

CLINICAL
RESEARCH TRIALS

Using

NORDIC NATURALS
FISH OILS

ABSTRACTS



INTRODUCTION

To date, the omega-3 fatty acids from fish (EPA and DHA) have been evaluated in over 15,000 laboratory investigations and clinical trials. The interest in these two fatty acids is based on their central importance to optimal cell membrane structure, cell signaling, and gene transcription in cells throughout the body. The need for EPA and DHA begins early in life, as evidenced by benefits accrued to the mother and infant during pregnancy, and continues through childhood, adolescence, and adulthood, where they support normal/optimal cell, tissue, and organ function and reduce the risk and/or help mitigate the effects of many chronic inflammatory disorders, particularly those associated with the cardiovascular and nervous systems.

Nordic Naturals fish oils are used by clinical and laboratory research scientists at major universities and institutions worldwide because of their independently tested and validated purity and clean taste (extraordinarily low oxidation), and are products that offer a wide range of EPA and/or DHA concentrations, all in a natural triglyceride form.

Supporting well-designed basic laboratory and applied clinical research studies that increase our knowledge and understanding of EPA and DHA within the human body is a foundational principle at Nordic Naturals. The abstracts presented here are evidence of this principle in action and are intended to provide an easily accessible resource for new insight and study.

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PART I

SUMMARY TABLE OF PUBLISHED CLINICAL RESEARCH TRIALS

Using

NORDIC NATURALS FISH OILS

| Investigation | Product | Study Design | Subjects | Publication | Organization |
|---|---|--|---|---|--|
| fish oil and heart rate variability in anxiety | ProOmega® (35/25) 6 soft gels/day 56 days | clinical/pilot study | 25 adults | <i>Neuropsychopharmacology</i> 2005 Dec;30(1):S104 | Duke University Medical Center Psychiatry Durham, NC |
| fish oil and behavioral outcomes in challenged children | ProEFA®-3.6.9 Junior (18/12) 1–2 soft gels/day 180 days | clinical study | 20 orphaned children with functional challenges | <i>Adoption Today</i> 2006 Dec/Jan:38–39 | HANDLE® Institute/ Rays of Hope Orphanage Saltillo, Mexico |
| fish oil and anxiety measures | ProEPA™ (45/10) 5 soft gels/day 90 days | clinical study clinical/pilot study | 24 adult substance abusers | <i>J CI Psychopharmacol</i> 2006 Dec;26(6):661–5 | VA New York Harbor Healthcare System Brooklyn, NY |
| fish oil and decreased anger in substance abusers | ProEPA™ (45/10) 5 soft gels/day 90 days | clinical study | 24 adults in drug treatment | <i>Psychiatry Res</i> 2008 Jan 15;157(1–3):95–104 | VA New York Harbor Healthcare System Brooklyn, NY |
| omega-3 to enhance antidepressant response in major depressive disorder | ProEPA™ (45/10) 4 soft gels/day 9 weeks | clinical study | 42 depressed adults | <i>J Clin Psychopharmacol</i> 2012 Feb;32(1):61–4 | California Clinical Trials Medical Group, Inc. Glendale, CA |
| fish oil and inflammation, reduction of NSAIDs use | ProEPA™ (45/10) 2–4 soft gels/day 75 days | clinical study | 250 adults with non-surgical neck/back pain | <i>Surg Neurol</i> 2006 Apr;65(4):326–31 | University of Pittsburgh Medical Center Pittsburgh, PA |
| fish oil and exercise for cognitive and neurological enhancement | ProDHA™ (10/50) N/A 12 days | pre-clinical study | animal study | <i>Neuroscience</i> 2008 Aug 26;155(3):751–9 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| fish oil and exercise combination for adult brain synaptic improvement | ProDHA™ (10/50) N/A 12 days | pre-clinical study | animal study | <i>Brain Res</i> 2010 Jun 23;1341:32–40 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| fish oil + GLA in developmental language and learning | ProEFA®-3.6.9 (18/12) 1 soft gel/day 90 days | clinical/pilot study | 22 children with autism/asperger's syndrome | <i>Autism-Asperger's Digest</i> 2005 Jan/Feb:36–37 | Pediatric Clinic Tucson, AZ |
| fish oil and exercise combination for balanced brain chemistry | ProDHA™ (10/50) N/A 14 days | pre-clinical study | animal study | <i>Neuroscience</i> 2010 Jun 16;168(1):130–7 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| DHA protection against reduced plasticity of brain and spinal cord after brain trauma | ProDHA™ (10/50) N/A 12 days | pre-clinical study | animal study | <i>J Neurotrauma</i> 2011 Oct;28(10):2113–22 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| adequate levels of dietary DHA crucial for building long-term neuronal resilience, adulthood plasticity | ProDHA™ (10/50) N/A 105 days | pre-clinical study | animal study | <i>PLOS ONE</i> 2011;6(12):e28451 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| “metabolic syndrome” in the brain: deficiency effects of omega-3 fatty acids | ProDHA™ (10/50) N/A 6 weeks | pre-clinical study | animal study | <i>J Physiol</i> 2012 May 15;590(10):2485–99 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| high-fat diet transition reduces brain DHA levels | ProDHA™ (10/50) N/A 15 weeks | pre-clinical study | animal study | <i>Sci Rep</i> 2012;2:431 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| dietary therapy to promote neuroprotection in chronic spinal cord injury | ProDHA™ (10/50) N/A 6 weeks | pre-clinical study | animal study | <i>J Neurosurg Spine</i> 2012 Aug;17(2):134–40 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| effects of diet containing omega-3 DHA and curcumin on spinal cord learning | ProDHA™ (10/50) N/A 4 weeks | pre-clinical study | animal study | <i>PLOS ONE</i> 2012;7(7):e41288 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| dietary omega-3 builds resistance against effects of traumatic brain injury | ProDHA™ (10/50) N/A 3 weeks | pre-clinical study | animal study | <i>PLOS ONE</i> 2012;7(12):e52998 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| omega-3-deficient western diet and brain trauma | ProDHA™ (10/50) N/A 15 weeks | pre-clinical study | animal study | <i>PLOS ONE</i> 2013;8(3):e57945 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| DHA after brain trauma: implications for plasticity and cognition | ProDHA™ (10/50) N/A 14 days | pre-clinical study | animal study | <i>Neurorehabil Neural Repair</i> 2014 Jan;28(1):75–84 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |

| Investigation | Product | Study Design | Subjects | Publication | Organization |
|--|--|--------------------|--|---|---|
| DHA preconditioning for long-term neuronal resilience against TBI incurred during adulthood | ProDHA™ (10/50) N/A 14 weeks | pre-clinical study | animal study | <i>Biochim Biophys Acta</i> 2014 Apr;1842(4):535–46 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| DHA as crucial for supporting plasma membrane function, signaling, and cognition | ProDHA™ (10/50) N/A 11 weeks | pre-clinical study | animal study | <i>Exp Neurol</i> 2014 Mar;253:41–51 | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| fish oil and alpha-lipoic acid in the progression of Alzheimer's disease | ProOmega® (35/25) 3 soft gels/day 1 year | clinical study | 39 senior adults with MCI or Alzheimer's disease | <i>J Alzheimers Dis</i> 2014;38(1):111–20 | Oregon Health & Science University Portland, OR |
| fish oil, comparing EPA vs. DHA for major depression | ProEPA™ Xtra (60/15) vs. ProDHA™ 2 and 4 soft gels/day 8 weeks | clinical study | 154 adults with major depressive disorder | <i>J Clin Psychiatry</i> . 2015 Jan;76(1):54–61. | Massachusetts Gen Hospital Harvard Medical School Boston, MA |
| fish oil as adjunct therapy in major depression | ProEPA™ Xtra (60/15) 2 soft gels/day 8 weeks | clinical study | 155 adults with major depression disorder | <i>Mol Psychiatry</i> 2016 Jan;21(1):71–9 | Emory University School of Medicine Atlanta, GA |
| fish oil for depression in multiple sclerosis | ProOmega® (35/25) 6 soft gels/day 3–6 months | clinical study | senior adults with relapsing-remitting multiple sclerosis and depression | <i>PLOS ONE</i> 2016 Jan 22;11(1):e0147195. | Oregon Health & Science University Portland, OR |
| DHA reverses fructose-induced brain imbalances | ProDHA™ (10/50) N/A 6 weeks | pre-clinical study | animal study | <i>EBioMedicine</i> 2016 Apr | UCLA Neurosurgery and Physiological Sciences Los Angeles, CA |
| quality nutrition during brain formation is a predictor of brain functional capacity and plasticity during adulthood | ProDHA™ (10/50) n/a 7 weeks | pre-clinical study | animal study | <i>Neurobiol Dis</i> 2015Jan;73:307-18. | UCLA / Neurosurgery & Physiological Sciences Los Angeles, CA |
| fish oil and inositol in pediatric mania and depression (bipolar) | ProOmega® Jr (35/25) 6 soft gels/day 12 weeks (84) | clinical study | children (6-17 yrs) | <i>J Clin Psychiatry</i> 2015 Nov;76(11):1548-55. | Massachusetts Gen Hospital Harvard Medical School Boston, MA |
| behavioral and cellular effects of morphine reduced or reversed by omega-3 PUFA | ProDHA™ (10/50) n/a 8 weeks | pre-clinical study | animal study | <i>PLoS One</i> . 2017 Apr 5;12(4): e0175090. | UCLA / Neurosurgery & Physiological Sciences Los Angeles, CA |
| fish oil (omega-3 and -6 fatty acids) and language development in toddlers with ASD symptomology | ProEFA®-3.6.9 Jr. (18/12), liquid 1/2 tsp/day 6 weeks | clinical study | 31 preterm children at 1.5-3 yrs old exhibiting ASD symptoms | <i>J Autism Dev Disord</i> . 2017 Jul 26. | Nationwide Children's Hospital, Cntr for Bio-Behavioral Health Columbus, OH |
| fish oil (omega-3 and -6 fatty acids) and sensory processing in toddlers with ASD symptomology | ProEFA®-3.6.9 Jr. (18/12), liquid 1/2 tsp/day 6 weeks | clinical study | 31 preterm children at 1.5-3 yrs old exhibiting ASD symptoms | <i>Early Human Development</i> 115 (2017) 64–70 | Nationwide Children's Hospital, Cntr for Bio-Behavioral Health Columbus, OH |
| fish oil as adjunct therapy for residual DESR in treated ADHD youth | ProOmega® Jr (35/25) 2-6 soft gels/day 12 weeks | clinical study | Children with ADHD | <i>J Child Adolesc Psychopharmacol</i> . 2017 Oct;27(8):755–756 | Massachusetts General Hospital/Harvard Boston, MA |
| effects of fish oil on cholesterol subfractions (CAD risk predictors) | ProEPA™ Xtra (60/15) 3 soft gels/day 28 days | clinical study | 24 healthy adults | <i>J of Am Dietetic Assoc</i> 2008 Sept;108;9:A104 | San Jose State University San Jose, CA |
| fish oil, lipid profiles, and cardiovascular risk | ProOmega® (35/25) 4 soft gels/day 60 days | clinical study | 36 professional football players | <i>Sports Health</i> 2009 Jan;1(1)21–30 | University of Pittsburgh Medical Center Pittsburgh, PA |
| fish oil effects on c-reactive protein levels | ProEPA™ (45/10) 3 soft gels/day 8 weeks | clinical study | 53 adults | <i>Clin Lipidol</i> 2011;6(6),723–729 | The Cleveland Clinic Cleveland, OH |
| fish oils to raise omega-3 index (O-3), predictor of CVD mortality | Arctic Omega™ (18/12) 0–6 soft gels/day 6 months | clinical study | 125 adult students | <i>J Am Heart Assoc</i> 2013 Nov 19;2(6):e000513 | Penn State University Department of Nutritional Science University Park, PA |
| omega-3 fatty acid bioavailability offered by 4 different natural health products | ProOmega® (35/25) 1–2 soft gels/day 28 weeks | clinical study | 35 healthy adults | <i>Lipids Health Dis</i> 2014 Jun 21;13:99 | Nutrasource Diagnostic, Inc. Guelph, ON, Canada |
| anti-inflammatory effects of EPA and DHA | Arctic Omega™ (18/12) 0–6 soft gels/day 6 months | clinical study | 125 adult students | <i>Prostaglandins Leukot Essent Fatty Acids</i> 2014 Oct;91(4):161–8 | Penn State University Department of Nutritional Science University Park, PA |

| Investigation | Product | Study Design | Subjects | Publication | Organization |
|---|--|--------------------|---|---|--|
| fish oil on endothelial function/vascular inflammation in patients with peripheral arterial disease | ProOmega® (35/25) 8 soft gels/day 3 weeks | clinical study | 80 elderly adults with peripheral arterial disease (PAD) | <i>J Am Heart Assoc</i> 2015 Aug 21;4(8):e002034 | UCSF Vascular & Endovascular Surgery San Francisco, CA |
| atheroprotective mechanisms of borage and echium oils | Nordic™ GLA (borage oil) n/a 8 weeks | pre-clinical study | animal study | <i>J Lipid Res.</i> 2017 Jan; 58(1):236-246. | Wake Forest University Dept. of Physiology Winston-Salem, NC |
| omega-3 Index changes in mediators in the biochemical pathways of resolution | ProOmega® (35/25) 8 soft gels/day 4 weeks | clinical study | 80 elderly adults with peripheral arterial disease (PAD) | <i>J Clin Lipidol.</i> 2017 Sep - Oct;11 (5):1289-1295. | University California, SF Vascular & Endovascular Surgery, SF, CA |
| fish oil and liver function, non-alcoholic steatohepatitis | ProOmega® (35/25) 3 soft gels/day 1 year | clinical study | 64 adults with non-alcoholic steatohepatitis fatty liver (NASH) | <i>J Hepatol</i> 2015 Jan;62(1):190-7 | University of Virginia School of Medicine Charlottesville, VA |
| fish oil supplement for healing gut inflammation and improving gut's capacity to absorb nutrients | ProOmega® (35/25) 1 mL/day 185 days | clinical study | 230 African children (2-3 years) | <i>J Nutr</i> 2014 Dec;144(12):2059-65 | Washington University School of Medicine St Louis, MO |
| colon cancer prevention with omega-3 fatty acids in obesity | ProEPA™ Xtra (60/15) 1 soft gel/day 12 weeks | clinical study | 48 adults with cancer and abdominal obesity | <i>Cancer Prev Res</i> 2017 Nov 13. | U of Michigan, Family Medicine & Environ. Health Sci., Ann Arbor, MI |
| fish oil and GI health, cognition, and morbidity in rural infants | Arctic Omega™ (18/12) ½ teaspoon/day 24 weeks | clinical study | 172 Infants (3-9 months) | <i>Matern Child Nutr.</i> 2011 Apr;7 Suppl 2:89-98. | Medical Research Council Gambia, Africa / UK |
| fish oil and immune health, reducing allergy predispositions | ProEPA™ Xtra (60/15) 2 soft gels/day 6 weeks | clinical study | 86 pregnant women | <i>Am J Obstet Gynecol</i> 2013 Apr;208(4):316.e1-6 | University of Michigan Institute for Clinical & Health Research Ann Arbor, MI |
| the effects of fish oil on the immune response to an acute bout of endurance exercise | ProEPA™ (45/10) 3 soft gels/day 6 weeks | clinical study | 16 healthy males | <i>Brain Behav Immun</i> 2012 Nov;26(8):1265-72 | University of Aberdeen Institute of Medical Sciences Aberdeen, Scotland |
| fish oil on the immune response to an acute bout of endurance exercise | ProEPA™ (45/10) 3 soft gels/day 6 weeks | clinical study | 20 healthy males | <i>Int J Sport Nutr Exerc Metab</i> 2014 Apr;24(2):206-14 | University of Aberdeen Institute of Medical Sciences Aberdeen, Scotland |
| fish oil and Montelukost on asthma | ProOmega® (35/25) 10 soft gels/day 42 days | clinical study | 20 asthmatic adults | <i>PLOS ONE</i> 2010 Oct 18;5(10):e13487 | Indiana University Department of Kinesiology Bloomington, IN |
| effects of fish oil on acute lung injury/inflammation | ProOmega® (35/25) 7.5cc enterally up to 14 days | clinical study | 85 hospitalized patients with acute lung injury | <i>Crit Care Med</i> 2011 Jul;39(7):1655-62 | University of Vermont College of Medicine Burlington, VT |
| fish oil and exercise-induced bronchoconstriction | ProOmega® (35/25) 10 soft gels/day 8 weeks | clinical study | 30 adult students | <i>J Allergy Ther</i> 2014;5:184 | Indiana University Department of Kinesiology Bloomington, IN |
| fish oil compliance and adherence study | ProEPA™ Xtra (60/15) 4 soft gels/day 84 days | clinical study | 28 dialysis patients | <i>J Ren Nutr</i> 2010 Sep;20(5):329-33 | The Institute of Health Queensland University of Technology Queensland, Australia |
| fish oil to decrease the metabolic precursors of kidney stones | ProOmega® (35/25) 2 soft gels/day 30 days | clinical study | 15 healthy, non-stone-forming subjects | <i>Urology.</i> 2014 Oct;84(4):779-81. | Wake Forest University Dept. of Urology Winston-Salem, NC |
| fish oil and glucose uptake with insulin present | ProOmega® ProEPA™, ProDHA™ Arctic Omega™ n/a | pre-clinical study | skeletal muscle cells | <i>Diabetes</i> 2006 June;55(6):A382 | Texas A & M University College Station, TX |
| fish oil (EPA vs. DHA) for postpartum and pregnancy depression | ProEPA™ Xtra (60/15) vs. ProDHA™ (10/50) 2 and 4 soft gels/day 6 weeks | clinical study | 126 pregnant women | <i>Am J Obstet Gynecol.</i> 2013 Apr;208(4):313.e1-9. | University of Michigan Institution for Clinical & Health Research, Ann Arbor, MI |
| DHA for attenuating effects of maternal stress during late pregnancy | ProDHA™ (10/50) 2 soft gels/day 150+ days | clinical study | 90 pregnant African-American women | <i>Obstet Gynecol.</i> 2014 Dec;124(6):1080-7. | University of Pittsburgh Medical Clinic Pittsburgh, PA |

PART 2

CLINICAL ABSTRACTS SUMMARIZED

by

ORGAN SYSTEMS

LIST OF STUDIES ASSOCIATED WITH EACH ORGAN SYSTEM

Nervous System

- 1) Connor / Heart Rate in Anxiety. Abstract
A Pilot Study of the Effect of Omega-3 Fatty Acids on Heart Rate Variability
in Anxiety Disorders / Duke University Medical Center, Durham, NC
- 2) Suliteanu / Behavior. Abstract
Functional and Nutrition Interventions with Foster-Adopt Children Using the HANDLE® Approach:
An Outcome Study / HANDLE Institute/Rays of Hope Orphanage, Saltillo, Mexico
- 3) Buydens-Branchey / Anxiety. Abstract
N-3 Polyunsaturated Fatty Acids Decrease Anxiety Feelings in a Population
of Substance Abusers / VA New York Harbor Healthcare System, Brooklyn, NY
- 4) Buydens-Branchey / Anger. Abstract
Long-Chain N-3 Polyunsaturated Fatty Acids Decrease Feelings of Anger
in Substance Abusers / VA New York Harbor Healthcare System, Brooklyn, NY
- 5) Gertsik / Major Depressive Disorder. Abstract
Omega-3 Fatty Acid Augmentation of Citalopram Treatment for Patients with
Major Depressive Disorder / California Clinical Trials Medical Group, Inc., Glendale, CA
- 6) Maroon / Pain. Abstract
Omega-3 Fatty Acids (Fish Oil) as an Anti-Inflammatory: An Alternative to Non-Steroidal Anti-Inflammatory
Drugs for Discogenic Pain / University of Pittsburgh Medical Center, Pittsburgh, PA
- 7) Wu / Cognition. Abstract
Docosahexaenoic Acid Dietary Supplementation Enhances the Effects of Exercise on Synaptic
Plasticity and Cognition / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 8) Chytrova / Cognition. Abstract
Exercise Contributes to the Effects of DHA Dietary Supplementation by Acting on Membrane-Related
Synaptic Systems / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 9) Patrick / Autism. Abstract
Benefits of Essential Fatty Acid Supplementation on Language and Learning Skills in Children
with Autism and Asperger's Syndrome / Pediatric Clinic, Tucson, AZ
- 10) Gomez-Pinilla / Cognition. Abstract
Differential Effects of Exercise and Dietary Docosahexaenoic Acid on Molecular Systems
Associated with Control of Allostasis in the Hypothalamus and Hippocampus /
UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 11) Wu / Cognition. Abstract
The Salutary Effects of DHA Dietary Supplementation on Cognition, Neuroplasticity, and Membrane
Homeostasis after Brain Trauma / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 12) Bhatia / Cognition. Abstract
Omega-3 Fatty Acid Deficiency during Brain Maturation Reduces Neuronal and Behavioral Plasticity
in Adulthood / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 13) Agrawal / Brain Signaling and Cognition. Abstract
"Metabolic Syndrome" in the Brain: Deficiency in Omega-3 Fatty Acid
Exacerbates Dysfunctions in Insulin Receptor Signaling and Cognition /
UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 14) Sharma / Brain Plasticity and Behavior. Abstract
High-Fat Diet Transition Reduces Brain DHA Levels Associated with Altered Brain Plasticity
and Behavior / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 15) Holly / Neuroprotection. Abstract
Dietary Therapy to Promote Neuroprotection in Chronic Spinal Cord Injury /
UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 16) Joseph / Spinal Cord Learning. Abstract
Effects of Diet and/or Exercise in Enhancing Spinal Cord Sensorimotor Learning /
UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 17) Ying / Brain Injury. Abstract
Dietary Omega-3 Deficiency from Gestation Increases Spinal Cord Vulnerability to Traumatic
Brain Injury-Induced Damage / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA

- 18) Tyagi / Brain TraumaAbstract
Vulnerability Imposed by Diet and Brain Trauma for Anxiety-Like Phenotype: Implications for Post-Traumatic Stress Disorders / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 19) Wu / Brain TraumaAbstract
Dietary Strategy to Repair Plasma Membrane after Brain Trauma: Implications for Plasticity and Cognition / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 20) Agrawal / Brain TraumaAbstract
Coupling Energy Homeostasis with a Mechanism to Support Plasticity in Brain Trauma / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 21) Tyagi / Brain HealthAbstract
TBI and Sex: Crucial Role of Progesterone Protecting the Brain in an Omega-3-Deficient Condition / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 22) Shinto / Alzheimer's DiseaseAbstract
A Randomized Placebo-Controlled Pilot Trial of Omega-3 Fatty Acids and Alpha-Lipoic Acid in Alzheimer's Disease / Oregon Health & Science University, Department of Neurology, Portland, OR
- 23) Mischoulon / Major Depressive DisorderAbstract
A Double-Blind, Randomized Controlled Clinical Trial Comparing Eicosapentaenoic Acid Versus Docosahexaenoic Acid for Depression / Massachusetts General Hospital, Harvard Medical School, Boston, MA
- 24) Rapaport / Major Depressive DisorderAbstract
Inflammation as a Predictive Biomarker for Response to Omega-3 Fatty Acids in Major Depressive Disorder: A Proof-of-Concept Study / Emory University School of Medicine, Atlanta, GA
- 25) Shinto / Depression in Multiple SclerosisAbstract
Omega-3 Fatty Acids for Depression in Multiple Sclerosis: A Randomized Pilot Study / Oregon Health & Science University, Department of Neurology, Portland, OR
- 26) Meng / NeuroprotectionAbstract
Systems Nutrigenomics Reveals Brain Gene Networks Linking Metabolic and Brain Disorders / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 27) Tyagi / NeuroprotectionAbstract
Interactive Actions of Bdnf Methylation and Cell Metabolism for Building Neural Resilience Under the Influence of Diet / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 28) Wozniak / NeurophysiologyAbstract
A Randomized Clinical Trial of High Eicosapentaenoic Acid Omega-3 Fatty Acids and Inositol as Monotherapy and in Combination in the Treatment of Pediatric Bipolar Spectrum Disorders: A Pilot Study / Mass General Hospital/Harvard Medical School, Boston, MA
- 29) Hakimian / CognitionAbstract
Specific Behavioral and Cellular Adaptations Induced by Chronic Morphine are Reduced by Dietary Omega-3 Polyunsaturated Fatty Acids / UCLA, Neurosurgery and Physiological Sciences, Los Angeles, CA
- 30) Sheppard / ASD symptomologyAbstract
Effect of Omega-3 and -6 Supplementation on Language in Preterm Toddlers Exhibiting Autism Spectrum Disorder Symptoms / Nationwide Children's Hospital, Columbus, OH
- 31) Boone / ASD symptomologyAbstract
Omega-3 and -6 Fatty Acid Supplementation and Sensory Processing in Toddlers with ASD Symptomology Born Preterm: A Randomized Controlled Trial / Nationwide Children's Hospital, Columbus, OH
- 32) Wilens / ADHD and DESRAbstract
Pilot Data Supporting Omega-3 Fatty Acids Supplementation in Medicated Children with Attention-Deficit/Hyperactivity Disorder and Deficits in Emotional Self-Regulation / Massachusetts General Hospital, Boston, MA

Cardiovascular System

- 33) Henderson / LipidsAbstract
The Effects of a 4:1 Eicosapentaenoic Acid/Docosahexaenoic Acid Fish Oil Supplement on Plasma Lipid Profile / San Jose State University, San Jose, CA
- 34) Maroon / LipidsAbstract
Lipid Profiles and the Use of Omega-3 Essential Fatty Acids in Professional Football Players / University of Pittsburgh Medical Center, Pittsburgh, PA
- 35) Muhammad / Inflammatory MarkersAbstract
Treatment with N-3 Fatty Acids Reduces Serum C-reactive Protein Concentration / The Cleveland Clinic, Cleveland, OH

- 36) Flock / O-3 Index as a Biomarker of EPA+DHA ConsumptionAbstract
 Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response
 to Fish Oil Supplementation: A Dose-Response Randomized Controlled Trial /
 Penn State University, Department of Nutritional Science, University Park, PA
- 37) Laidlaw / Cardiovascular Risk ReductionAbstract
 A Randomized Clinical Trial to Determine the Efficacy of Manufacturers’ Recommended Doses
 of Omega-3 Fatty Acids from Different Sources in Facilitating Cardiovascular Disease Risk Reduction /
 Nutrasource Diagnostic, Inc., Guelph, ON, Canada
- 38) Flock / Inflammatory Markers.Abstract
 Effects of Supplemental Long-Chain Omega-3 Fatty Acids and Erythrocyte Membrane Fatty Acid
 Content on Circulating Inflammatory Markers in a Randomized Controlled Trial of Healthy Adults /
 Penn State University, Department of Nutritional Science, University Park, PA
- 39) Grenon / Peripheral Artery Disease.Abstract
 Short-Term, High-Dose Fish Oil Supplementation Increases the Production of Omega-3 Fatty Acid-
 Derived Mediators in Patients with Peripheral Artery Disease (the OMEGA-PAD I Trial) /
 UCSF, Vascular & Endovascular Surgery, San Francisco, CA
- 40) Shewale / AtherosclerosisAbstract
 In Vivo Activation of Leukocyte GPR120/FFAR4 by PUFAs Has Minimal Impact on
 Atherosclerosis in LDL Receptor Knockout Mice / Wake Forest School of Medicine, Winston-Salem, NC
- 41) Schaller / The Omega-3 IndexAbstract
 Relationship Between the Omega-3 Index and Specialized Pro-Resolving Lipid Mediators in Patients with Peripheral
 Arterial Disease Taking Fish Oil Supplements / Vascular & Endovascular Surgery, UCSF, San Francisco, CA

Digestive System

- 42) Argo / Liver FunctionAbstract
 Effects of N-3 Fish Oil on Metabolic and Histological Parameters in NASH: A Double-Blind,
 Randomized, Placebo-Controlled Trial / University of Virginia School of Medicine, Charlottesville, VA
- 43) Smith / Gut InflammationAbstract
 Multiple Micronutrient Supplementation Transiently Ameliorates Environmental Enteropathy
 in Malawian Children Aged 12–35 Months in a Randomized Controlled Clinical Trial /
 Washington University School of Medicine, St Louis, MO
- 44) Djuric / Affects of Obesity on CancerAbstract
 The Anti-Inflammatory Effect of Personalized Omega-3 Fatty Acid Dosing for Reducing Prostaglandin E2 in the Colonic
 Mucosa Is Attenuated in Obesity / University of Michigan Medical School, Ann Arbor, MI

Immune System

- 45) van der Merwe / Immune Response: GutAbstract
 Impact of Fatty Acid Status on Immune Function of Children in Low-Income Countries /
 Medical Research Council, Gambia, Africa/UK
- 46) Romero / Immune Response: DevelopmentAbstract
 Developmental Programming for Allergy: A Secondary Analysis of the Mothers, Omega-3, and
 Mental Health Study / University of Michigan, Institute for Clinical & Health Research, Ann Arbor, MI
- 47) Gray / Immune Response: Exercise.Abstract
 Fish Oil Supplementation Augments Post-Exercise Immune Function in Young Males /
 University of Aberdeen Institute of Medical Sciences, Aberdeen, Scotland

Musculoskeletal System

- 48) Gray / Oxidative Stress MarkersAbstract
 Fish Oil Supplementation Reduces Markers of Oxidative Stress but Not Muscle Soreness after
 Eccentric Exercise / University of Aberdeen Institute of Medical Sciences, Aberdeen, Scotland

Respiratory System

- 49) Tecklenburg-Lund / Inflammation: AirwaysAbstract
 Randomized Controlled Trial of Fish Oil and Montelukast and Their Combination
 on Airway Inflammation and Hyperpnea-Induced Bronchoconstriction /
 Indiana University, Department of Kinesiology, Bloomington, IN
- 50) Stapleton / Lung InjuryAbstract
 A Phase II Randomized Placebo-Controlled Trial of Omega-3 Fatty Acids for the Treatment
 of Acute Lung Injury / University of Vermont, College of Medicine, Burlington, VT
- 51) Mickleborough / Inflammation: AirwaysAbstract
 The Effect of Combining Fish Oil and Vitamin C on Airway Inflammation
 and Hyperpnea-Induced Bronchoconstriction in Asthma/
 Indiana University, Department of Kinesiology, Bloomington, IN

Urinary System

- 52) Zabel / Renal DiseaseAbstract
 Adherence to Fish Oil Intervention in Patients with Chronic Kidney Disease /
 The Institute of Health, Queensland University of Technology, Queensland, Australia
- 53) Lange / Urinary OxalatesAbstract
 Fish Oil Supplementation and Urinary Oxalate Excretion in Normal Subjects on a Low-Oxalate Diet / Wake
 Forest Baptist Health Medical Center, Winston-Salem, NC

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- 54) Deyhim / Blood Sugar DysregulationAbstract
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- 55) Mozurkewich / Pre and Postnatal DepressionAbstract
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STUDY ABSTRACTS
ASSOCIATED

with the

NERVOUS SYSTEM

A B S T R A C T

A Pilot Study of the Effect of Omega-3 Fatty Acids on Heart Rate Variability in Anxiety Disorders

Connor K, Zhang W, Payne V, et al. *Neuropsychopharmacology* 2005 Dec;30 Suppl 1:S104.

Background: There is evidence of an effect for omega-3 fatty acids (O3FA) in major depression and for comparable mood stabilizing properties in bipolar disorder. Recognizing the substantial overlap between symptoms of depression and anxiety and high rates of comorbidity between these disorders, it is possible that O3FA may have a role in treating anxiety. A potential role for O3FA in anxiety is suggested by animal data. One mechanism for the activity of O3FA may be through modulation of autonomic balance, as evidenced by improvement in heart rate variability (HRV), which has been found to be impaired in anxiety. Treatment with O3FA can increase HRV in survivors of myocardial infarction. The purpose of this study was to 1) collect pilot data on the effect of O3FA in patients with clinically significant anxiety disorders, and 2) evaluate the effect of O3FA on heart rate variability in this population.

Methods: Adult outpatients aged 18–60 with a primary DSM-IV anxiety disorder and a clinically significant level of symptoms were entered into the trial. Subjects with a history of cardiovascular disease, hypertension, or diabetes, and those taking psychotropic medications or O3FA supplements, were excluded. Eligible subjects received 8 weeks of open label treatment with an O3FA supplement (2100 mg EPA; 1500 mg DHA) daily. Baseline and post-treatment assessments included measures of anxiety, depression, resilience, general psychopathology, global improvement, heart rate variability, and side effects. Treatment response was evaluated by the pre- to post-treatment change in the Hospital Anxiety and Depression Scale (HADS) anxiety subscale score and was analyzed using a Wilcoxon Signed Rank Test. The effects of treatment on autonomic indices (HRV, baroreflex sensitivity, blood pressure, heart rate) and on affective variables of interest were compared using repeated measures ANOVA. Pre- to post-treatment changes in other measures were evaluated as secondary outcomes.

Results: Twenty-five subjects were enrolled, 24 of whom returned for at least one post-baseline assessment. Subjects were predominantly females with either generalized anxiety disorder or social anxiety disorder. Significant improvement was observed on measures of all clinical and self ratings ($p < 0.05$). However, no changes were found on autonomic indices. The treatment was well tolerated.

Discussion: Adults treated with O3FA supplements for 8 weeks demonstrate significant improvement in anxiety, depressive symptoms, general psychopathology, and stress coping. The mechanism by which this occurs does not appear to be through improvement in autonomic tone. Nonetheless, further controlled trials of fatty supplements in anxiety disorders are needed.

PMID: 16299493

Source: <http://www.nature.com/npp/journal/v30/n1s/pdf/1300969a.pdf>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2005 Connor K, et al.

ABSTRACT

Functional and Nutrition Interventions with Foster-Adopt Children Using the HANDLE® Approach: An Outcome Study

Marlene Suliteanu, OTR/L, Vista, CA. Adoption Today 2006 Dec/Jan:38–39.

Introduction: Essential fatty acids in conjunction with neurodevelopmental interventions may contribute to positive behavioral changes in challenged children.

Methods: In an evaluation study of the HANDLE (Holistic Approach to NeuroDevelopment and Learning Efficiency) program, ten boys and ten girls aged 5–14 who were living in a Mexican orphanage were screened according to program criteria and independently ranked by caregivers for behavioral and functional difficulties. Ranking ranged from 0 (“not a problem”) to 8 (“prevents function”). The difficulties included hyperactivity, aggression, impulsivity, emotional lability, reading and math difficulties, and social isolation, among others. Changes were then made to their diet, and activity programs designed to address the functional issues were implemented and carried out by trained caregivers for five months. At the end of the intervention, the children were screened and ranked again. Blinding was maintained in screening and data analysis.

The HANDLE program calls for both functional activities and dietary changes. The HANDLE program is based on specific neurological stimulation and structured movements, dictated by the principle of Gentle Enhancement®. The dietary changes involved making water the principal beverage (replacing a powder-based sugar drink), ensuring a daily portion of animal protein, and adding an essential fatty acid supplement. The children were given 1 gram of ProEFA® Junior [Complete Omega™ Junior], a lemon-flavored blend of fish oil providing EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), and borage oil providing GLA (gamma-linolenic acid), from Nordic Naturals, Watsonville, CA. ProEFA Junior provides 135 mg EPA, 90 mg DHA, and 33 mg GLA per gram. The supplement was well accepted by the children.

Results: After five months, 17 of the 20 children demonstrated significant improvements as measured by decreases in the amount of interference they experienced from their identified functional and behavioral issues. The greatest improvement in function was seen in the 2 children with the most significant problems, whose scores decreased from 59 to 12 and from 36 to 6, respectively. The 3 children who showed little improvement had very low scores at baseline.

Conclusions: This pilot evaluation suggests that behavioral and basic nutritional interventions, including pure essential fatty acid supplements, may contribute to positive functional changes in challenged children.

Healthcare professionals interested in more detail may email Marlene@GetAbleTherapy.com.

Source: <http://adoptinfo.net/> (2006 Dec/Jan)

Study was conducted using ProEFA Jr.™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

Study Details: email Marlene@GetAbleTherapy.com.

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A B S T R A C T

N-3 Polyunsaturated Fatty Acids Decrease Anxiety Feelings in a Population of Substance Abusers

Buydens-Branchey L, Branchey M. J Clin Psychopharmacol 2006 Dec;26(6):661–5.

There is mounting evidence that low levels of n-3 polyunsaturated fatty acids (PUFA) play a role in the pathophysiology of a number of psychiatric disorders. Preclinical studies have shown that n-3 PUFA decrease anxiety-like behaviors, but there is a paucity of information about their effects on anxiety in humans. In light of our observation that substance abusers have poor dietary habits and the strong association between anxiety disorders and substance use disorders, the possibility that the administration of supplements of n-3 PUFA would decrease the anxiety level of a group of substance abusers was explored. Thirteen patients were given, on a daily basis, soft gels containing 3 grams of n-3 PUFA (eicosapentaenoic acid + docosahexaenoic acid). Eleven patients received similar-looking placebo soft gels containing vegetable oil. The trial was double-blind, randomized, and lasted 3 months. A scale assessing anxiety feelings was administered at baseline and on a monthly basis thereafter. Six PUFA group patients and eight placebo group patients were followed for an additional 3 months after treatment discontinuation and administered the same questionnaire monthly. Patients who received n-3 PUFA for 3 months showed a progressive decline in anxiety scores. This was not the case for patients who received placebos. A comparison of the two groups was significant ($P=0.010$). Anxiety scores remained significantly decreased in the PUFA group for 3 months after treatment discontinuation. A comparison of the two groups followed for 6 months was also significant ($P=0.042$). In conclusion, these preliminary data indicate that n-3 PUFA supplementation could be beneficial in the treatment of some patients with anxiety disorders.

PMID: 17110827

Source: <https://www.ncbi.nlm.nih.gov/pubmed/17110827>

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2006 Buydens-Branchey L, et al.

ABSTRACT

Long-Chain N-3 Polyunsaturated Fatty Acids Decrease Feelings of Anger in Substance Abusers

Buydens-Branchey L, Branchey M. Psychiatry Res 2008 Jan 15;157(1-3):95-104.

It has been suggested that low levels of n-3 polyunsaturated fatty acids (PUFA) play a role in the pathophysiology of some psychiatric disorders. In light of the existence of strong associations between high-frequency and high-severity aggressive behaviors and substance use disorders and of our observation that substance abusers have poor dietary habits, the possibility that the administration of supplements of n-3 PUFA would decrease their anger levels was explored.

A lifelong history of aggressive behaviors and problems with the law was obtained in twenty-four patients. Thirteen patients received, on a daily basis, soft gels containing 3 grams of n-3 PUFA (EPA+DHA). Eleven patients received placebo soft gels. The trial was double-blind, randomized, and lasted 3 months. An anger scale was administered at baseline and every month thereafter. Six PUFA group patients and eight placebo group patients were followed for an additional 3 months after treatment discontinuation. Four patients in each group had a history of assaultive behavior.

The baseline fish and n-3 PUFA intakes of these eight patients were significantly lower than those of the non-aggressive patients. When given for 3 months, n-3 PUFA were superior to placebo in diminishing anger scores. These scores remained decreased for 3 months following treatment discontinuation.

These data provide further support to emerging evidence indicating that supplementation with long-chain n-3 PUFA could be beneficial in the treatment of some individuals with aggressive tendencies.

This study was conducted using Nordic Naturals ProEPA™/EPA. The dose used was 5 soft gels/day.

PMID: 17900705

Source: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2225526/?tool=pubmed>

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Omega-3 Fatty Acid Augmentation of Citalopram Treatment for Patients with Major Depressive Disorder

Gertsik L, Poland RE, Bresee C, et al. J Clin Psychopharmacol 2012 Feb;32(1):61–4.

Objective: The objective of this study was to explore the efficacy of combination therapy with citalopram plus omega-3 fatty acids versus citalopram plus placebo (olive oil) in the initial treatment of individuals with major depressive disorder (MDD). We hypothesized that combination therapy would lead not only to greater efficacy but also to a more rapid onset of therapeutic response.

Methods: Forty-two subjects participated in this 9-week randomized, masked, placebo-controlled study of combination therapy (2 one-gram soft gels containing a blend of 900 mg of eicosapentaenoic acid, 200 mg of docosahexaenoic acid, and 100 mg of other omega-3 fatty acids twice daily plus citalopram) versus monotherapy (2 one-gram soft gels of olive oil per day plus citalopram) treatment of MDD.

Results: The combination therapy demonstrated significantly greater improvement in Hamilton Depression Rating scale scores over time ($F=7.32$; $df 1,177$; $P=0.008$) beginning at week four ($t=-2.48$; $df 177$; $P=0.014$).

Conclusions: Combination therapy was more effective than monotherapy in decreasing signs and symptoms of MDD during the 8 weeks of active treatment; however, combination therapy did not seem to enhance the speed of the initial antidepressant response. These findings suggest that there may be an advantage to combining omega-3 fatty acids with a selective serotonin reuptake inhibitor in the initial treatment of individuals with MDD. A larger definitive study is warranted.

This study was conducted using Nordic Naturals ProEPA™/EPA. The dose used was 4 soft gels/day.

PMID: 22198441

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375825/>

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2006 Gertsik L, et al.

ABSTRACT

Omega-3 Fatty Acids (Fish Oil) as an Anti-Inflammatory: An Alternative to Nonsteroidal Anti-Inflammatory Drugs for Discogenic Pain

Maroon JC, Bost JW. Surg Neurol 2006 Apr;65(4):326-31.

Background: The use of NSAID medications is a well-established effective therapy for both acute and chronic nonspecific neck and back pain. Extreme complications, including gastric ulcers, bleeding, myocardial infarction, and even deaths, are associated with their use. An alternative treatment with fewer side effects that also reduces the inflammatory response and thereby reduces pain is believed to be omega-3 EFAs found in fish oil. We report our experience in a neurosurgical practice using fish oil supplements for pain relief.

Methods: From March to June 2004, 250 patients who had been seen by a neurosurgeon and were found to have nonsurgical neck or back pain were asked to take a total of 1200 mg/day of omega-3 EFAs (eicosapentaenoic acid and docosahexaenoic acid) found in fish oil supplements. A questionnaire was sent approximately 1 month after starting the supplement.

Results: Of the 250 patients, 125 returned the questionnaire at an average of 75 days on fish oil. Seventy-eight percent were taking 1200 mg and 22% were taking 2400 mg of EFAs. Fifty-nine percent discontinued taking their prescription NSAID medications for pain. Sixty percent stated that their overall pain was improved, and 60% stated that their joint pain had improved. Eighty percent stated they were satisfied with their improvement, and 88% stated they would continue to take the fish oil. There were no significant side effects reported.

Conclusions: Our results mirror other controlled studies that compared ibuprofen and omega-3 EFAs demonstrating equivalent effect in reducing arthritic pain. Omega-3 EFA fish oil supplements appear to be a safer alternative to NSAIDs for treatment of nonsurgical neck or back pain in this selective group.

PMID: 16531187

Source: [http://www.worldneurosurgery.org/article/S0090-3019\(05\)00774-3/abstract](http://www.worldneurosurgery.org/article/S0090-3019(05)00774-3/abstract)

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Docosahexaenoic Acid Dietary Supplementation Enhances the Effects of Exercise on Synaptic Plasticity and Cognition

Wu A, Ying Z, Gomez-Pinilla F. Neuroscience 2008 Aug 26;155(3):751–9.

Omega-3 fatty acids (e.g., docosahexaenoic acid; DHA), similar to exercise, improve cognitive function, promote neuroplasticity, and protect against neurological lesion. In this study, we investigated a possible synergistic action between DHA dietary supplementation and voluntary exercise on modulating synaptic plasticity and cognition. Rats received DHA dietary supplementation (1.25% DHA) with or without voluntary exercise for 12 days. We found that the DHA-enriched diet significantly increased spatial learning ability, and these effects were enhanced by exercise. The DHA-enriched diet increased levels of pro-brain-derived neurotrophic factor (BDNF) and mature BDNF, whereas the additional application of exercise boosted the levels of both. Furthermore, the levels of the activated forms of CREB and synapsin I were incremented by the DHA-enriched diet with greater elevation by the concurrent application of exercise. While the DHA diet reduced hippocampal oxidized protein levels, a combination of a DHA diet and exercise resulted in a greater reduction rate. The levels of activated forms of hippocampal Akt and CaMKII were increased by the DHA-enriched diet, and with even greater elevation by a combination of diet and exercise. Akt and CaMKII signaling are crucial step by which BDNF exerts its action on synaptic plasticity and learning and memory. These results indicate that the DHA diet enhanced the effects of exercise on cognition and BDNF-related synaptic plasticity, a capacity that may be used to promote mental health and reduce risk of neurological disorders.

PMID: 18620024

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208643/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2008 Wu A, et al.

ABSTRACT

Exercise Contributes to the Effects of DHA Dietary Supplementation by Acting on Membrane-Related Synaptic Systems

Chytrova G, Ying Z, Gomez-Pinilla F. Brain Res 2010 Jun 23;1341:32–40.

Dietary omega-3 fatty acids (e.g., docosahexaenoic acid [DHA]) and exercise are gaining recognition for supporting brain function under normal and challenging conditions. Here we evaluate the possibility that the interaction of DHA and exercise can involve specific elements of the synaptic plasma membrane. We found that voluntary exercise potentiated the effects of a 12-day DHA dietary supplementation regimen on increasing the levels of syntaxin 3 (STX-3) and the growth-associated protein (GAP-43) in the adult rat hippocampus region. STX-3 is a synaptic membrane-bound protein involved in the effects of DHA on membrane expansion. The DHA diet and exercise also elevated levels of the NMDA receptor subunit NR2B, which is important for synaptic function underlying learning and memory. The actions of exercise and DHA dietary supplementation reflected on enhanced learning performance in the Morris water maze as learning ability was associated with higher levels of STX-3 and NR2B. The overall findings reveal a mechanism by which exercise can interact with the function of DHA dietary enrichment to elevate the capacity of the adult brain for axonal growth, synaptic plasticity, and cognitive function.

PMID: 19446534

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2884051/>

Study was conducted using ProDHA™ (in chow) a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2008 Chytrova G, et al.

ABSTRACT

Benefits of Essential Fatty Acid Supplementation on Language and Learning Skills in Children with Autism and Asperger's Syndrome

Patrick L, Salik R. Autism-Asperger's Digest 2005 Jan/Feb:36-37.

Fish oil provides essential fatty acids, which are critical for brain health. Children aged 3–10 years who had been professionally diagnosed with autism or Asperger's syndrome were each given 1 gram of Nordic Naturals ProEFA®-3.6.9 [Complete Omega™] per day for 90 days. On days 0, 45, and 90 of supplementation, 49 developmental items from the Assessment of Basic Language and Learning Skills (ABLLS), a criterion-referenced tool, were used to measure eight primary areas of language and learning: receptive language, requesting, labeling, intraverbals, imitation, play skills, social interaction, and generalization. Eighteen of the initial 22 children completed the 90-day trial. All of the children displayed significant increases in their language and learning skills based upon the ABLLS. A t-test analysis of the data showed high statistical significance in all areas: receptive language, requesting, play skills, intraverbals, and social interaction resulted in a p-value of <0.0001. A p-value of <0.001 was obtained in the areas of labeling and generalization. In addition, a p-value of <0.01 was obtained for vocal imitation. No adverse effects were noted. The highly significant results of this small, open label pilot trial show promise for children with autism spectrum disorder.

Publisher: Autism Ausbergers Digest Magazine – January-February 2005 Issue; <http://fhautism.com/>

Source: <http://store.fhautism.com/p-206-january-february-2005.asp>

Study was conducted using ProEFA™ (formally Complete Omega-3.6.9™), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Differential Effects of Exercise and Dietary Docosahexaenoic Acid on Molecular Systems Associated with Control of Allostasis in the Hypothalamus and Hippocampus

Gomez-Pinilla F, Ying Z. Neuroscience 2010 Jun 16;168(1):130–7.

Given the robust influence of diet and exercise on brain plasticity and disease, we conducted studies to determine their effects on molecular systems important for control of brain homeostasis. Studies were centered on a battery of proteins implicated in metabolic homeostasis that have the potential to modulate brain plasticity and cognitive function, in rat hypothalamus and hippocampus. Adult male rats were exposed to a docosahexaenoic acid (DHA)-enriched diet (1.25% DHA) with or without voluntary exercise for 14 days. Here we report that the DHA diet and exercise influence protein levels of molecular systems important for the control of energy metabolism (primarily phospho-AMPK, silent information regulator type 1), food intake (primarily leptin and ghrelin receptors), stress (primarily glucocorticoid receptors), and 11beta-hydroxysteroid dehydrogenase 1 (11betaHSD1). Exercise or DHA dietary supplementation had differential effects on several of these class proteins, and the concurrent application of both altered the pattern of response elicited by the single applications of diet or exercise. For example, exercise elevated levels of glucocorticoids receptors in the hypothalamus, and the DHA diet had opposite effects, while the concurrent application of diet and exercise suppressed the single effects of diet or exercise. In most of the cases, the hypothalamus and the hippocampus had a distinctive pattern of response to the diet or exercise. The results harmonize with the concept that exercise and dietary DHA exert specific actions on the hypothalamus and hippocampus, with implications for the regulations of brain plasticity and cognitive function.

PMID: 20303394

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225187/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

The Salutary Effects of DHA Dietary Supplementation on Cognition, Neuroplasticity, and Membrane Homeostasis after Brain Trauma

Wu A, Ying Z, Gomez-Pinilla F. *J Neurotrauma* 2011 Oct;28(10):2113–22.

The pathology of traumatic brain injury (TBI) is characterized by the decreased capacity of neurons to metabolize energy and sustain synaptic function, likely resulting in cognitive and emotional disorders. Based on the broad nature of the pathology, we have assessed the potential of the omega-3 fatty acid docosahexaenoic acid (DHA) to counteract the effects of concussive injury on important aspects of neuronal function and cognition. Fluid percussion injury (FPI) or sham injury was performed, and rats were then maintained on a diet high in DHA (1.2% DHA) for 12 days. We found that DHA supplementation, which elevates brain DHA content, normalized levels of brain-derived neurotrophic factor (BDNF), synapsin I (Syn-1), cAMP-responsive element-binding protein (CREB), and calcium/calmodulin-dependent kinase II (CaMKII), and improved learning ability in FPI rats. It is known that BDNF facilitates synaptic transmission and learning ability by modulating Syn-I, CREB, and CaMKII signaling. The DHA diet also counteracted the FPI-reduced manganese superoxide dismutase (SOD) and Sir2 (a NAD⁺-dependent deacetylase). Given the involvement of SOD and Sir2 in promoting metabolic homeostasis, DHA may help the injured brain by providing resistance to oxidative stress. Furthermore, DHA normalized levels of calcium-independent phospholipase A2 (iPLA2) and syntaxin-3, which may help preserve membrane homeostasis and function after FPI. The overall results emphasize the potential of dietary DHA to counteract broad and fundamental aspects of TBI pathology that may translate into preserved cognitive capacity.

PMID: 21851229

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191367/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Omega-3 Fatty Acid Deficiency during Brain Maturation Reduces Neuronal and Behavioral Plasticity in Adulthood

Bhatia HS, Agrawal R, Sharma S, et al. PLOS ONE 2011;6(12):e28451.

Omega-3-fatty acid DHA is a structural component of brain plasma membranes, thereby crucial for neuronal signaling; however, the brain is inefficient at synthesizing DHA. We have asked how levels of dietary n-3 fatty acids during brain growth would affect brain function and plasticity during adult life. Pregnant rats and their male offspring were fed an n-3-adequate diet or n-3-deficient diet for 15 weeks. Results showed that the n-3 deficiency increased parameters of anxiety-like behavior using open field and elevated plus maze tests in the male offspring. Behavioral changes were accompanied by a level reduction in the anxiolytic-related neuropeptide Y-1 receptor, and an increase in the anxiogenic-related glucocorticoid receptor in the cognitive related frontal cortex, hypothalamus, and hippocampus. The n-3 deficiency reduced brain levels of docosahexaenoic acid (DHA) and increased the ratio of n-6/n-3 assessed by gas chromatography. The n-3 deficiency reduced the levels of BDNF and signaling through the BDNF receptor TrkB, in proportion to brain DHA levels, and reduced the activation of the BDNF-related signaling molecule CREB in selected brain regions. The n-3 deficiency also disrupted the insulin signaling pathways as evidenced by changes in insulin receptor (IR) and insulin receptor substrate (IRS). DHA deficiency during brain maturation reduces plasticity and compromises brain function in adulthood. Adequate levels of dietary DHA seem crucial for building long-term neuronal resilience for optimal brain performance and aiding in the battle against neurological disorders.

PMID: 22163304

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3233581/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2011 Bhatia H, et al.

ABSTRACT

“Metabolic Syndrome” in the Brain: Deficiency in Omega-3 Fatty Acid Exacerbates Dysfunctions in Insulin Receptor Signaling and Cognition

Agrawal R, Gomez-Pinilla F. J Physiol 2012 May 15;590(10):2485–99.

We provide novel evidence for the effects of metabolic dysfunctions on brain function using the rat model of metabolic syndrome induced by high fructose intake.

We describe that the deleterious consequences of unhealthy dietary habits can be partially counteracted by dietary supplementation of n-3 fatty acid.

High sugar consumption impaired cognitive abilities and disrupted insulin signaling by engaging molecules associated with energy metabolism and synaptic plasticity; in turn, the presence of docosahexaenoic acid, an n-3 fatty acid, restored metabolic homeostasis.

These findings expand the concept of metabolic syndrome affecting the brain and provide the mechanistic evidence of how dietary habits can interact to regulate brain functions, which can further alter lifelong susceptibility to the metabolic disorders.

PMID: 22473784

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424766/>

Study was conducted using ProDHA™ (in chow) a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

High-Fat Diet Transition Reduces Brain DHA Levels Associated with Altered Brain Plasticity and Behavior

Sharma S, Zhuang Y, Gomez-Pinilla F. Sci Rep 2012;2:431.

To assess how the shift from a healthy diet rich in omega-3 fatty acids to a diet rich in saturated fatty acids affects the substrates for brain plasticity and function, we used pregnant rats fed with omega-3-supplemented diet from their second day of gestation period as well as their male pups for twelve weeks.

Afterwards, the animals were randomly assigned to either a group fed on the same diet or a group fed on a high-fat diet (HFD) rich in saturated fats for three weeks. We found that the HFD increased vulnerability for anxiety-like behavior, and that these modifications harmonized with changes in the anxiety-related NPY1 receptor and the reduced levels of BDNF, and its signalling receptor pTrkB, as well as the CREB protein.

Brain DHA contents were significantly associated with the levels of anxiety-like behavior in these rats.

PMID: 22666534

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362800/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Dietary Therapy to Promote Neuroprotection in Chronic Spinal Cord Injury

Holly LT, Blaskiewicz D, Wu A, et al.. J Neurosurg Spine 2012 Aug;17(2):134–40.

Object: The pathogenesis of cervical spondylotic myelopathy (CSM) is related to both primary mechanical and secondary biological injury. The authors of this study explored a novel, noninvasive method of promoting neuroprotection in myelopathy by using curcumin to minimize oxidative cellular injury and the capacity of omega-3 fatty acids to support membrane structure and improve neurotransmission.

Methods: An animal model of CSM was created using a nonresorbable expandable polymer placed in the thoracic epidural space, which induced delayed myelopathy. Animals that underwent placement of the expandable polymer were exposed to either a diet rich in docosahexaenoic acid and curcumin (DHA-Cur) or a standard Western diet (WD). Twenty-seven animals underwent serial gait testing, and spinal cord molecular assessments were performed after the 6-week study period.

Results: At the conclusion of the study period, gait analysis revealed significantly worse function in the WD group than in the DHA-Cur group. Levels of brain-derived neurotrophic factor (BDNF), syntaxin-3, and 4-hydroxynonenal (4-HNE) were measured in the thoracic region affected by compression and lumbar enlargement. Results showed that BDNF levels in the DHA-Cur group were not significantly different from those in the intact animals but were significantly greater than in the WD group. Significantly higher lumbar enlargement syntaxin-3 in the DHA-Cur animals combined with a reduction in lipid peroxidation (4-HNE) indicated a possible healing effect on the plasma membrane.

Conclusions: Data in this study demonstrated that DHA-Cur can promote spinal cord neuroprotection and neutralize the clinical and biochemical effects of myelopathy.

PMID: 22735048

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951955/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Effects of Diet and/or Exercise in Enhancing Spinal Cord Sensorimotor Learning

Joseph MS, Ying Z, Zhuang Y, et al. PLOS ONE 2012;7(7):e41288.

Given that the spinal cord is capable of learning sensorimotor tasks and that dietary interventions can influence learning involving supraspinal centers, we asked whether the presence of omega-3 fatty acid docosahexaenoic acid (DHA) and the curry spice curcumin (Cur) by themselves or in combination with voluntary exercise could affect spinal cord learning in adult spinal mice.

Using an instrumental learning paradigm to assess spinal learning, we observed that mice fed a diet containing DHA/Cur performed better in the spinal learning paradigm than mice fed a diet deficient in DHA/Cur. The enhanced performance was accompanied by increases in the mRNA levels of molecular markers of learning; i.e., BDNF, CREB, CaMKII, and syntaxin 3. Concurrent exposure to exercise was complementary to the dietary treatment effects on spinal learning.

The diet containing DHA/Cur resulted in higher levels of DHA and lower levels of omega-6 fatty acid arachidonic acid (AA) in the spinal cord than the diet deficient in DHA/Cur. The level of spinal learning was inversely related to the ratio of AA:DHA.

These results emphasize the capacity of select dietary factors and exercise to foster spinal cord learning. Given the non-invasiveness and safety of the modulation of diet and exercise, these interventions should be considered in light of their potential to enhance relearning of sensorimotor tasks during rehabilitative training paradigms after a spinal cord injury.

PMID: 22911773

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3401098/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Dietary Omega-3 Deficiency from Gestation Increases Spinal Cord Vulnerability to Traumatic Brain Injury-Induced Damage

Ying Z, Feng C, Agrawal R, et al. PLOS ONE 2012;7(12):e52998.

Although traumatic brain injury (TBI) is often associated with gait deficits, the effects of TBI on spinal cord centers are poorly understood. We seek to determine the influence of TBI on the spinal cord, and the potential of dietary omega-3 (n-3) fatty acids to counteract these effects.

Male rodents exposed to diets containing adequate or deficient levels of n-3 since gestation received a moderate fluid percussion injury when becoming 14 weeks old.

TBI reduced levels of molecular systems important for synaptic plasticity (BDNF, TrkB, and CREB) and plasma membrane homeostasis (4-HNE, iPLA2, syntaxin-3) in the lumbar spinal cord.

These effects of TBI were more dramatic in the animals exposed to the n-3 deficient diet. Results emphasize the comprehensive action of TBI across the neuroaxis, and the critical role of dietary n-3 as a means to build resistance against the effects of TBI.

PMID: 23300842

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3532480/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

© 2012 Ying Z, et al.

ABSTRACT

Vulnerability Imposed by Diet and Brain Trauma for Anxiety-Like Phenotype: Implications for Post-Traumatic Stress Disorders

Tyagi E, Agrawal R, Zhuang Y, et al. PLOS ONE 2013;8(3):e57945.

Mild traumatic brain injury (mTBI, cerebral concussion) is a risk factor for the development of psychiatric illness such as posttraumatic stress disorder (PTSD).

We sought to evaluate how omega-3 fatty acids during brain maturation can influence challenges incurred during adulthood (transitioning to unhealthy diet and mTBI) and predispose the brain to a PTSD-like pathobiology. Rats exposed to diets enriched or deficient in omega-3 fatty acids (n-3) during their brain maturation period were transitioned to a western diet (WD) when becoming adult and then subjected to mTBI.

TBI resulted in an increase in anxiety-like behavior and its molecular counterpart NPY1R, a hallmark of PTSD, but these effects were more pronounced in the animals exposed to an n-3-deficient diet and switched to WD.

The n-3 deficiency followed by WD disrupted BDNF signaling and the activation of elements of BDNF signaling pathway (TrkB, CaMKII, Akt, and CREB) in frontal cortex. TBI worsened these effects, and more prominently in combination with the n-3-deficiency condition. Moreover, the n-3 deficiency primed the immune system to the challenges imposed by the WD and brain trauma as evidenced by results showing that the WD or mTBI affected brain IL1b levels and peripheral Th17 and Treg subsets only in animals previously conditioned to the n-3-deficient diet.

These results provide novel evidence for the capacity of maladaptive dietary habits to lower the threshold for neurological disorders in response to challenges.

PMID: 23483949

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3590222/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Dietary Strategy to Repair Plasma Membrane after Brain Trauma: Implications for Plasticity and Cognition

Wu A, Ying Z, Gomez-Pinilla F. *Neurorehabil Neural Repair* 2014 Jan;28(1):75–84.

Damage to the plasma membrane is a prevalent but often-neglected aspect of traumatic brain injury (TBI), which can impair neuronal signaling and hamper neurological recovery.

Objective: This study was performed to assess a new noninvasive intervention to counteract peroxidative damage to the phospholipids in the membrane using the powerful action of foods. Although dietary docosahexaenoic acid (C22:6n-3; DHA) provides protection against TBI, the pervasive effects of TBI that cause phospholipid damage, including to DHA, raises concerns about how to preserve DHA in the brain for optimal functional recovery.

Methods: Rats were maintained on curcumin and/or DHA-enriched diets for 2 weeks post injury, and their brains were subjected to analyses.

Results: Fluid percussion injury reduced DHA levels as well as levels of enzymes involved in the metabolism of DHA, such as FADS2 and 17 β -HSD4, and elevated levels of markers of lipid peroxidation, such as 4-hydroxy-2-nonenal (4-HNE) and 4-hydroxy-2-hexenal (4-HHE). These effects were counteracted by DHA or curcumin, whereas the combination of curcumin and DHA had an enhanced effect on DHA and 4-HNE. The combination of curcumin and DHA was also efficient in counteracting reductions in the plasticity markers, brain-derived neurotrophic factor and its receptor p-trkB, and learning ability, which had been lessened after TBI.

Conclusions: Curcumin complements the action of DHA on TBI pathology, and this property appears to be a viable strategy to counteract neuronal dysfunction after TBI and complement the application of rehabilitative interventions to foster functional recovery.

PMID: 23911971

Source: [http://journals.sagepub.com/doi/abs/10.1177/1545968313498650?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&Study was conducted using ProDHA™ \(in chow\), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.](http://journals.sagepub.com/doi/abs/10.1177/1545968313498650?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&Study%20was%20conducted%20using%20ProDHA%20(in%20chow),%20a%20patented%20fish%20oil%20blend%20from%20Nordic%20Naturals%20Inc.,%20Watsonville%20CA)

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ABSTRACT

Coupling Energy Homeostasis with a Mechanism to Support Plasticity in Brain Trauma

Agrawal R, Tyagi E, Vergnes L, et al. Biochim Biophys Acta 2014 Apr;1842(4):535–46.

Metabolic dysfunction occurring after traumatic brain injury (TBI) is an important risk factor for the development of psychiatric illness.

In the present study, we utilized an omega-3 diet during early life as a metabolic preconditioning to alter the course of TBI during adulthood. TBI animals under omega-3 deficiency were more prone to alterations in energy homeostasis (adenosine monophosphate-activated protein kinase; AMPK phosphorylation and cytochrome C oxidase II; COII levels) and mitochondrial biogenesis (peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC-1 α and mitochondrial transcription factor A; TFAM).

A similar response was found for brain-derived neurotrophic factor (BDNF) and its signaling through tropomyosin receptor kinase B (TrkB). The results from *in vitro* studies showed that 7,8-dihydroxyflavone (7,8-DHF), a TrkB receptor agonist, upregulates the levels of biogenesis activator PGC-1 α , and CREB phosphorylation in neuroblastoma cells, suggesting that BDNF-TrkB signaling is pivotal for engaging signals related to synaptic plasticity and energy metabolism.

The treatment with 7,8-DHF elevated the mitochondrial respiratory capacity, which emphasizes the role of BDNF-TrkB signaling as mitochondrial bioenergetics stimulator.

Omega-3 deficiency worsened the effects of TBI on anxiety-like behavior and potentiated a reduction of anxiolytic neuropeptide Y1 receptor (NPY1R). These results highlight the action of metabolic preconditioning for building long-term neuronal resilience against TBI incurred during adulthood.

Overall, the results emphasize the interactive action of metabolic and plasticity signals for supporting neurological health.

PMID: 24345766

Source: <http://www.sciencedirect.com/science/article/pii/S0925443913003591>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

TBI and Sex: Crucial Role of Progesterone Protecting the Brain in an Omega-3 Deficient Condition

Tyagi E, Agrawal R, Ying Z, et al. Exp Neurol 2014 Mar;253:41–51.

We assessed whether the protective action of progesterone on traumatic brain injury (TBI) could be influenced by the consumption of omega-3 fatty acids during early life.

Pregnant Sprague-Dawley rats were fed an omega-3-adequate or -deficient diet from third day of pregnancy, and their female offspring were kept on the same diets up to the age of 15 weeks. Ovariectomy was performed at the age of 12 weeks to deprive animals from endogenous steroids until the time of a fluid percussion injury (FPI).

Dietary n-3 fatty acid deficiency increased anxiety in sham animals, and TBI aggravated the effects of the deficiency. Progesterone replacement counteracted the effects of TBI on the animals reared under n-3 deficiency. A similar pattern was observed for markers of membrane homeostasis such as 4-Hydroxynonenal (HNE) and secreted phospholipases A2 (sPLA2), synaptic plasticity such as brain-derived neurotrophic factor (BDNF), syntaxin (STX)-3 and growth-associated protein (GAP)-43, and for growth-inhibitory molecules such as myelin-associated glycoprotein (MAG) and Nogo-A.

Results that progesterone had no effects on sham n-3-deficient animals suggest that the availability of progesterone is essential under injury conditions. Progesterone treatment counteracted several parameters related to synaptic plasticity and membrane stability reduced by FPI and n-3 deficiency suggest potential targets for therapeutic applications.

These results reveal the importance of n-3 preconditioning during early life and the efficacy of progesterone therapy during adulthood to counteract weaknesses in neuronal and behavioral plasticity.

PMID: 24361060

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005409/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

A Randomized Placebo-Controlled Pilot Trial of Omega-3 Fatty Acids and Alpha-Lipoic Acid in Alzheimer's Disease

Shinto L, Quinn J, Montine T, et al. J Alzheimers Dis 2014;38(1):111–20.

Oxidative stress, inflammation, and increased cholesterol levels are all mechanisms that have been associated with Alzheimer's disease (AD) pathology. Several epidemiologic studies have reported a decreased risk of AD with fish consumption.

This pilot study was designed to evaluate the effects of supplementation with omega-3 fatty acids alone (ω -3) or omega-3 plus alpha-lipoic acid (ω -3 + LA) compared to placebo on oxidative stress biomarkers in AD.

The primary outcome measure was peripheral F2-isoprostane levels (oxidative stress measure). Secondary outcome measures included performance on: Mini-Mental State Examination (MMSE), Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL), and Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog).

Thirty-nine AD subjects were randomized to one of three groups:

- 1) placebo,
- 2) ω -3, or
- 3) ω -3 + LA for a treatment duration of 12 months.

Eighty seven percent (34/39) of the subjects completed the 12-month intervention. There was no difference between groups at 12 months in peripheral F2-isoprostane levels ($p=0.83$). The ω -3 + LA and ω -3 were not significantly different than the placebo group in ADAS-cog ($p=0.98$, $p=0.86$) and in ADL ($p=0.15$, $p=0.82$).

Compared to placebo, the ω -3 + LA showed less decline in MMSE ($p<0.01$) and IADL ($p=0.01$), and the ω -3 group showed less decline in IADL ($p<0.01$). The combination of ω -3 + LA slowed cognitive and functional decline in AD over 12 months.

Because the results were generated from a small sample size, further evaluation of the combination of omega-3 fatty acids plus alpha-lipoic acid as a potential treatment in AD is warranted.

PMID: 24077434

Clinical Trial Registration: NCT00090402

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886557/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

A Double Blind, Randomized Controlled Clinical Trial Comparing Eicosapentaenoic Acid versus Docosahexaenoic Acid for Depression

Mischoulon D, Nierenberg A, Schettler P, et al. J Clin Psychiatry. 2014 Sep 16.

Objective: To compare two omega-3 (n-3) preparations enriched with eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA), as monotherapy for major depressive disorder (MDD) in a 2-site, placebo-controlled, randomized, double-blind clinical trial.

Methods: 196 adults (53% female; age 44.7 ± 13.4 years) with DSM-IV MDD and a baseline 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 15 , were randomized equally from 05/18/06 to 06/30/11, to 8 weeks of double-blind treatment with oral EPA-enriched n-3 1000 mg/day, DHA-enriched n-3 1000 mg/day, or placebo.

Results: 154 subjects completed the study. Modified Intent-to-Treat (MITT) analysis (n=177 subjects with ≥ 1 post-baseline visit; 59.3% female, age 45.8 ± 12.5 years) employed mixed model repeated measures (MMRM). All "牧峻癯" 3 groups demonstrated statistically significant improvement in the HAM-D-17 (primary outcome measure), Quick Inventory of Depressive Symptomatology (QIDS-SR), and Clinical Global Improvement-Severity Scale (CGI-S) ($P < 0.05$), but neither n-3 preparation separated from placebo ($P > 0.05$). Response and remission rates were in the range of 40-50% and 30% respectively, for all treatments, with no significant differences between groups. One EPA-enriched subject discontinued due to worsening depression, and one placebo subject discontinued due to an unspecified "negative reaction" to pills.

Conclusions: Neither EPA-enriched nor DHA-enriched n-3 was superior to placebo for the treatment of MDD.

PMID: 25272149

Clinical Trial Registration: NCT00517036

Source: <https://www.ncbi.nlm.nih.gov/pubmed/25272149>

Study was conducted using Nordic Naturals EPA Xtra[®] vs. DHA[®], patented fish oil blends from Nordic Naturals, Inc, Watsonville, CA.

ABSTRACT

Inflammation as a Predictive Biomarker for Response to Omega-3 Fatty Acids in Major Depressive Disorder: A Proof-of-Concept Study

Rapaport MH, Nierenberg AA, Schettler PJ, et al. *Mol Psychiatry* 2016 Jan;21(1):71–9.

Objective: This study explores whether inflammatory biomarkers act as moderators of clinical response to omega-3 (n-3) fatty acids in subjects with major depressive disorder (MDD).

Methods: One hundred fifty-five subjects with *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) MDD, a baseline 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 15 , and baseline biomarker data (interleukin [IL]-1ra, IL-6, high-sensitivity C-reactive protein [hs-CRP], leptin, and adiponectin) were randomized between May 18, 2006 and June 30, 2011 to 8 weeks of double-blind treatment with eicosapentaenoic acid (EPA)-enriched n-3 1060 mg day⁻¹, docosahexaenoic acid (DHA)-enriched n-3 900 mg day⁻¹, or placebo. Outcomes were determined using mixed model repeated measures analysis for “high” and “low” inflammation groups based on individual and combined biomarkers. Results are presented in terms of standardized treatment effect size (ES) for change in HAM-D-17 from baseline to treatment week 8.

Results: Although overall treatment group differences were negligible (ES=-0.13 to +0.04), subjects with any “high” inflammation improved more on EPA than placebo (ES=-0.39) or DHA (ES=-0.60), and less on DHA than placebo (ES=+0.21); furthermore, EPA-placebo separation increased with increasing numbers of markers of high inflammation. Subjects randomized to EPA with “high” IL-1ra or hs-CRP or low adiponectin (“high” inflammation) had medium ES decreases in HAM-D-17 scores *versus* subjects “low” on these biomarkers. Subjects with “high” hs-CRP, IL-6, or leptin were less placebo-responsive than subjects with low levels of these biomarkers (medium to large ES differences).

Conclusions: Employing multiple markers of inflammation facilitated identification of a more homogeneous cohort of subjects with MDD responding to EPA *versus* placebo in our cohort. Studies are needed to replicate and extend this proof-of-concept work.

PMID: 25802980

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4581883/>

Study was conducted using ProEP Xtra™ vs. ProDHA™, patented fish oil blends from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Omega-3 Fatty Acids for Depression in Multiple Sclerosis: A Randomized Pilot Study

Shinto L, Marracci G, Mohr DC, et al. PLOS ONE 2016 Jan 22;11(1):e0147195.

Multiple sclerosis is the most common chronic disabling disease in the central nervous system in young to middle aged adults. Depression is common in multiple sclerosis (MS), affecting 50–60% of patients. Pilot studies in unipolar depression report an improvement in depression when omega-3 fatty acids are given with antidepressants. The objective of this study was to investigate whether omega-3 fatty acid supplementation, as an augmentation therapy, improves treatment-resistant major depressive disorder (MDD) in people with MS. We performed a randomized, double-blind, placebo-controlled pilot study of omega-3 fatty acids 6 g/day over three months. The primary outcome was a 50% or greater improvement on the Montgomery-Asberg Depression Rating Scale (MADRS). Thirty-nine participants were randomized and thirty-one completed the 3-month intervention. Improvement on MADRS between groups was not significantly different at the 3-month end point, with 47.4% in the omega-3 fatty acid group and 45.5% in the placebo group showing 50% or greater improvement ($p=0.30$). Omega-3 fatty acids as an augmentation therapy for treatment-resistant depression in MS was not significantly different than placebo in this pilot trial. Omega-3 fatty acid supplementation at the dose given was well-tolerated over 3 months.

PMID: 26799942

Clinical Trial Registration: NCT00122954

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723316/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Systems Nutrigenomics Reveals Brain Gene Networks Linking Metabolic and Brain Disorders

Meng Q, Ying Z, Noble E, et al. EBioMedicine 2016 April.

Nutrition plays a significant role in the increasing prevalence of metabolic and brain disorders. Here we employ systems nutrigenomics to scrutinize the genomic bases of nutrient-host interaction underlying disease predisposition or therapeutic potential.

We conducted transcriptome and epigenome sequencing of hypothalamus (metabolic control) and hippocampus (cognitive processing) from a rodent model of fructose consumption, and identified significant reprogramming of DNA methylation, transcript abundance, alternative splicing, and gene networks governing cell metabolism, cell communication, inflammation, and neuronal signaling. These signals converged with genetic causal risks of metabolic, neurological, and psychiatric disorders revealed in humans.

Gene network modeling uncovered the extracellular matrix genes *Bgn* and *Fmod* as main orchestrators of the effects of fructose, as validated using two knockout mouse models. We further demonstrate that an omega-3 fatty acid, DHA, reverses the genomic and network perturbations elicited by fructose, providing molecular support for nutritional interventions to counteract diet-induced metabolic and brain disorders.

Our integrative approach complementing rodent and human studies supports the applicability of nutrigenomics principles to predict disease susceptibility and to guide personalized medicine.

PMID: 27322469

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4909610/>

Study was conducted using ProDHA™ (in chow), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Interactive Actions of Bdnf Methylation and Cell Metabolism for Building Neural Resilience Under the Influence of Diet

Tyagi E, Zhuang Y, Agrawal R., et al. Neurobiol Dis. 2015 Jan;73:307-18.

Quality nutrition during the period of brain formation is a predictor of brain functional capacity and plasticity during adulthood; however it is not clear how this conferred plasticity imparts long-term neural resilience. Here we report that early exposure to dietary omega-3 fatty acids orchestrates key interactions between metabolic signals and Bdnf methylation creating a reservoir of neuroplasticity that can protect the brain against the deleterious effects of switching to a Western diet (WD).

We observed that the switch to a WD increased Bdnf methylation specific to exon IV, in proportion to anxiety-like behavior, in Sprague Dawley rats reared in low omega-3 fatty acid diet, and these effects were abolished by the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine. Blocking methylation also counteracted the reducing action of WD on the transcription regulator CTCF binding to Bdnf promoter IV. In vitro studies confirmed that CTCF binding to Bdnf promoter IV is essential for the action of DHA on BDNF regulation.

Diet is also intrinsically associated to cell metabolism, and here we show that the switch to WD downregulated cell metabolism (NAD/NADH ratio and SIRT1). The fact that DNA methyltransferase inhibitor did not alter these parameters suggests they occur upstream to methylation. In turn, the methylation inhibitor counteracted the action of WD on PGC-1, a mitochondrial transcription co-activator and BDNF regulator, suggesting that PGC-1 is an effector of Bdnf methylation.

Results support a model in which diet can build an "epigenetic memory" during brain formation that confers resilience to metabolic perturbations occurring in adulthood.

PMID: 25283985

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4754354/>

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ABSTRACT

A Randomized Clinical Trial of High Eicosapentaenoic Acid Omega-3 Fatty Acids and Inositol as Monotherapy and in Combination in the Treatment of Pediatric Bipolar Spectrum Disorders: A Pilot Study

Wozniak J., Faraone S., Chan J., et al. J Clin Psychiatry. 2015 Nov;76(11):1548-55.

Objective: We conducted a 12-week, randomized, doubleblind controlled clinical trial to evaluate the effectiveness and tolerability of high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega-3 fatty acids and inositol as monotherapy and in combination in children with Bipolar spectrum disorders.

Method: Participants were children 5–12 years of age meeting DSM-IV diagnostic criteria for bipolar spectrum disorders (bipolar I or II disorder or bipolar disorder not otherwise specified [NOS]) and displaying mixed, manic, or hypomanic symptoms. Subjects with severe illness were excluded. Subjects were randomized to 1 of 3 treatment arms: inositol plus placebo, omega-3 fatty acids plus placebo, and the combined active treatment of omega-3 fatty acids plus inositol. Data were collected from February 2012 to November 2013.

Results: Twenty-four subjects were exposed to treatment (≥ 1 week of study completed) (inositol [$n = 7$], omega-3 fatty acids [$n = 7$], and omega-3 fatty acids plus inositol [$n = 10$]). Fiftyfour percent of the subjects completed the study. Subjects randomized to the omega-3 fatty acids plus inositol arm had the largest score decrease comparing improvement from baseline to end point with respect to the Young Mania Rating Scale ($P < .05$). Similar results were found for the Children's Depression Rating Scale ($P < .05$) and the Brief Psychiatric Rating Scale ($P < .05$).

Conclusions: Results of this pilot randomized, doubleblind, controlled trial suggest that the combined treatment of omega-3 fatty acids plus inositol reduced symptoms of mania and depression in prepubertal children with mild to moderate bipolar spectrum disorders. Results should be interpreted in light of limitations, which include exclusion of severely ill subjects, 54% completion rate, and small sample size.

PMID: 26646031

Trial Registration: NCT01396486

Source: <http://www.psychiatrist.com/jcp/article/Pages/2015/v76n11/v76n1124.aspx>

Study was conducted using ProOmega® Jr., a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Specific Behavioral And Cellular Adaptations Induced By Chronic Morphine Are Reduced By Dietary Omega-3 Polyunsaturated Fatty Acids

Hakimian J,†Minasyan A,†Zhe-Ying L, et al. PLoS One.†2017 Apr 5;12(4):e0175090.

Opiates, one of the oldest known drugs, are the benchmark for treating pain. Regular opioid exposure also induces euphoria making these compounds addictive and often misused, as shown by the current epidemic of opioid abuse and overdose mortalities. In addition to the effect of opioids on their cognate receptors and signaling cascades, these compounds also induce multiple adaptations at cellular and behavioral levels.

As omega-3 polyunsaturated fatty acids (n-3 PUFAs) play a ubiquitous role in behavioral and cellular processes, we proposed that supplemental n-3 PUFAs, enriched in docosahexanoic acid (DHA), could offset these adaptations following chronic opioid exposure. We used an 8 week regimen of n-3 PUFA supplementation followed by 8 days of morphine in the presence of this diet. We first assessed the effect of morphine in different behavioral measures and found that morphine increased anxiety and reduced wheel-running behavior.

These effects were reduced by dietary n-3 PUFAs without affecting morphine-induced analgesia or hyperlocomotion, known effects of this opiate acting at mu opioid receptors. At the cellular level we found that morphine reduced striatal DHA content and that this was reversed by supplemental n-3 PUFAs.

Chronic morphine also increased glutamatergic plasticity and the proportion of Grin2B-NMDARs in striatal projection neurons. This effect was similarly reversed by supplemental n-3 PUFAs.

Gene analysis showed that supplemental PUFAs offset the effect of morphine on genes found in neurons of the dopamine receptor 2 (D2)-enriched indirect pathway but not of genes found in dopamine receptor 1(D1)-enriched direct-pathway neurons. Analysis of the D2 striatal connectome by a retrogradely transported pseudorabies virus showed that n-3 PUFA supplementation reversed the effect of chronic morphine on the innervation of D2 neurons by the dorsomedial prefrontal and piriform cortices.

Together these changes outline specific behavioral and cellular effects of morphine that can be reduced or reversed by dietary n-3 PUFAs.

PMID: 28380057

Source: <https://www.ncbi.nlm.nih.gov/pubmed/28380057>

This study was conducted using ProDHA[®] in chow. ProDHA[®] a patented fish oil blend from Nordic Naturals, Inc, Watsonville, CA.

ABSTRACT

Effect of Omega-3 and -6 Supplementation on Language in Preterm Toddlers Exhibiting Autism Spectrum Disorder Symptoms

Sheppard KW, Boone KM, Gracious B, et al.

Delayed language development may be an early indicator of autism spectrum disorder (ASD). Early intervention is critical for children with†ASD, and the present study presents pilot data on a clinical trial of omega-3 and -6 fatty acid supplementation and language development, a secondary trial outcome, in children at risk for†ASD. We randomized 31 children to receive an omega-3 and -6 supplement or a placebo for 3 months, and measured their language abilities at baseline and after supplementation. Gesture use, but not word production, increased for children in the treatment group more than children in the placebo group. These results suggest possible effectiveness of omega-3 and -6 supplementation for language development in children at risk for†ASD.

PMID: 28748334

Clinical Trial Registration: NCT01683565

Source: <https://www.ncbi.nlm.nih.gov/pubmed/28748334>

This study was conducted using Complete Omega, Junioró, liquid a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Omega-3 and -6 Fatty Acid Supplementation and Sensory Processing In Toddlers With ASD Symptomology Born Preterm: A Randomized Controlled Trial

Boone K, Gracious B, Klebanoff M, et al. Early Human Development 115 (2017) 64–70.

Background: Despite advances in the health and long-term survival of infants born preterm, they continue to face developmental challenges including higher risk for autism spectrum disorder (ASD) and atypical sensory processing patterns.

Aims: This secondary analysis aimed to describe sensory profiles and explore effects of combined dietary docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and gamma-linolenic acid (GLA) supplementation on parent-reported sensory processing in toddlers born preterm who were exhibiting ASD symptoms.

Study design: 31 children aged 18

Study design: 31 children aged 18–38 months who were born at ≤ 29 weeks' gestation.

Outcome measure: Mixed effects regression analyses followed intent to treat and explored effects on parent reported sensory processing measured by the Infant/Toddler Sensory Profile (ITSP).

Results: Baseline ITSP scores reflected atypical sensory processing, with the majority of atypical scores falling below the mean. Sensory processing sections: auditory (above =0%, below =65%), vestibular (above =13%, below =48%), tactile (above=3%, below=35%), oral sensory (above =10%; below =26%), visual (above =10%, below=16%); sensory processing quadrants: low registration (above=3%; below=71%), sensation avoiding (above =3%; below =39%), sensory sensitivity (above =3%; below =35%), and sensation seeking (above =10%; below=19%). Twenty-eight of 31 children randomized had complete outcome data. Although not statistically significant ($p= 0.13$), the magnitude of the effect for reduction in behaviors associated with sensory sensitivity was medium to large (effect size =0.57). No other scales reflected a similar magnitude of effect size (range: 0.10 to 0.32).

Conclusions: The findings provide support for larger randomized trials of omega fatty acid supplementation for children at risk of sensory processing difficulties, especially those born preterm.

PMID: 28941976

Clinical Trial Registration: NCT01683565

Source: <https://www.ncbi.nlm.nih.gov/pubmed/28941976>

ABSTRACT

Pilot Data Supporting Omega-3 Fatty Acids Supplementation in Medicated Children with Attention-Deficit/Hyperactivity Disorder and Deficits in Emotional Self-Regulation

Wilens TE,†Carrellas NW,†Zulauf C, et al. J Child Adolesc Psychopharmacol.†2017 Oct;27(8):755-756.

Recent work has demonstrated that individuals with attention-deficit/hyperactivity disorder (ADHD) are at elevated risk for deficits in emotional self-regulation (DESR) (Surman et al. 2010). DESR traits include low frustration tolerance, impatience, quickness to anger, moodiness, and being easily (over)excited to emotional reactions (Barkley 2010). Research also suggests that changes in DESR may not routinely follow changes in ADHD symptoms during treatment trials (Shaw et al. 2014). Despite the link between ADHD and DESR, little has been completed in terms targeted treatment trials of individuals with ADHD who manifest DESR. Although limited, the literature suggests that omega-3 fatty acids (FAs) supplementation may have a modest impact in the management of severe mood dysregulation (Osher et al. 2005; Wozniak et al. 2007). To this end, we examined the effectiveness and tolerability of adjunct omega-3 FAs for the treatment of DESR and ADHD symptoms in children with ADHD who were treated with stimulant or nonstimulant medications and who continued to manifest clinically significant DESR.

Our findings derived from omega-3 FA supplementation to ADHD medication in children with ADHD and DESR showed relatively rapid improvements in mood (DESR), but few improvements in ADHD symptoms. The omega-3 FAs were well tolerated. These pilot data with a nutraceutical provide encouraging support for a larger controlled trial of omega-3 FAs as adjunct therapy for residual DESR in treated ADHD youth.

PMID: 28661708

Source: <https://www.ncbi.nlm.nih.gov/pubmed/28661708>

STUDY ABSTRACTS
ASSOCIATED
with the

CARDIOVASCULAR SYSTEM

ABSTRACT

The Effects of a 4:1 Eicosapentaenoic Acid/ Docosahexaenoic Acid Fish Oil Supplement on Plasma Lipid Profile

Henderson S, Lampel J, Hollenbeck C. J Am Dietetic Assoc 2008 Sept;108;9:A104.

Learning Objectives: Participants will learn the effects of 4 weeks of supplementation with a 4:1 mixture of EPA/DHA on plasma lipids in normal, healthy individuals.

Abstract Text: Previous research reports that diet supplementation with omega-3 fatty acids in a 3:2 EPA/DHA ratio from fish oil has been associated with reduced risk of myocardial infarction and coronary heart disease. The purpose of this study was to assess the effects of 4:1 EPA/DHA fish oil supplements on plasma lipid levels.

A 4-week randomized, double-blind, placebo-controlled, parallel designed study was carried out in 25 healthy, normal-lipemic adult subjects. The experimental group (n=13) was supplemented with 3 g/day of 4:1 EPA/DHA fish oil soft gels, while the control group (n=12) received a placebo containing 3 g/day of soybean oil. Both soft gels contained lemon oil to disguise the nature of the oil. All subjects were instructed to maintain usual diet and lifestyle patterns throughout the study. Blood samples were obtained after a 12-hour fast at baseline and at 4 weeks following supplementation for the measurement of total cholesterol (Total-C), VLDL-C, LDL-C, HDL-C, and total triglyceride (T-TG).

There were no significant differences in age, gender, T-TGs, VLDL-C, LDL-C, HDL-C, or T-TG at baseline between the experimental and control group. At the end of 4 weeks there was a small, quantitative increase in LDL-C in the experimental group, as a function of VLDL clearance, and a significant decrease in T-TGs (97 ± 13 versus 74 ± 7).

The results of the present study demonstrate that 3 g/day of 4:1 EPA/DHA fish oil supplement had a significant effect on plasma triglyceride concentrations, and suggest that supplementation of omega-3 fatty acids may provide clinical benefit in healthy, normal-lipemic individuals.

Source: [http://www.andjrn.org/article/S0002-8223\(08\)01139-5/fulltext](http://www.andjrn.org/article/S0002-8223(08)01139-5/fulltext)

Study was conducted using ProEPA Xtra™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Lipid Profiles and the Use of Omega-3 Essential Fatty Acids in Professional Football Players

Joseph Maroon, MD, Pittsburgh, PA.

Review of the article, "Evaluation of lipid profiles and the use of omega-3 essential fatty acids in professional football players." Authors: Anthony Yates, MD, John Norwig, ATC, Joseph C. Maroon, MD, Jeffrey Bost, PA-C, James P. Bradley, MD, Mark Duca, MD, Daniel A. Wecht, MD, Ryan Grove, ATC, Ariko Iso, ATC, Ingrid Cobb, MD, Nathan Ross, BS and Meghan Borden, BD; published in Sports Health: A Multidisciplinary Approach, 2009;1:21.

Introduction: The following review summarizes a recent study done with professional football players and how blood cholesterol (lipid) subfractions levels may improve using omega-3 essential fatty acids (EFAs), in the form of fish oil soft gels. Omega-3 EFAs are known to improve blood cholesterol profiles in those with abnormal values, and thereby help to reduce specific risk factors of heart and vascular disease. This study evaluated healthy athletes to determine if similar improvements could be seen.

Methods: In this reviewed study of 36 active football players, 20 were provided daily fish oil soft gels (2200 mg of mixed DHA [docosahexaenoic acid] and EPA [eicosapentaenoic acid] and 360 mg of other omega-3s) provided by Nordic Naturals (ProOmega®). The remaining 16 players participated as controls. The study was for a 60-day time period. A special, more modern, blood cholesterol test, called the VAP®*, was used to investigate the presence of smaller blood cholesterol subfractions not typically examined by commonly used cholesterol analysis. Blood levels of omega-3s were also assessed.

Results: The group given omega-3s showed an increase in the "good" cholesterol HDL and a decrease in the smaller, more dangerous forms of cholesterol: LDL (-27%), vLDL (-17%), and RLP (-24%). The results also showed significantly decreased levels of triglycerides (-8.06%). Blood tests showed an increase in DHA levels of 107% and EPA levels of 366% compared to controls.

Conclusions: Approximately half of individuals in western society with heart disease have "normal" levels of the more commonly tested blood cholesterol types.^{1,2} This fact is prompting physicians to analyze these smaller and potentially more dangerous forms to make more accurate predictions of cardiovascular risk. The results of this study suggest that omega-3 supplementation can have a significant effect on these key blood cholesterol subfraction which may positively impact risk factors for heart and vascular disease.

PMID: 23015851

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3445114/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Treatment with N-3 Fatty Acids Reduces Serum C-reactive Protein Concentration

Muhammad K, Morledge T, Sachar R, et al. Clin Lipidol 2011;6(6),723–729.

Background: Studies have demonstrated that patients with diets high in n-3 fatty acids have a lower risk of adverse cardiovascular events. C-reactive protein (CRP), a marker of inflammation, is a strong predictor of future cardiovascular events. N-3 fatty acids have been shown to have anti-inflammatory properties. However, there is a paucity of data examining the effect of n-3 fatty acids on CRP levels. This randomized, double-blind, placebo-controlled trial tested the hypothesis that treatment with n-3 polyunsaturated fatty acids (n-3 PUFA) would reduce serum high-sensitivity CRP levels.

Materials & Methods: Fifty-three patients with elevated baseline CRP (>3 mg/l) were randomized to n-3 PUFA (27 patients) or placebo (26 patients). Patients with active infection, inflammatory disease, baseline CRP >10 mg/l, or those started on HMG-CoA reductase inhibitor therapy during the study period were excluded. The primary end point was CRP level following 8 weeks of treatment.

Results: After 8 weeks of treatment with the study drug, the median CRP level in the n-3 PUFA group was 3.4 mg/l compared with 4.0 mg/l in the placebo group ($p=0.36$). After controlling for baseline CRP, there was a significant percentage decrease in CRP from baseline in the n-3 PUFA group (-40.3% ; $p=0.009$) but not in the placebo group (-16.4% ; $p=0.32$).

Conclusions: Treatment for 8 weeks with n-3 fatty acids resulted in a significant percentage reduction of CRP levels as compared with baseline, a finding not seen with placebo.

Source: <http://www.futuremedicine.com/doi/abs/10.2217/clp.11.54?journalCode=clp>

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose-Response Randomized Controlled Trial

Flock MR, Skulas-Ray AC, Harris WS, et al. J Am Heart Assoc 2013 Nov 19;2(6):e000513.

Background: The erythrocyte membrane content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which constitutes the omega-3 index (O3I), predicts cardiovascular disease mortality. The amount of EPA+DHA needed to achieve a target O3I is poorly defined, as are the determinants of the O3I response to a change in EPA+DHA intake. The objective of this study was to develop a predictive model of the O3I response to EPA+DHA supplementation in healthy adults, specifically identifying factors that determine the response.

Methods and Results: A randomized, placebo-controlled, double-blind, parallel-group study was conducted in 115 healthy men and women. One of five doses (0, 300, 600, 900, or 1800 mg/day EPA+DHA) was given daily as placebo or fish oil supplements for ≈5 months. The O3I was measured at baseline and at the end of the study. There were no significant differences in the clinical characteristics between the groups at baseline. The O3I increased in a dose-dependent manner ($P<0.0001$), with the dose of EPA+DHA alone accounting for 68% (quadratic, $P<0.0001$) of the variability in the O3I response. Dose adjusted per unit body weight (g/kg) accounted for 70% (linear, $P<0.0001$). Additional factors that improved prediction of treatment response were baseline O3I, age, sex, and physical activity. Collectively, these explained 78% of the response variability ($P<0.0001$).

Conclusions: Our findings validate the O3I as a biomarker of EPA+DHA consumption and identify additional factors, particularly body weight, that can be used to tailor EPA+DHA recommendations to achieve a target O3I.

PMID: 24252845

Clinical Trial Registration: NCT01078909.

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886744/>

Study was conducted using Arctic Omega™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

A Randomized Clinical Trial to Determine the Efficacy of Manufacturers' Recommended Doses of Omega-3 Fatty Acids from Different Sources in Facilitating Cardiovascular Disease Risk Reduction

Laidlaw M, Cockerline CA, Rowe WJ. Lipids Health Dis 2014 Jun 21;13:99.

Background: Omega-3 fatty acids confer beneficial health effects, but North Americans are lacking in their dietary omega-3 intake. Supplementation is an alternative to consumption of fish; however, not all omega-3 products are created equal. The trial objective was to compare the increases in blood levels of omega-3 fatty acids after consumption of four different omega-3 supplements, and to assess potential changes in cardiovascular disease risk following supplementation.

Methods: This was an open-label, randomized cross-over involving thirty-five healthy subjects. Supplements and daily doses (as recommended on product labels) were: Concentrated Triglyceride (rTG) fish oil: 650 mg EPA, 450 mg DHA; Ethyl Ester (EE) fish oil: 756 mg EPA, 228 mg DHA; Phospholipid (PL) krill oil: 150 mg EPA, 90 mg DHA; Triglyceride (TG) salmon oil: 180 mg EPA, 220 mg DHA. Subjects were randomly assigned to consume one of four products, in random order, for a 28-day period, followed by a 4-week washout period. Subsequent testing of the remaining three products, followed by 4-week washout periods, continued until each subject had consumed each of the products. Blood samples before and after supplementation were quantified for fatty acid analysis using gas chromatography, and statistically analyzed using ANOVA for repeated measures.

Results: At the prescribed dosage, the statistical ranking of the four products in terms of increase in whole blood omega-3 fatty acid levels was concentrated rTG fish oil > EE fish oil > triglyceride TG salmon oil > PL krill oil. Whole blood EPA percentage increase in subjects consuming concentrated rTG fish oil was more than four times that of krill and salmon oil. Risk reduction in several elements of cardiovascular disease was achieved to a greater extent by the concentrated rTG fish oil than by any other supplement. Krill oil and (unconcentrated) triglyceride oil were relatively unsuccessful in this aspect of the study.

Conclusions: For the general population, the form and dose of omega-3 supplements may be immaterial. However, given these results, the form and dose may be important for those interested in reducing their risk of cardiovascular disease.

PMID: 24952576

Clinical Trial Registration: NCT01960660

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085663/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Effects of Supplemental Long-Chain Omega-3 Fatty Acids and Erythrocyte Membrane Fatty Acid Content on Circulating Inflammatory Markers in a Randomized Controlled Trial of Healthy Adults

Flock MR, Skulas-Ray AC, Harris WS, et al. Prostaglandins Leukot Essent Fatty Acids. 2014 Oct;91(4):161–8.

The long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may have anti-inflammatory effects. We evaluated the dose-response effect of EPA+DHA supplementation on circulating TNF- α , IL-6, and CRP, and explored associations between red blood cell (RBC) membrane PUFA content and TNF- α , IL-6, and CRP.

Young adults with low fish intake (n=116) received one of five doses (0, 300, 600, 900, or 1800 mg/day EPA+DHA) for 5 months. There were no significant effects of supplemental EPA+DHA on IL-6 or CRP; however, there was a marginal treatment effect for TNF- α (p<0.08). At baseline, higher quartiles of RBC DHA were associated with lower TNF- α (p=0.001); higher quartiles of arachidonic acid were associated with higher TNF- α (p=0.005).

EPA+DHA supplementation had no dose-response effect on TNF- α , IL-6, or CRP in healthy young adults; however, associations between inflammatory markers and RBC PUFA warrant further investigation.

PMID: 25091379

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4156902/>

Study was conducted using Arctic Omega™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Short-Term, High-Dose Fish Oil Supplementation Increases the Production of Omega-3 Fatty Acid-Derived Mediators in Patients With Peripheral Artery Disease (the OMEGA-PAD I Trial)

Grenon SM, Owens CD, Nosova EV, et al. 2015 Aug 21;4(8):e002034.

Background: Patients with peripheral artery disease (PAD) experience significant morbidity and mortality. The OMEGA-PAD I Trial, a randomized, double-blinded, placebo-controlled trial, addressed the hypothesis that short-duration, high-dose n-3 polyunsaturated fatty acid (n-3 PUFA) oral supplementation improves endothelial function and inflammation in PAD.

Methods and Results: Eighty patients with stable claudication received 4.4 g of fish oil or placebo for one month. The primary end point was endothelial function as measured by brachial artery flow-mediated vasodilation. Secondary end points included biomarkers of inflammation, n-3 polyunsaturated fatty acids metabolome changes, lipid profile, and walking impairment questionnaires. Although there was a significant increase in FMD in the fish oil group following treatment ($0.7 \pm 1.8\%$ increase from baseline, $P=0.04$), this response was not different from that of the placebo group ($0.6 \pm 2.5\%$ increase from baseline, $P=0.18$; between group $P=0.86$), leading to a negative finding for the primary endpoint. There was, however, a significant reduction in triglycerides (fish oil: -34 ± 46 mg/dL, $P<0.001$; placebo -10 ± 43 mg/dL, $P=0.20$; between-group differential P -value: 0.02), and an increase in the omega-3 index of 4.1% ($P<0.001$) in the fish oil group (placebo $0.1 \pm 0.9\%$, $P=0.49$; between-group $P<0.0001$). We observed a significant increase in the production of pathway markers of specialized pro-resolving mediators generated from n-3 polyunsaturated fatty acids in the fish oil group.

Conclusions: High-dose, short-duration fish oil supplementation did not lead to a different response in the primary end point of endothelial function between the treatment and placebo group, but improved serum triglycerides and increased the production of downstream n-3 polyunsaturated fatty acid-derived products and mediators in patients with PAD.

PMID: 26296857

Clinical Trial Registration: NCT01310270.

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4599461>

Study was conducted using ProOmega™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

In Vivo Activation of Leukocyte GPR120/FFAR4 by PUFAs Has Minimal Impact on Atherosclerosis in LDL Receptor Knockout Mice

S. Shewale, A. Brown, Z Bi, E. Boudyguina, J. Sawyer, M. Alexander-Miller, J. Parks. J Lipid Res. 2017 Jan;58(1):236-246.

G protein-coupled receptor (GPR)120/FFA receptor (FFAR)4 (GPR120/FFAR4) activation by n-3 PUFAs attenuates inflammation, but its impact on atherosclerosis is unknown.

We determined whether in vivo activation of leukocyte GPR120/FFAR4 by n-3 versus n-6 PUFAs is atheroprotective. Leukocyte GPR120/FFAR4 WT or KO mice in the LDL receptor KO background were generated by bone marrow transplantation. Mice were fed one of the four atherogenic diets containing 0.2% cholesterol and 10% calories as palm oil (PO) + 10% calories as: 1) PO, 2) fish oil (FO; 20:5 n-3 and 22:6 n-3 enriched), 3) echium oil (EO; 18:4 n-3 enriched), or 4) borage oil (BO; 18:3 n-6 enriched) for 16 weeks.

Compared with PO, mice fed BO, EO, and FO had significantly reduced plasma cholesterol, TG, VLDL cholesterol, hepatic neutral lipid, and atherosclerosis that were equivalent for WT and KO mice. In BO-, EO-, and FO-fed mice, but not PO-fed mice, lack of leukocyte GPR120/FFAR4 resulted in neutrophilia, pro-inflammatory Ly6Chi monocytosis, increased aortic root monocyte recruitment, and increased hepatic inflammatory gene expression.

In conclusion, leukocyte GPR120 expression has minimal effects on dietary PUFA-induced plasma lipid/lipoprotein reduction and atheroprotection, and there is no distinction between n-3 versus n-6 PUFAs in activating anti-inflammatory effects of leukocyte GPR120/FFAR4 in vivo.

PMID: 27811230

Source: <http://www.jlr.org/content/58/1/236.long>

This study was conducted using Nordic GLA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Relationship Between the Omega-3 Index and Specialized Pro-Resolving Lipid Mediators in Patients With Peripheral Arterial Disease Taking Fish Oil Supplements

MS Schaller, GJ Zahner, WJ Gasper, WS Harris, MS Conte, NK Hills, SM Grenon.

Background: Oral supplementation with n-3 polyunsaturated fatty acids (PUFA) increases the omega-3 index, a biomarker of red blood cell eicosapentaenoic acid and docosahexaenoic acid, and plasma levels of biosynthesis pathway markers and potent lipid mediators involved in the resolution of inflammation among patients with peripheral arterial disease (PAD).

Objective: We aimed to quantify the association between an upstream change in the omega-3 index and downstream changes in lipid mediator production.

Methods: We conducted a secondary analysis of the OMEGA-PAD I Trial, a randomized, placebo controlled trial investigating high-dose n-3 PUFA oral supplementation in PAD patients. Eighty subjects were randomized to either 4.4 g of fish oil or placebo for 1 month. Regression analyses using generalized estimating equation techniques were used to investigate the relationship between changes in the omega-3 index and changes in lipid mediators, pre- and post-intervention.

Results: In the fish oil group, there was a significant increase in the omega-3 index ($5 \pm 1\%$ to $9 \pm 2\%$, $P < .001$) as well as in the plasma levels of several downstream lipid mediator pathway markers of resolution, which are involved with the regulation of leukocyte effector function and host defense. A doubling of the omega-3 index correlated with increases of 2.3-fold in 18-hydroxy-eicosapentaenoic acid (HEPE; $P < .0001$), 1.7-fold in 15-HEPE ($P = .03$), 1.9-fold in 5-HEPE ($P = .04$), and 3.6-fold in 4-hydroxy-docosahexaenoic acid ($P < .001$).

Conclusions: Among subjects with symptomatic PAD who took oral fish oil supplements for 1 month, observed changes in the omega-3 index were strongly associated with increases in downstream mediators in the biochemical pathways of resolution.

PMID: 28778393

Source: <https://www.ncbi.nlm.nih.gov/pubmed/28778393>

Study was conducted using ProOmega, a patented fish oil blend from Nordic Naturals, Inc, Watsonville, CA.

STUDY ABSTRACTS
ASSOCIATED

with the

DIGESTIVE SYSTEM

ABSTRACT

Effects of N-3 Fish Oil on Metabolic and Histological Parameters in NASH: A Double-Blind, Randomized, Placebo-Controlled Trial

Argo CK, Patrie JT, Lackner C, et al. J Hepatol 2015 Jan;62(1):190–7.

Background: This study's aim was to assess the histological and metabolic effects of n-3 polyunsaturated fatty acids (PUFA) *versus* placebo while adjusting for the impact of age and weight changes in NASH patients. (ClinicalTrials.gov: NCT00681408).

Methods: Forty-one subjects with non-cirrhotic NASH were enrolled, and 34 completed the study. Seventeen received n-3 fish oil 3000 mg/day, and 17 received placebo daily for one year with typical counseling on caloric intake and physical activity for all subjects.

Results: N-3- and placebo-treated groups showed no significant difference for the primary endpoint of NAS reduction ≥ 2 points without fibrosis progression after adjustment for known covariates (n-3, 4/17 [23.5%]; placebo, 3/17, [17.6%], $p=0.99$). Among subjects with increased or stable weight, n-3 subjects showed a larger decrease in liver fat content by MRI than placebo-treated subjects ($p=0.014$ for 2nd quartile, $p=0.003$ for 3rd quartile of weight change). N-3 treatment showed significant fat reduction on paired analysis of image-assisted fat morphometry regardless of weight loss or gain. Exercise capacity remained markedly reduced in all subjects. No independent effects on markers of hepatocyte injury or insulin sensitivity indices were observed.

Conclusions: N-3 PUFA at 3000 mg/day for one year did not lead to improvement in the primary outcome of histological activity in NASH patients (≥ 2 point NAS reduction). N-3 led to reduced liver fat by multiple measures. Other metabolic effects were not seen, although no detrimental effects were apparent. Whether longer duration, higher dose, or different composition of n-3 therapy would lead to additional benefit is uncertain.

PMID: 25195547

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4272639/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Multiple Micronutrient Supplementation Transiently Ameliorates Environmental Enteropathy in Malawian Children Aged 12–35 Months in a Randomized Controlled Clinical Trial

Smith HE, Ryan KN, Stephenson KB, et al. J Nutr 2014 Dec;144(12):2059–65.

Background: Environmental enteropathy (EE) is subclinical, diffuse villous atrophy characterized by T cell infiltration of the small intestinal mucosa associated with nutrient malabsorption and stunting. EE is assessed by the lactulose:mannitol (L:M) test, whereby nonmetabolized sugars are ingested and quantified in the urine. Multiple-micronutrient (MN) deficiency morphologically mimics EE, and ω -3 (n-3) polyunsaturated fatty acids reduce mucosal inflammation in Crohn's Disease.

Objective: We tested the hypothesis that supplementary MNs, with or without fish oil (FO), would improve L:M in rural Malawian children aged 1–3 years compared with a control (C) group receiving a placebo.

Methods: The MNs and FO provided the Recommended Dietary Intake for 26 vitamins, minerals, eicosapentaenoic acid, and docosahexaenoic acid. This was a 3-arm, randomized, double-blind, placebo-controlled clinical trial, with the primary outcomes being the change in L:M (Δ L:M) after 12 and 24 weeks of supplementation. Comparisons were made for Δ L:M after 12 and 24 weeks within each group by using a Wilcoxon matched pairs signed rank test, because the data are not normally distributed.

Results: A total of 230 children had specimens adequate for analysis; all had an abnormal baseline L:M, defined as >0.10 . After 12 weeks, children who received MNs + FO had a Δ L:M [mean (95% CI)] of -0.10 (-0.04 , -0.15 ; $P=0.001$), and children receiving only MNs had Δ L:M of -0.12 (-0.03 , -0.21 ; $P=0.002$). After 24 weeks, children who received MNs + FO had a Δ L:M of -0.09 (-0.03 , -0.15 ; $P=0.001$); children receiving only MNs had a Δ L:M of -0.11 (-0.02 , -0.20 ; $P=0.001$), and the C group had Δ L:M of -0.07 (0.02 , -0.16); $P=0.002$). Linear growth was similar in all groups, ~ 4.3 cm over 24 weeks.

Conclusions: Although the effect was modest, these data suggest MNs can transiently ameliorate EE in rural African children.

PMID: 25411039

Source: <http://jn.nutrition.org/content/144/12/2059.long>

Study was conducted using ProOmega® (liquid), a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

The Anti-inflammatory Effect of Personalized Omega-3 Fatty Acid Dosing for Reducing Prostaglandin E2 in the Colonic Mucosa Is Attenuated in Obesity

Djuric Z, Turgeon DK, Sen A, et al.

This clinical trial developed a personalized dosing model for reducing prostaglandin E2 (PGE2) in colonic mucosa using O-3 fatty acid supplementation. The model utilized serum eicosapentaenoic acid (EPA, O-3):arachidonic acid (AA, O-6) ratios as biomarkers of colonic mucosal PGE2 concentration.

Normal human volunteers were given low and high O-3 fatty acid test doses for 2 weeks. This established a slope and intercept of the line for dose versus serum EPA:AA ratio in each individual. The slope and intercept was utilized to calculate a personalized target dose that was given for 12 weeks. This target dose was calculated on the basis of a model, initially derived from lean rodents, showing a log-linear relationship between serum EPA:AA ratios and colonic mucosal PGE2 red 攪拌湯 □

uction. Bayesian methods allowed addition of human data to the rodent model as the trial progressed. The dosing model aimed to achieve a serum EPA:AA ratio that is associated with a 50% reduction in colonic PGE2.

Mean colonic mucosal PGE2 concentrations were 6.55 ng/mg protein (SD, 5.78) before any supplementation and 3.59 ng/mg protein (SD, 3.29) after 12 weeks of target dosing. In secondary analyses, the decreases in PGE2 were significantly attenuated in overweight and obese participants. This occurred despite a higher target dose for the obese versus normal weight participants, as generated by the pharmacodynamic predictive model. Large decreases also were observed in 12-hydroxyicosatetraenoic acids, and PGE3 increased substantially.

Future biomarker-driven dosing models for cancer prevention therefore should consider energy balance as well as overall eicosanoid homeostasis in normal tissue.

PMID: 29133307

Source: <https://www.ncbi.nlm.nih.gov/pubmed/29133307>

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udy was conducted using ProEPA XtraE, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
ASSOCIATED

with the

IMMUNE SYSTEM

ABSTRACT

Impact of Fatty Acid Status on Immune Function of Children in Low-Income Countries

Prentice AM, van der Merwe L. Matern Child Nutr 2011 Apr; 7 Suppl 2:89–98.

In vitro and animal studies point to numerous mechanisms by which fatty acids, especially long-chain polyunsaturated fatty acids (LCPUFA), can modulate the innate and adaptive arms of the immune system. These data strongly suggest that improving the fatty acid supply of young children in low-income countries might have immune benefits.

Unfortunately, there have been virtually no studies of fatty acid/immune interactions in such settings. Clinical trial registers list over 150 randomized, controlled trials (RCTs) involving PUFA, with only one in a low-income setting (the Gambia). We summarize those results here. There was evidence for improved growth and nutritional status, but the primary end point of chronic environmental enteropathy showed no benefit, possibly because the infants were still substantially breast-fed.

In high-income settings, there have been RCTs with fatty acids (usually LCPUFA) in relation to 18 disease end points, for some of which there have been numerous trials (asthma, inflammatory bowel disease, and rheumatoid arthritis). For these diseases, the evidence is judged reasonable for risk reduction for childhood asthma (but not in adults), as yielding possible benefit in Crohn's disease (insufficient evidence in ulcerative colitis), and for convincing evidence for rheumatoid arthritis at sufficient dose levels, though formal meta-analyses are not yet available.

This analysis suggests that fatty acid interventions could yield immune benefits in children in poor settings, especially in non-breast-fed children and in relation to inflammatory conditions such as persistent enteropathy. Benefits might include improved responses to enteric vaccines, which frequently perform poorly in low-income settings, and these questions merit randomized trials.

PMID: 21366869

Source: <http://onlinelibrary.wiley.com/doi/10.1111/j.1740-8709.2011.00313.x/abstract;jsessionid=317750A7F143727840F4B833C22F34DF.f02t02>

Study was conducted using Arctic Omega™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Developmental Programming for Allergy: A Secondary Analysis of the Mothers, Omega-3, and Mental Health Study

Romero VC, Somers EC, Stolberg V, et al. Am J Obstet Gynecol 2013 Apr;208(4):316.e1–6.

Objective: Fetal dysregulation of T helper cell pathways may predispose to allergy, as high cord blood T helper 2/T helper 1 ratios have been shown to precede development of allergic diseases. We aimed to determine whether prenatal eicosapentaenoic acid and docosahexaenoic acid supplementation reduces T helper 2 to T helper 1-associated chemokine ratios. We also explored the effect of mode of delivery on T helper 2/T helper 1 ratios.

Methods: We conducted a secondary analysis of a randomized, placebo-controlled trial initially performed to assess the effects of docosahexaenoic acid or eicosapentaenoic acid supplementation on pregnancy-related depressive symptoms among 126 participants. Cord plasma specimens from 98 newborns were assayed for chemokines associated with T helper 2 (thymus and activation-regulated chemokine [CCL17], macrophage-derived chemokine [CCL22], eotaxin [CCL 11]), and T helper 1 (interferon-inducible protein-10 [CXCL 10]) by enzyme-linked immunosorbent assay and Multiplex immunoassays. Ratios of log-transformed chemokines macrophage-derived chemokine/interferon-inducible protein-10 and thymus and activation-regulated chemokine/interferon-inducible protein-10 were compared between groups by analyses of variance. Multiple linear regression was performed to examine associations between treatments and chemokine ratios, adjusting for covariates.

Results: After adjusting for gestational age at delivery, birth weight, and mode of delivery, both omega-3 supplementation groups were associated with lower macrophage-derived chemokine/interferon-inducible protein-10 ratios than placebo (eicosapentaenoic acid: coefficient -1.8 ; 95% confidence interval [CI], -3.6 to -0.05 ; $P=0.04$; docosahexaenoic acid: -2.0 ; 95% CI, -3.9 to -0.07 ; $P=0.04$). Similar associations were found for thymus and activation-regulated chemokine/interferon-inducible protein-10 (eicosapentaenoic acid: -1.5 ; 95% CI, -3.0 to 0.06 ; $P=0.06$; docosahexaenoic acid -2.2 ; 95% CI, -3.8 to -0.52 ; $P=0.01$). Cesarean delivery was associated with higher macrophage-derived chemokine/interferon-inducible protein-10 (1.6 ; 95% CI, 0.01 – 3.3 ; $P=0.049$) and thymus and activation-regulated chemokine/interferon-inducible protein-10 (1.5 ; 95% CI, 0.1 – 2.9 ; $P=0.042$) ratios than vaginal delivery.

Conclusions: Prenatal supplementation with eicosapentaenoic acid and docosahexaenoic acid resulted in decreased cord blood T helper 2/T helper 1 chemokine ratios. Cesarean delivery was associated with a pronounced T helper 2 deviation at birth.

This study was conducted using Nordic Naturals ProEPA™ Xtra and ProDHA™. The dose used was 2–4 soft gels/day.

PMID: 23531329

Source: <http://www.ncbi.nlm.nih.gov/pubmed/23531329>

Study was conducted using ProEPA Xtra™ and ProDHA™, patented fish oil blends from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Fish Oil Supplementation Augments Post-Exercise Immune Function in Young Males

Gray P, Gabriel B, Thies F, et al. *Brain Behav Immun* 2012 Nov;26(8):1265–72.

Purpose: Fish oils and related fatty acid components have anti-inflammatory properties, with beneficial effects against various disorders such as cardiovascular disease. A single bout of exercise can alter immune function. However, the effects of fish oil on immune function after a single bout of exercise are currently unknown. This study investigated the effect of supplementation with fish oil on the immune response to an acute bout of endurance exercise.

Methods: Sixteen male subjects underwent a 6-week double-blind, randomized, placebo-controlled supplementation trial involving two groups (fish oil or placebo oil, 3 g/day). They attended for two visits; the first involving a maximal exercise test, and the second involving a 1-hour bout of endurance exercise on a cycle ergometer at 70% (V)O₂(peak). Blood samples were taken presupplementation, pre-exercise (postsupplementation), immediately, and 1 and 3 hours postexercise. Samples were analyzed for plasma IL-6, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and cortisol; peripheral blood mononuclear cell (PBMC) IL-2, IL-4, and IFN- γ production; neutrophil phagocytosis/oxidative burst; and natural killer (NK) cell cytotoxic activity.

Results: Postsupplementation EPA concentration was increased ($P=0.0127$) in the fish oil group. At 3 hours postexercise, PBMC IL-2 ($P=0.0067$) and NK cell activity ($P=0.0163$) were greater in the fish oil compared with the control group. However, PBMC IL-4 and IFN- γ productions, plasma IL-6 and cortisol concentrations, as well as neutrophil activity, were unaffected by fish oil supplementation.

Conclusions: The current study demonstrates that fish oil supplementation reduces increased PBMC IL-2 production and NK cell cytotoxic activity in the recovery period after exercise.

PMID: 22902522

Source: <https://www.ncbi.nlm.nih.gov/pubmed/22902522>

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
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MUSCULOSKELETAL SYSTEM

ABSTRACT

Fish Oil Supplementation Reduces Markers of Oxidative Stress but Not Muscle Soreness after Eccentric Exercise

Gray P, Chappell A, Jenkinson AM, et al. *Int J Sport Nutr Exerc Metab* 2014 Apr;24(2):206–14.

Due to the potential anti-inflammatory properties of fish-derived long-chain n-3 fatty acids, it has been suggested that athletes should regularly consume fish oils; although evidence in support of this recommendation is not clear. While fish oils can positively modulate immune function, it remains possible that, due to their high number of double bonds, there may be concurrent increases in lipid peroxidation. The current study aims to investigate the effect of fish oil supplementation on exercise-induced markers of oxidative stress and muscle damage.

Twenty males underwent a 6-week double-blind, randomized, placebo-controlled supplementation trial involving two groups (fish oil or placebo). After supplementation, participants undertook 200 repetitions of eccentric knee contractions. Blood samples were taken presupplementation, postsupplementation, immediately, and 24, 48, and 72 hours postexercise, and muscle soreness/maximal voluntary contraction (MVC) assessed.

There were no differences in creatine kinase, protein carbonyls, endogenous DNA damage, muscle soreness, or MVC between groups. Plasma thiobarbituric acid-reactive substances (TBARS) were lower ($p < 0.05$) at 48 and 72 hours postexercise, and H₂O₂-stimulated DNA damage was lower ($p < 0.05$) immediately postexercise in the fish oil, compared with the control group.

The current study demonstrates that fish oil supplementation reduces selected markers of oxidative stress after a single bout of eccentric exercise.

PMID: 24225668

Source: http://journals.humankinetics.com/doi/abs/10.1123/ijsnem.2013-0081?url_ver=Z39.88-2003&rft_id=ori%3Arid%3Acrref.org&rft_dat=cr_pub%3Dpubmed&

Study was conducted using ProEPA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
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RESPIRATORY SYSTEM

ABSTRACT

Randomized Controlled Trial of Fish Oil and Montelukast and Their Combination on Airway Inflammation and Hyperpnea-Induced Bronchoconstriction

Tecklenburg-Lund S, Mickleborough TD, Turner LA, et al. PLOS ONE 2010 Oct 18;5(10):e13487.

Background: Both fish oil and montelukast have been shown to reduce the severity of exercise-induced bronchoconstriction (EIB). The purpose of this study was to compare the effects of fish oil and montelukast, alone and in combination, on airway inflammation and bronchoconstriction induced by eucapnic voluntary hyperpnea (EVH) in asthmatics.

Methods: In this model of EIB, twenty asthmatic subjects with documented hyperpnea-induced bronchoconstriction (HIB) entered a randomized, double-blind trial. All subjects entered on their usual diet (pre-treatment, n=20) and were then randomly assigned to receive either one active 10 mg montelukast tablet and 10 placebo fish oil soft gels (n=10) or one placebo montelukast tablet and 10 active fish oil soft gels totaling 3.2 g EPA and 2.0 g DHA (n=10) taken daily for 3 weeks. Thereafter, all subjects (combination treatment; n=20) underwent another 3-week treatment period consisting of a 10 mg active montelukast tablet or 10 active fish oil soft gels taken daily.

Results: While HIB was significantly inhibited (p,0.05) by montelukast, fish oil and combination treatment compared to pre-treatment, there was no significant difference (p,0.017) between treatment groups; percent fall in forced expiratory volume in 1-sec was 218.462.1%, 29.362.8%, 211.662.8% and 210.861.7% on usual diet (pre-treatment), fish oil, montelukast, and combination treatment respectively. All three treatments were associated with a significant reduction (p,0.05) in FENO, exhaled breathe condensate pH, and cysteinyl-leukotrienes, while the fish oil and combination treatment significantly reduced (p,0.05) urinary 9a, 11b-prostaglandin F2 after EVH compared to the usual diet; however, there was no significant difference (p,0.017) in these biomarkers between treatments.

Conclusion: While fish oil and montelukast are both effective in attenuating airway inflammation and HIB, combining fish oil with montelukast did not confer a greater protective effect than either intervention alone. Fish oil supplementation should be considered as an alternative treatment for EIB.

PMID: 20976161

Clinical Trial Registration: NCT00676468

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2956690/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

A Phase II Randomized Placebo-Controlled Trial of Omega-3 Fatty Acids for the Treatment of Acute Lung Injury

Stapleton RD, Martin TR, Weiss NS, et al. Crit Care Med 2011 Jul;39(7):1655–62.

Objectives: Administration of eicosapentaenoic acid and docosahexaenoic acid, omega-3 fatty acids in fish oil, has been associated with improved patient outcomes in acute lung injury when studied in a commercial enteral formula. However, fish oil has not been tested independently in acute lung injury. We therefore sought to determine whether enteral fish oil alone would reduce pulmonary and systemic inflammation in patients with acute lung injury.

Design: Phase II randomized, controlled trial.

Setting: Five North American medical centers.

Patients: Mechanically ventilated patients with acute lung injury ≥ 18 years of age.

Interventions: Subjects were randomized to receive enteral fish oil (9.75 g eicosapentaenoic acid and 6.75 g docosahexaenoic acid daily) or saline placebo for up to 14 days.

Measurements and Main Results: Bronchoalveolar lavage fluid and blood were collected at baseline (day 0), day 4 \pm 1, and day 8 \pm 1. The primary end point was bronchoalveolar lavage fluid interleukin-8 levels. Forty-one participants received fish oil, and forty-nine received placebo. Enteral fish oil administration was associated with increased serum eicosapentaenoic acid concentration ($p < 0.0001$). However, there was no significant difference in the change in bronchoalveolar lavage fluid interleukin-8 from baseline to day 4 ($p = 0.37$) or day 8 ($p = 0.55$) between treatment arms. There were no appreciable improvements in other bronchoalveolar lavage fluid or plasma biomarkers in the fish oil group compared with the control group. Similarly, organ failure score, ventilator-free days, intensive care unit-free days, and 60-day mortality did not differ between the groups.

Conclusions: Fish oil did not reduce biomarkers of pulmonary or systemic inflammation in patients with acute lung injury, and the results do not support the conduct of a larger clinical trial in this population with this agent. This experimental approach is feasible for proof-of-concept studies evaluating new treatments for acute lung injury.

PMID: 21423000

Clinical Trial Registration: NCT00351533

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3125670/>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

The Effect of Combining Fish Oil and Vitamin C on Airway Inflammation and Hyperpnea-Induced Bronchoconstriction in Asthma

Mickleborough TD, Lindley MR. J Allergy Ther 2014;5:184.

Purpose: To compare the effects of two monotherapies (fish oil and vitamin C), alone and in combination, on airway inflammation and the bronchoconstrictor response to eucapnic voluntary hyperpnea (EVH) in asthmatics.

Methods: Sixteen asthmatic subjects with hyperpnea-induced bronchoconstriction (HIB) entered the study on their usual diet (pre-treatment, n=16) and then randomly assigned to receive either active vitamin C tablets (1.5 g) and placebo fish oil soft gels (n=8), or active fish oil soft gels (3.2 g EPA/2.0 g DHA) and placebo vitamin C tablets (n=8) taken for 3 weeks. Thereafter, all subjects (combination treatment; n=16) underwent a further 3-week treatment period consisting of active vitamin C tablets and active fish oil soft gels taken daily.

Results: HIB was significantly inhibited ($p < 0.017$) by fish oil, vitamin C, and combination treatment compared to pre-treatment (usual diet); percent fall in post-EVH forced expiratory volume in 1-sec was $18.8 \pm 5.7\%$, $9.7 \pm 5.4\%$, $10.5 \pm 10.2\%$, and $10.7 \pm 9.3\%$ on the usual diet, fish oil, vitamin C, and combination treatment respectively. All three treatments, compared to the usual diet, were associated with a significant reduction ($p < 0.017$) in the fraction of exhaled nitric oxide and bronchodilator use, and improvement in asthma symptom scores and exhaled breath condensate pH. There was no significant difference between treatment groups for any dependent variables.

Conclusion: While fish oil and vitamin C supplementation are both effective in attenuating airway inflammation and HIB, combining these two nutrients does not confer a greater anti-inflammatory effect or suppression of HIB than either intervention alone.

Clinical Trial Registration: NCT01057615

Source: <https://www.omicsonline.org/open-access/the-effect-of-combining-fish-oil-and-vitamin-c-on-airway-inflammation-2155-6121.1000184.php?aid=28393>

Study was conducted using ProOmega®, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
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URINARY SYSTEM

ABSTRACT

Adherence to Fish Oil Intervention in Patients with Chronic Kidney Disease

Zabel R, Ash S, King N, et al. *J Ren Nutr* 2010 Sep;20(5):329–33.

Objective: With growing recognition of the role of inflammation in the development of chronic and acute disease, fish oil is increasingly used as a therapeutic agent, but the nature of the intervention may pose barriers to adherence in clinical populations. Our objective was to investigate the feasibility of using a fish oil supplement in hemodialysis patients.

Design: This was a nonrandomized intervention study.

Setting: Eligible patients were recruited at the Hemodialysis Unit of Wesley Hospital, Brisbane, Queensland, Australia.

Patients: The sample included 28 maintenance hemodialysis patients out of 43 eligible patients in the unit. Exclusion criteria involved patients regularly taking a fish oil supplement at baseline, receiving hemodialysis for less than 3 months, or being unable to give informed consent.

Intervention: Eicosapentaenoic acid (EPA) was administered at 2000 mg/day (4 soft gels) for 12 weeks. Adherence was measured at baseline and weekly throughout the study according to changes in plasma EPA, and was further measured subjectively by self report.

Results: Twenty patients (74%) adhered to the prescription based on changes in plasma EPA, whereas an additional two patients self reported their adherence. There was a positive relationship between fish oil intake and change in plasma EPA. Most patients did not report problems with taking the fish oil. Using the baseline data, it was not possible to characterize adherent patients.

Conclusions: Despite potential barriers, including the need to take a large number of prescribed medications already, 74% of hemodialysis patients adhered to the intervention. This study demonstrated the feasibility of using fish oil in a clinical population.

PMID: 20303787

Source: [http://www.jrnjournal.org/article/S1051-2276\(10\)00004-X/abstract](http://www.jrnjournal.org/article/S1051-2276(10)00004-X/abstract)

Study was conducted using ProEPA Xtra™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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A B S T R A C T

Fish Oil Supplementation and Urinary Oxalate Excretion in Normal Subjects on a Low-oxalate Diet

Objective: To determine if fish oil supplementation reduces endogenous oxalate synthesis in healthy subjects.

Materials and Methods: Fifteen healthy non-stone-forming adults participated in this study. Subjects first abstained from using vitamins, medications, or foods enriched in omega-3 fatty acids for 30 days. Next, they collected two 24-hour urine specimens while consuming a self-selected diet. Subjects consumed an extremely low-oxalate and normal-calcium diet for 5 days and collected 24-hour urine specimens on the last 3 days of this diet. Next, the subjects took 2 fish oil capsules containing 650-mg eicosapentaenoic acid and 450-mg docosahexaenoic acid twice daily for 30 days. They consumed a self-selected diet on days 1-25 and the controlled diet on days 26-30. Twenty-four-hour urine samples were collected on days 28-30. Excretion levels of urinary analytes including oxalate and glycolate were analyzed.

Results: Although there was a significant reduction in urinary oxalate, magnesium, and potassium excretions and an increase in uric acid excretion during the controlled dietary phases compared with the self-selected diet, there were no significant differences in their excretion during controlled diet phases with and without fish oil supplementation.

Conclusion: These results suggest that fish oil supplementation does not reduce endogenous oxalate synthesis or urinary oxalate excretion in normal adults during periods of extremely low oxalate intake. However, these results do not challenge the previously described reduction in urinary oxalate excretion demonstrated in normal subjects consuming a moderate amount of oxalate in conjunction with fish oil.

PMID: 25102784

Source: <https://www.ncbi.nlm.nih.gov/pubmed/25102784>

Study was conducted using Nordic Naturals ProOmega[®], a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
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ENDOCRINE SYSTEM

ABSTRACT

The Beneficial Effect of Arctic Omega™ Liquid and ProOmega® Liquid on Glucose Uptake and Cell Livability in L6 Muscle Cell Line

Deyhim F, Olivarez O. Texas A&M University, Kingsville, TX. Diabetes 2006 Jun;55 Suppl 1:A1-617.

Previous research has shown that populations eating a lot of fish containing omega-3 fatty acids have lower rates of type 2 diabetes compared with those eating less fish.

The objective of the present study was to evaluate whether saponified fish oil influences glucose uptake and survival rate of L6 muscle cells. The L6 rat muscle cells were grown to confluence in either low (5 mM) or high (25 mM) glucose media for seven days in the presence of either 3 µg/mL or 30 µg/mL saponified Arctic Omega liquid (863 mg omega-3), ProOmega liquid (1601 mg omega-3), ProDHA™ (580 mg omega-3), and ProEFA® liquid (706 mg omega-3 + 83 mg GLA) for the final 24 hours of incubation.

After 24 hours of incubation with varied doses of saponified fish oil, cells were exposed to 2-deoxy-glucose, 14C glucose, or 3H-palmitate in the presence of insulin (1000 nm). Also, superoxide anion production and cell livability were assessed. 14C glucose incorporation to glycogen, glucose uptake and palmitate uptake per gram protein, and cell livability significantly decreased ($P<0.05$), while superoxide anion production significantly increased ($P<0.05$) after exposure to 25 mM glucose compared to 5 mM glucose media.

Despite a numerical dose response, saponified Arctic Omega liquid, ProOmega liquid, and ProDHA significantly increased ($p<0.05$), while ProEFA liquid numerically improved glucose uptake. The fish oil examined in this study did not ($P>0.1$) affect 14C glucose incorporation to glycogen, palmitate uptake, or superoxide anion production. Saponified Arctic Omega exhibited a numerical improvement in cell livability compared to ProOmega and a significant ($P<0.05$) enhancement in cell livability compared to ProDHA and ProEFA. Saponified ProOmega exhibited a numerical improvement in cell livability compared to ProDHA and a significant ($P<0.05$) enhancement in cell livability compared to ProEFA.

In conclusion, the potential benefit of fish oil on glucose uptake and cell livability depends on the concentration of omega-3 taken up by the L6 muscle cells.

PMID: 17511053

Source: <http://professional.diabetes.org/abstract/beneficial-effect-arctic-omegaliquid-and-pro-omega-liquid-glucose-uptake-and-cell>

Study was conducted using ProOmega®, ProDHA™, ProEFA™/Complete Omega (formerly Complete Omega 3-6-9), and Arctic Omega™ patented fish oil blends from Nordic Naturals, Inc., Watsonville, CA.

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STUDY ABSTRACTS
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REPRODUCTIVE SYSTEM

A B S T R A C T

The Mothers, Omega-3, and Mental Health Study: A Double-blind, Randomized Controlled Trial

Mozurkewich, et al. Am J Obstet Gynecol 2013;208:313.e1-9.

Objective: Maternal deficiency of the omega-3 fatty acid, docosahexaenoic acid (DHA), has been associated with perinatal depression, but there is evidence that supplementation with eicosapentaenoic acid (EPA) may be more effective than DHA in treating depressive symptoms. This trial tested the relative effects of EPA- and DHA-rich fish oils on prevention of depressive symptoms among pregnant women at an increased risk of depression.

Study Design: We enrolled 126 pregnant women at risk for depression (Edinburgh Postnatal Depression Scale score 9-19 or a history of depression) in early pregnancy and randomly assigned them to receive EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), DHA-rich fish oil (900 mg DHA plus 180 mg EPA), or soy oil placebo. Subjects completed

the Beck Depression Inventory (BDI) and Mini-International Neuropsychiatric Interview at enrollment, 26-28 weeks, 34-36 weeks, and at 6-8 weeks postpartum. Serum fatty acids were analyzed at entry and at 34-36 weeks gestation.

Results: One hundred eighteen women completed the trial. There were no differences between groups in BDI scores or other depression endpoints at any of the 3 time points after supplementation. The EPA and DHA-rich fish oil groups exhibited significantly increased post supplementation concentrations of serum EPA and serum DHA respectively. Serum DHA- concentrations at 34-36 weeks were inversely related to BDI scores in late pregnancy.

Conclusions: EPA-rich fish oil and DHA-rich fish oil supplementation did not prevent depressive symptoms during pregnancy or postpartum

PMID: 23531328

Clinical Trial Registration: NCT00711971

Source: <https://www.ncbi.nlm.nih.gov/pubmed/23531328>

Study was conducted using Nordic Naturals ProDHA[®] and ProEPA Xtra[®], patented fish oil blends from Nordic Naturals, Inc., Watsonville, CA.

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ABSTRACT

Association between Fatty Acid Supplementation and Prenatal Stress in African Americans: A Randomized Controlled Trial

Keenan K, Hipwell AE, Bortner J, et al. Obstet Gynecol 2014 Dec;124(6):1080–7.

Objective: To test the association between docosahexaenoic acid (DHA) supplementation and perceived stress and cortisol response to a stressor during pregnancy in a sample of African-American women living in low-income environments.

Methods: Sixty-four African-American women were enrolled at 16–21 weeks of gestation. Power calculations were computed using published standard deviations for the Perceived Stress Scale and the Trier Social Stress Test. Participants were randomized to either 450 mg/day of DHA (n=43) or placebo (n=21). At baseline and 24 and 30 weeks of gestation, perceived stress was assessed by self-report. Cortisol response to a controlled stressor, the Trier Social Stress Test (TSST), was measured from saliva samples collected upon arrival to the laboratory and after the completion of the TSST.

Results: Women in the DHA supplementation group reported lower levels of perceived stress at 30 weeks of gestation, controlling for depression and negative life events (mean=27.4 *versus* 29.5, $F [3,47]=5.06$, $p=0.029$, *cohen's d*=0.65). Women in the DHA supplementation had lower cortisol output in response to arriving to the laboratory and a more modulated response to the stressor ($F [1.78, 83.85]=6.24$, $p=0.004$, *cohen's d*=0.76).

Conclusions: Pregnant women living in urban low-income environments who received DHA reported reduced perceived stress and lower levels of stress hormones in the third trimester. DHA supplementation may be a method for attenuating the effects of maternal stress during late pregnancy and improving the uterine environment with regard to fetal exposure to glucocorticoids.

PMID: 25415158

Clinical Trial Registration: NCT01158976

Source: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4241554/>

Study was conducted using ProDHA™, a patented fish oil blend from Nordic Naturals, Inc., Watsonville, CA.

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