synovial joint fluid, causing chronic inflammation
- To some extent symptoms are the result of pro-inflammatory eicosanoid production such as prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄)
- PGE₂ and LTB₄ are products of arachidonic acid (AA)
- EPA and DHA have shown to inhibit NF-κB, IL-1β, and TNF-α



Omega-3 Fatty Acids: Rheumatoid Arthritis

Objective: To assess the effects of omega-3 FA on clinical outcomes in patients with rheumatoid arthritis (RA)

Design:

- Meta-analysis of 10 RCTs involving 183 RA patients
- Treatment group consumed ≥ 2.7 g/day omega-3 FA for at least 3 months
- 9/10 RCTs supplemented with EPA+DHA daily (range: 2.9 -5.2 g/day)
- 1/10 RCTs supplemented with 9.6 g/d ALA

Results:

- Statistically significant reductions in the usage of NSAIDs in the treatment group
- Showed a trend toward symptoms improvement:
 - Tender joint count
 - Swollen joint count
 - Morning stiffness
 - Physical function

Conclusion: These findings suggest that omega-3s (specifically EPA+DHA) at dosages ≥ 2.7 g/day reduces NSAID consumption in patients suffering from RA. Furthermore, there are improvements in physical symptoms associated with RA. The 1 ALA study yielded no RA benefits. Further studies with longer duration are needed to explore significant clinical effects of omega-3s in RA.

Omega-3 Fatty Acids: Neuropathic Pain

Objective: To investigate and report on patients with neuropathic pain who responded to treatment with omega-3 fatty acids

Design:

- Case series of 5 patients with different underlying diagnoses including cervical radiculopathy, thoracic outlet syndrome, fibromyalgia, carpal tunnel syndrome, and burn injury who were treated with high oral doses of omega 3 fish oil (varying from 2400-7200 mg/day of EPA-DHA)

Results:

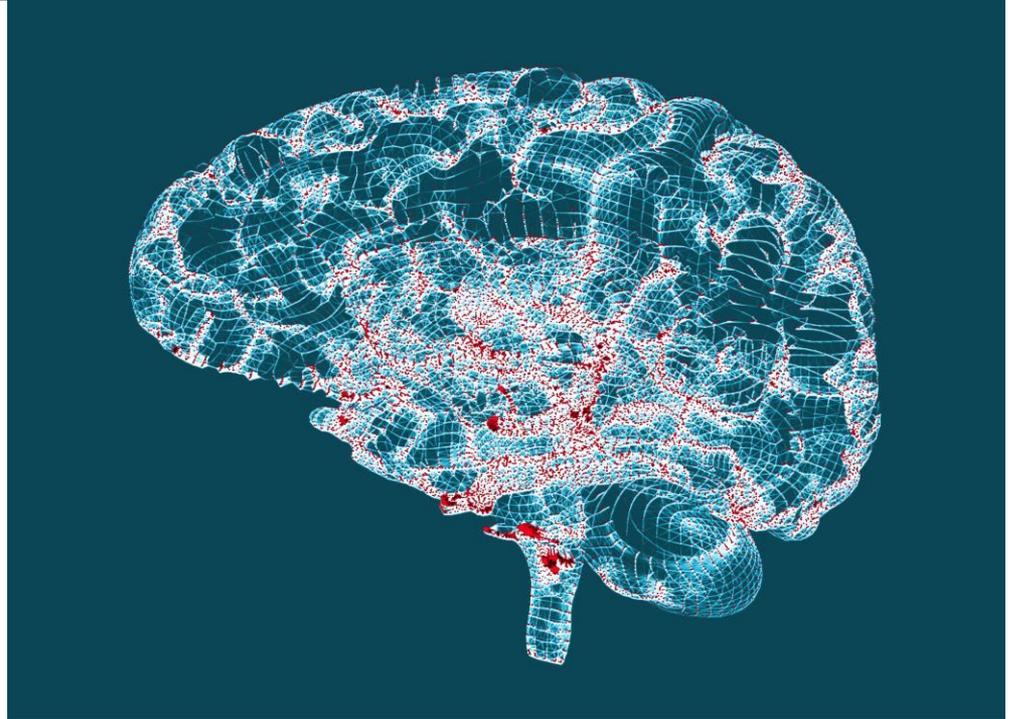
- Improvements were noted across a number of validated surveys, objective clinical tools and EMG nerve conduction studies
- No serious adverse effects were reported

Conclusion: This first-ever reported case series suggests that omega-3 fatty acids may be of benefit in the management of patients with neuropathic pain. Further work is required to understand the optimal treatment protocol for this patient group.

Omega-3 Fatty Acids: Depression

Depression stats:

- Depression affects about 16 million American adults each year, and 1 in 6 adults will have depression within their lifetime
- 10.4% of physician office visits have depression indicated on the medical record
- The exact cause of depression is unknown but is believed to be a combination of genetic, biological, environmental, and psychological factors
- Antidepressants are one of the three most commonly used therapeutic drug classes in the United States, and use has increased almost 65% in a 15-year period
- 12.7% of people over aged 12 estimated to take anti-depressant medication within the past month; ~25% of those taking antidepressant medication had done so for 10 years or more



<https://www.cdc.gov/nchs/fastats/depression.htm>. Accessed May 16th 2018.

<https://www.cdc.gov/nchs/products/databriefs/db283.htm>. Accessed May 16th 2018.

<https://www.cdc.gov/tobacco/campaign/tips/diseases/depression-anxiety.html>. Accessed May 16th 2018.

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Omega-3 Fatty Acids: Depression

Objective: Determine the impact of EPA and DHA supplementation on depression scores in patients with depression

Design:

- Meta-analysis of 15 double-blind RCTs of fish oil supplementation (n=916) in patients with depression
- Analysis focused on understanding the effect of supplementation on mean depression scores and on formulas containing higher ($\geq 60\%$) vs. lower ($< 60\%$) EPA

Results:

- Supplements with EPA $\geq 60\%$ showed significant benefit for reducing standardized mean depression scores
- Supplements with EPA $< 60\%$ were ineffective
- A nonlinear dose effect was seen such that 200-2,000mg/day of unopposed EPA was seen to be effective

Conclusion: This analysis highlights the role of EPA in the management of patients with depression and shows that higher EPA ($> 60\%$) formulas at doses up to 2,000mg/day of unopposed EPA led to significant improvements in mean depression scores. Neuroprotective, anti-inflammatory effects of EPA have been suggested to drive this effect, although more studies are needed to fully understand the mechanisms.

Summary: Omega-3 Fatty Acid Recommendations

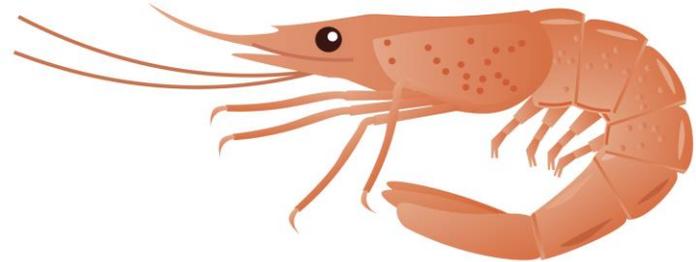
Health Category	Recommendation
Coronary heart disease	At least 1g of EPA+DHA per day
Heart rate reduction	~3g DHA per day
Vascular function	~4g DHA per day
Plasma triglyceride management	2-4g per day
NAFLD	>2g EPA+DHA per day
Mild cognitive impairment	~2 g DHA per day
Depression	~2g EPA per day
Alzheimer's disease	~2g per day—higher DHA formulations
Age-related macular degeneration	~1g+ DHA per day
Rheumatoid arthritis	~3g EPA+DHA per day
Neuropathic pain	2400-7200 mg/day of EPA-DHA

Overview of Fish Oils

- Different types of oils
 - Krill
 - Algae
- Production methods
 - Molecular distillation
 - Supercritical fluid extraction
- Fatty acid forms
- Quality
- Different forms
- Drug/nutrient interactions
- Safety

Krill Oil

- Small shrimp-like crustaceans found in the ocean
- Serve as a major food source for marine life
- Krill consume a diet rich in algae; therefore are a natural source of EPA/DHA
- Contains astaxanthin, a carotenoid antioxidant responsible for the red color
 - Some studies indicate astaxanthin contains HDL-C increasing properties
- Krill oil only available as a supplement



Krill Oil vs. Fish Oil

	Krill Oil	Fish Oil
Fatty acid form	<ul style="list-style-type: none"> Phospholipids 	<ul style="list-style-type: none"> Triglycerides Ethyl esters
EPA/DHA dose per serving	<ul style="list-style-type: none"> 45-200mg 	<ul style="list-style-type: none"> 300-2,250mg
	<ul style="list-style-type: none"> Greater pill burden to increase EPA+DHA status 	
Formulation	<ul style="list-style-type: none"> Softgel supplement 	<ul style="list-style-type: none"> Prescription Supplement
Properties	<ul style="list-style-type: none"> Less fish burp 	<ul style="list-style-type: none"> More fish burp
Bioavailability	<ul style="list-style-type: none"> Comparable 	<ul style="list-style-type: none"> Comparable
Cost	<ul style="list-style-type: none"> \$.30/100mg EPA+DHA 	<ul style="list-style-type: none"> \$.01-.15/100mg EPA+DHA
Spoilage/degradation	<ul style="list-style-type: none"> More spoilage, less EPA+DHA content 	<ul style="list-style-type: none"> Less spoilage
Sustainability	<ul style="list-style-type: none"> Less sustainable 	<ul style="list-style-type: none"> More sustainable

Krill Oil vs. Fish Oil: Results from a Clinical Study

Objective: To compare the oral bioavailability of the same dose of EPA/DHA in fish oil-EE vs. fish oil-TG vs. krill oil in plasma

Design:

- 66 participants (22/arm) randomized to 1 of the 3 formulations; consumed 1.3g/d dose of EPA/DHA for 4 weeks
- Dietary intake of omega-3s were assessed by a food frequency questionnaire (FFQ)

Results:

- Baseline plasma EPA/DHA levels not significantly different among the 3 groups
- Mean plasma EPA/DHA levels not significantly different among the 3 groups (i.e. similar bioavailability) at week 4
 - All 3 formulations had higher EPA content; with EPA:DHA ratio of 1.6:1

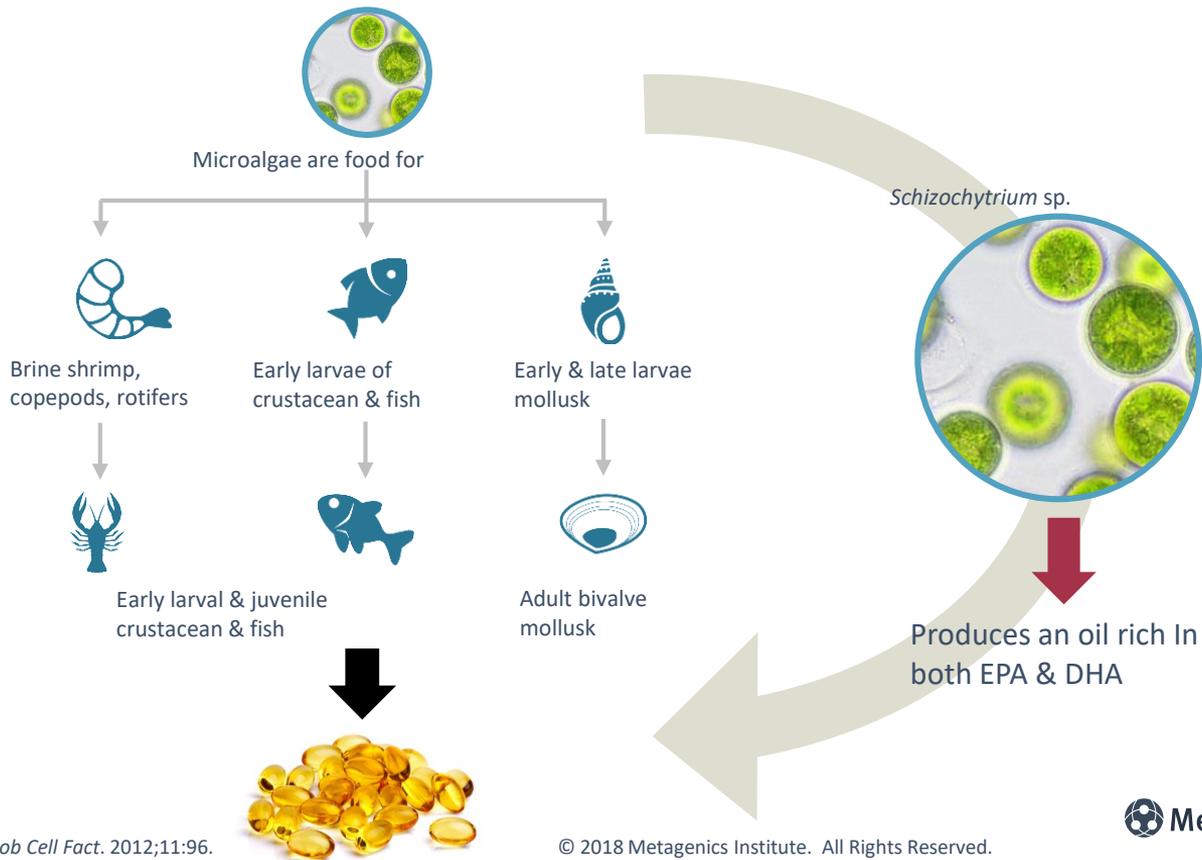
Conclusion: The findings suggest similar plasma and RBC levels of EPA+DHA were achieved across fish and krill oil products when matched for dose, EPA, and DHA concentration in this study. This indicates similar bioavailability in fish oil (EE and TG) and krill oil formulations.

Algal Oil

- Derived from micro-algae in the ocean
- Is a vegetarian source of EPA+DHA
- RCT conducted to compare nutritional bioavailability of DHA from algal-oil compared with cooked salmon
 - 32 healthy adults consumed 600mg/day DHA from either algal oil supplements vs. cooked salmon for 2 weeks
 - DHA levels increased by 80% in plasma phospholipids and 25% in erythrocytes in both groups
 - Both tolerated well; no adverse effects found
 - Results indicate equivalent tolerability and bioavailability

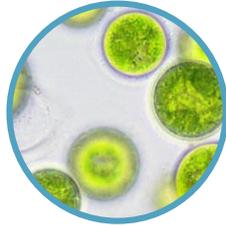


Sustainably Grown Marine Algae: Vegetarian Source of EPA and DHA



The EPA & DHA Molecule Are the Same, Regardless of the Source

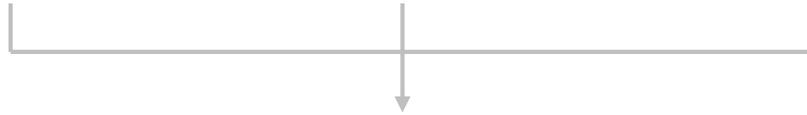
Algae



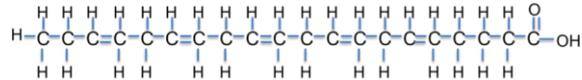
Fish Oil



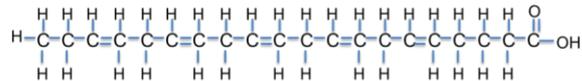
Fish



EPA

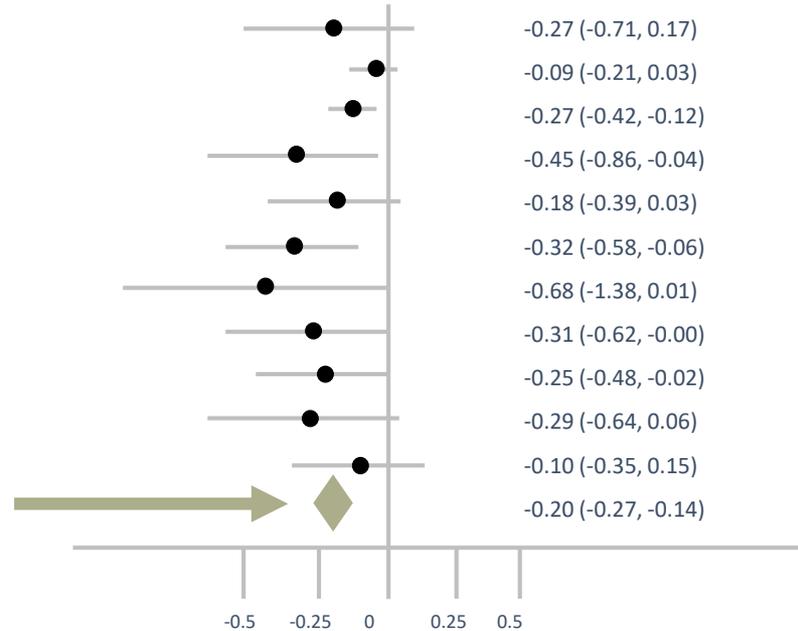


DHA



Long Chain Omega-3 Fatty Acids from Algae Reduce Plasma Triglycerides

Supplementation
with ~1.68g/day
(median intake) for
~6 weeks
significantly
reduced plasma
triglycerides



Desired/Most Effective Production Methods

- Molecular distillation is a type of very high vacuum distillation, which takes place in a specific apparatus
- This apparatus is constructed so that the distance the molecules must travel between evaporation and condensation is smaller than their average free path
- Due to this shortened distance, it is possible to protect the product from excessive exposure and deteriorating conditions; this feature makes molecular distillation a good alternative for application in the fractionation process of omega-3 fatty acids

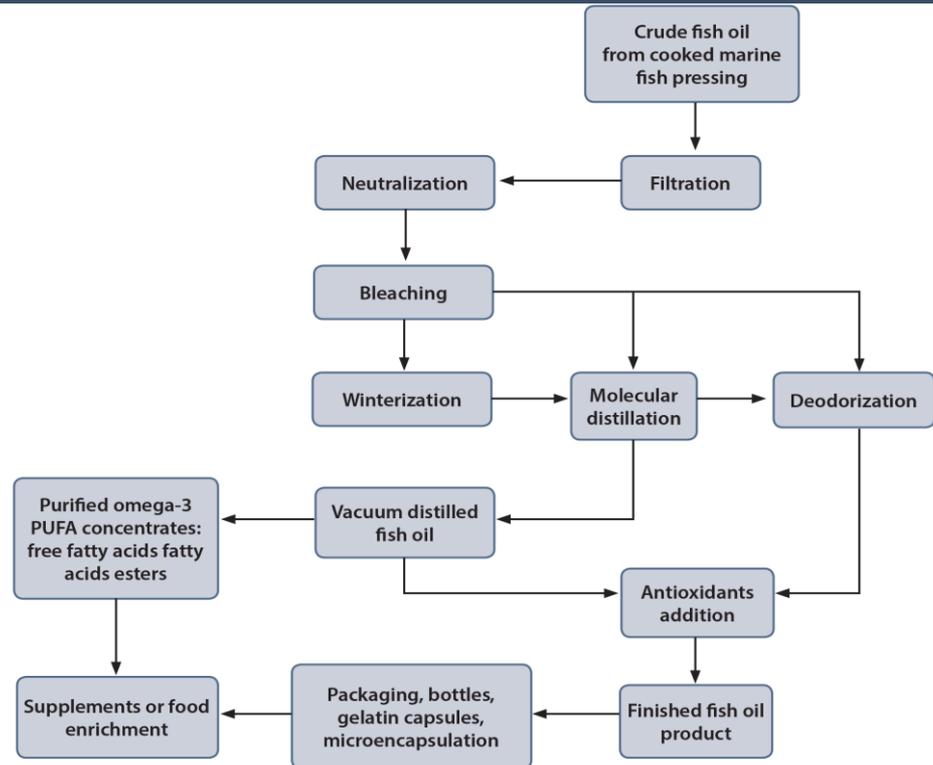


Image adapted from: Kolanowski W et al. *Int J Food Sci Nutr.* 1999;50(1):39-49.

Supercritical Fluid Extraction

- Uses supercritical fluids to separate extractant from matrix using CO₂ as solvent
 - Eliminates cholesterol, PCBs, dioxins, heavy metals
- Uses low temperature ranges to prevent thermal stress on the highly temperature-sensitive EPA/DHA
 - Environmentally friendly, non-toxic

Omega-3 Fatty Acids: Concentration Technology

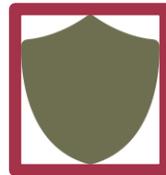
	Molecular Distillation	Supercritical Fluid Extraction
Operation temperature (°C)	140-160	35-50
Max viable concentration achieved	65-75%	99%
Decontamination efficacy	Very high	Very high
Risk of product oxidation	Low	Low

1. Grosso C et al. *Mar Drugs*. 2015;13:3182-3230.
2. Kolanowski W et al. *Int Sci J Food Sci Nutr*. 1999;50(1):39-49.

Omega-3 Supplement Quality: Third-Party Tested



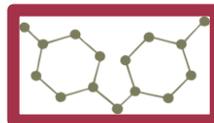
For rancidity:
By testing both peroxide and anisidine levels to determine TOTOX value



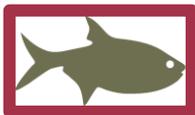
Antioxidant-stabilized:
Fortified with antioxidants to maintain freshness



Exceeding GOED standards for oxidation



Recent study shows EPA and DHA content lower than label claim in several commercially available formulas



For consistent dosing:
Ensuring the omega-3 content meets or exceeds label claim

Checking for several hundred contaminants

Omega-3 Fatty Acids: Supplement Quality

- Many dietary supplements do not always contain information stated on the label
- EPA/DHA content may vary from batch to batch
 - Analytic studies found EPA content ranged from 51-124%; DHA ranged from 61-153% of amounts stated on label
- May state the total EPA/DHA content but not the individual components
- May have additional unwanted ingredients:
 - Dietary cholesterol
 - Saturated fats



Omega-3 Fatty Acids: Supplement Quality

- May be highly oxidized
 - Peroxides
 - Anisidine
 - Total oxidation (TOTOX)
- Drug residues
 - Antibiotics
 - Antiparasitics
 - Hormones
- Pesticide residues
 - Insecticides
 - Herbicides
- Radioactive isotopes
- Inorganic contaminants
 - Heavy metals
 - Lead
 - Cadmium
 - Mercury
 - Arsenic
- Organic contaminants
 - Polychlorinated biphenyls (PCB)
 - Polycyclic aromatic hydrocarbons (PAH)
 - Dioxins
 - Phthalates
 - Mycotoxins

Omega-3 Fatty Acids: Triglyceride vs. Ethyl Ester

	Triglycerides (TG)	Ethyl Ester (EE)
Stability	No stability concerns	No stability concerns
Absorption	Greater absorption shown in acute intake studies over a period of 24 hours in several studies compared to EE form	Reduced absorption shown in acute intake studies over a period of 24 hours in several studies compared to TG form
Clinical effectiveness	Shown to be clinically effective	Shown to be clinically effective
Safety	No concerns with TG intake at appropriate dose of EPA + DHA	No concerns with EE intake at appropriate dose of EPA + DHA
Size	Larger than EE	Smaller than TG

Sustainability

- Fish supply
 - Need to follow the United Nations Food and Agriculture Organization's (FAO) Code of Conduct for Responsible Fisheries
 - Provides standards for conservation, management, and development of all fisheries
 - Strict catch limits are introduced each year based on census of fish biomass in the ocean



Drug Interactions

- High doses of fish oil, flaxseed oil, evening primrose oil, borage oil, etc., may prevent clumping of platelets in the blood
 - However, [recent research](#) shows no evidence of increased risk of bleeding with the use of omega-3s in patients using antithrombotic medications
- Evening primrose oil, borage oil, may increase the risk of seizures in people on phenothiazines



1. Vaddadi KS. *Prostaglandins Med.* 1981;6(4):375-379.
2. Bender NK et al. *J Thromb Thrombolysis.* 1998;5(3):257-261.
3. Jeansen S et al. *Clin Nutr.* 2018;37(3):948-957.

Nutrient Interactions

- Limited preclinical and clinical data suggest vitamin E helps to prevent the oxidative breakdown of lipids that occurs with PUFA consumption
- An intake of 0.6mg α -tocopherol per gram of LA is seen as adequate for human adults
- More research is needed to determine the vitamin E requirement when the intake of longer-chain, more unsaturated fatty acids is increased



Fatty Acids: Safety

- The Institute of Medicine has not set a Tolerable Upper Intake Level (UL – maximum daily level of intake unlikely to cause adverse health effects) for omega-3s due to the relative safety of fish oil consumption at higher doses as seen in human clinical trials (up to ~5g/d)
- Commonly reported side effects are mild, including bad breath, heartburn, nausea, GI discomfort, headache, diarrhea, and unpleasant taste
- Patients on certain prescription medications (e.g. Coumadin) or diagnosed with severe health conditions should seek proper dosage guidance from their physicians

1. <https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/#en162>. Accessed April 24, 2018.

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf. Accessed April 24, 2018.

Fatty Acids: Safety

- ALA: generally well tolerated; high doses of flaxseed oil may cause loose stools
- EPA/DHA: The Food and Drug Administration (FDA) recommends no more than 2g/day EPA+DHA from dietary supplementation for the general public
- GLA: generally well tolerated; high doses of evening primrose oil, black currant seed oil, borage oil may cause loose stools
 - Some evidence suggest evening primrose oil caused seizures in people with undiagnosed temporal lobe epilepsy; patients with history of seizure disorder should avoid GLA oils

Fatty Acids: Safety

- Infant formula
 - Some studies reported formulas enriched with EPA decreased plasma AA concentration, which is associated with decreased weight in infants
 - Currently available formulas contain only AA and DHA derived from algal or fungal sources
- Pregnancy and lactation
 - Safety of omega-3 supplements has not been established in pregnant or lactating women
 - Pregnant and lactating women should follow recommendation of limiting fatty fish to 2-3 servings per week

1. Carlson SE et al. *Lipids*. 1992;27(11):901-907.
2. Bradberry JC et al. *PT*. 2013; 38(11):681-691.
3. Vaddadi KS. *Prostaglandins Med*. 1981;6(4):375-379.

Summary: Key Points

- ALA and LA are considered essential; EPA and DHA are conditionally essential
- Standard American Diet (SAD) supplies more omega-6 compared to omega-3 fatty acids
- Omega-3s are important in disease prevention/treatment of several health conditions such as cardiovascular, cognition, eye, immune health
- Quality of fish oil matters
- Safety: adverse events are generally minor and typical symptoms are GI-related



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