

OAND 2023 - Omega-3 and Heart Health Research Update

Dr. Alexandra Verge, ND

Abdelhamid, A. S. *et al.* Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst. Rev.* **2020**, CD003177 (2020).

Aberra, T. *et al.* The association between triglycerides and incident cardiovascular disease: What is “optimal”? *J. Clin. Lipidol.* **14**, 438-447.e3 (2020).

Akintoye, E. *et al.* Fish Oil and Perioperative Bleeding. *Circ.: Cardiovasc. Qual. Outcomes* **11**, e004584 (2018).

Albert, C. M. *et al.* Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation. *JAMA* **325**, 1061–1073 (2021).

Aranceta, J. & Pérez-Rodrigo, C. Recommended dietary reference intakes, nutritional goals and dietary guidelines for fat and fatty acids: a systematic review. *Br. J. Nutr.* **107**, S8–S22 (2012).

Aung, T. *et al.* Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. *JAMA Cardiol.* **3**, 14–22 (2018).

Baker, E. J., Miles, E. A., Burdge, G. C., Yaqoob, P. & Calder, P. C. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. *Prog. Lipid Res.* **64**, 30–56 (2016).

Ballantyne, C. M. & Jia, X. Omega-3 Fatty Acids and Risk for Atrial Fibrillation Big Fish or Small Fry? *J. Am. Coll. Cardiol.* **82**, 350–352 (2023).

Bassuk, S. S., Manson, J. E. & Group, V. R. Marine omega-3 fatty acid supplementation and prevention of cardiovascular disease: update on the randomized trial evidence. *Cardiovasc. Res.* **119**, 1297–1309 (2022).

Bastías, J. M., Balladares, P., Acuña, S., Quevedo, R. & Muñoz, O. Determining the effect of different cooking methods on the nutritional composition of salmon (*Salmo salar*) and chilean jack mackerel (*Trachurus murphyi*) fillets. *PLoS ONE* **12**, e0180993 (2017).

Begtrup, K. M., Krag, A. E. & Hvas, A.-M. No impact of fish oil supplements on bleeding risk: a systematic review. *Dan. Méd. J.* **64**, (2017).

Bender, N. K. *et al.* Effects of Marine Fish Oils on the Anticoagulation Status of Patients Receiving Chronic Warfarin Therapy. *J. Thromb. Thrombolysis* **5**, 257–261 (1998).

Bianchi, M. *et al.* Assessing seafood nutritional diversity together with climate impacts informs more comprehensive dietary advice. *Commun. Earth Environ.* **3**, 188 (2022).

Block, R. C. et al. Aspirin and omega-3 fatty acid status interact in the prevention of cardiovascular diseases in Framingham Heart Study. *Prostaglandins, Leukot. Essent. Fat. Acids* **169**, 102283 (2021).

Bornfeldt, K. E. Triglyceride lowering by omega-3 fatty acids: a mechanism mediated by N-acyl taurines. *J. Clin. Investig.* **131**, e147558 (2021).

Bradberry, J. C. & Hilleman, D. E. Overview of omega-3 Fatty Acid therapies. *P T: a peer-Rev. J. Formul. Manag.* **38**, 681–91 (2013).

Buckley, M. S., Goff, A. D. & Knapp, W. E. Fish Oil Interaction with Warfarin. *Ann. Pharmacother.* **38**, 50–53 (2004).

Budoff, M. J. et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur. Hear. J.* **41**, 3925–3932 (2020).

Cabiddu, M. F., Russi, A., Appolloni, L., Mengato, D. & Chiumente, M. Omega-3 for the prevention of cardiovascular diseases: meta-analysis and trial-sequential analysis. *Eur. J. Hosp. Pharm.* **29**, 134–138 (2022).

Demonty, I., Langlois, K., Greene-Finestone, L. S., Zoka, R. & Nguyen, L. Proportions of long-chain  $\omega$ -3 fatty acids in erythrocyte membranes of Canadian adults: Results from the Canadian Health Measures Survey 2012–2015. *Am. J. Clin. Nutr.* **113**, nqaa401- (2020).

Dyerberg, J. & Bang, H. O. HÆMOSTATIC FUNCTION AND PLATELET POLYUNSATURATED FATTY ACIDS IN ESKIMOS. *Lancet* **314**, 433–435 (1979).

Farquharson, A. L. et al. Effect of Dietary Fish Oil on Atrial Fibrillation After Cardiac Surgery. *Am. J. Cardiol.* **108**, 851–856 (2011).

Fatkin, D., Cox, C. D. & Martinac, B. Fishing for Links Between Omega-3 Fatty Acids and Atrial Fibrillation. *Circulation* **145**, 1037–1039 (2022).

Gao, Z., Zhang, D., Yan, X., Shi, H. & Xian, X. Effects of  $\omega$ -3 Polyunsaturated Fatty Acids on Coronary *Atherosclerosis* and Inflammation: A Systematic Review and Meta-Analysis. *Front. Cardiovasc. Med.* **9**, 904250 (2022).

Gao, L. et al. Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: A meta-analysis of randomized controlled trials. *Atherosclerosis* **226**, 328–334 (2013).

Gencer, B. et al. Effect of Long-Term Marine Omega-3 Fatty Acids Supplementation on the Risk

of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *Circulation* (2021) doi:10.1161/circulationaha.121.055654.

George, M. & Gupta, A. Blood Pressure–Lowering Effects of Omega-3 Polyunsaturated Fatty Acids: Are These the Missing Link to Explain the Relationship Between Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Disease? *J Am Hear Assoc Cardiovasc Cerebrovasc Dis* **11**, e026258 (2022).

Gonçálinho, G. H. F., Sampaio, G. R., Soares-Freitas, R. A. M. & Damasceno, N. R. T. Omega-3 Fatty Acids in Erythrocyte Membranes as Predictors of Lower Cardiovascular Risk in Adults without Previous Cardiovascular Events. *Nutrients* **13**, 1919 (2021).

Group, A. S. C. et al. Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus. *N. Engl. J. Med.* **379**, 1540–1550 (2018).

Grześk, G. et al. The Clinical Significance of Drug–Food Interactions of Direct Oral Anticoagulants. *Int. J. Mol. Sci.* **22**, 8531 (2021).

Harris, W. S. et al. Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. *Nat. Commun.* **12**, 2329 (2021).

Harris, W. S., Tittle, N. L., Etherton, M. R. & Vasan, R. S. Erythrocyte long-chain omega-3 fatty acid levels are inversely associated with mortality and with incident cardiovascular disease: The Framingham Heart Study. *J. Clin. Lipidol.* **12**, 718-727.e6 (2018).

Harris, W. S. et al. Increases in erythrocyte DHA are not associated with increases in LDL-cholesterol: Cooper center longitudinal study. *J. Clin. Lipidol.* **15**, 212–217 (2021).

Harris, W. S. & Schacky, C. von. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev. Med.* **39**, 212–220 (2004).

Hu, Y., Hu, F. B. & Manson, J. E. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. *J. Am. Hear. Assoc.: Cardiovasc. Cerebrovasc. Dis.* **8**, e013543 (2019).

Huang, L. et al. Effect of Omega-3 Polyunsaturated Fatty Acids on Cardiovascular Outcomes in Patients with Diabetes: A Meta-analysis of Randomized Controlled Trials. *Adv. Nutr.* **14**, 629–636 (2023).

Hull, M. A. et al. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFood Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. *Lancet* **392**, 2583–2594 (2018).

Investigators, P. S. et al. Mercury exposure and risk of cardiovascular disease: a nested

case-control study in the PREDIMED (PREvention with MEDiterranean Diet) study. *BMC Cardiovasc. Disord.* **17**, 9 (2017).

Jalili, M. & Dehpour, A. R. Extremely Prolonged INR Associated with Warfarin in Combination with Both Trazodone and Omega-3 Fatty Acids. *Arch. Méd. Res.* **38**, 901–904 (2007).

Jensen, I.-J., Eilertsen, K.-E., Otnæs, C. H. A., Mæhre, H. K. & Elvevoll, E. O. An Update on the Content of Fatty Acids, Dioxins, PCBs and Heavy Metals in Farmed, Escaped and Wild Atlantic Salmon (*Salmo salar* L.) in Norway. *Foods* **9**, 1901 (2020).

Jiang, J. et al. Effect of Marine-Derived n-3 Polyunsaturated Fatty Acids on Major Eicosanoids: A Systematic Review and Meta-Analysis from 18 Randomized Controlled Trials. *PLoS ONE* **11**, e0147351 (2016).

Jurgens, C. Y. et al. State of the Science: The Relevance of Symptoms in Cardiovascular Disease and Research: A Scientific Statement From the American Heart Association. *Circulation* **101161CIR0000000000001089** (2022) doi:10.1161/cir.0000000000001089.

Kapoor, K. et al. Association Between Omega-3 Fatty Acid Levels and Risk for Incident Major Bleeding Events and Atrial Fibrillation: MESA. *J. Am. Hear. Assoc.* **10**, e021431 (2021).

Kavyani, Z. et al. Efficacy of the omega-3 fatty acids supplementation on inflammatory biomarkers: An umbrella meta-analysis. *Int. Immunopharmacol.* **111**, 109104 (2022).

Khan, S. U. et al. Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. *EClinicalMedicine* **38**, 100997 (2021).

Khan, S. U. et al. Effects of *Nutritional* Supplements and Dietary Interventions on Cardiovascular Outcomes: An Umbrella Review and Evidence Map. *Ann. Intern. Med.* **171**, 190 (2019).

Langlois, K. & Ratnayake, W. M. N. Omega-3 Index of Canadian adults. *Heal. Rep.* **26**, 3–11 (2015).

Le, V. T. et al. Higher docosahexaenoic acid levels lower the protective impact of eicosapentaenoic acid on long-term major cardiovascular events. *Front. Cardiovasc. Med.* **10**, 1229130 (2023).

Lechner, K. et al. Omega-3 fatty acid blood levels are inversely associated with cardiometabolic risk factors in HFpEF patients: the Aldo-DHF randomized controlled trial. *Clin. Res. Cardiol.* **111**, 308–321 (2022).

Maki, K. C. et al. A Head-to-Head Comparison of a Free Fatty Acid Formulation of Omega-3 Pentaenoic Acids Versus Icosapent Ethyl in Adults With Hypertriglyceridemia: The

ENHANCE-IT Study. *J. Am. Hear. Assoc.* 11, e024176 (2021).

Manson, J. E. et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N. Engl. J. Med.* **380**, 23–32 (2018).

Mar, P. L. et al. Drug Interactions Affecting Oral Anticoagulant Use. *Circ.: Arrhythmia Electrophysiol.* **15**, e007956 (2022).

Mason, R. P., Jacob, R. F., Shrivastava, S., Sherratt, S. C. R. & Chattopadhyay, A. Eicosapentaenoic acid reduces membrane fluidity, inhibits cholesterol domain formation, and normalizes bilayer width in atherosclerotic-like model membranes. *Biochim. Biophys. Acta (BBA) - Biomembr.* **1858**, 3131–3140 (2016).

McBurney, M. I., Tittle, N. L., Vasan, R. S., Sala-Vila, A. & Harris, W. S. Using an erythrocyte fatty acid fingerprint to predict risk of all-cause mortality: the Framingham Offspring Cohort. *Am. J. Clin. Nutr.* **114**, nqab195 (2021).

Minno, A. D. et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood Rev.* **31**, 193–203 (2017).

Musazadeh, V., Kavyani, Z., Naghshbandi, B., Dehghan, P. & Vajdi, M. The beneficial effects of omega-3 polyunsaturated fatty acids on controlling blood pressure: An umbrella meta-analysis. *Front. Nutr.* **9**, 985451 (2022).

Myhre, P. L. et al. Changes in eicosapentaenoic acid and docosahexaenoic acid and risk of cardiovascular events and atrial fibrillation: A secondary analysis of the OMEMI trial. *J Intern Med* **291**, 637–647 (2022).

Naghshi, S. et al. Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of cohort studies. *BMJ* **375**, n2213 (2021).

Nishizaki, Y. et al. Study protocol and baseline characteristics of Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy—Statin and Eicosapentaenoic Acid: RESPECT-EPA, the combination of a randomized control trial and an observational biomarker study. *Am Heart J* **257**, 1–8 (2023).

Pryce, R., Bernaitis, N., Davey, A. K., Badrick, T. & Anoopkumar-Dukie, S. The Use of Fish Oil with Warfarin Does Not Significantly Affect either the International Normalised Ratio or Incidence of Adverse Events in Patients with Atrial Fibrillation and Deep Vein Thrombosis: A Retrospective Study. *Nutrients* 8, 578 (2016).

Qian, F. et al. Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation. *J. Am. Coll. Cardiol.* 82, 336–349 (2023).

Ramirez, J. L. et al. Peripheral Artery Disease Is Associated with a Deficiency of Erythrocyte Membrane n-3 Polyunsaturated Fatty Acids. *Lipids* **54**, 211–219 (2019).

Ridker, P. M. et al. Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1 $\beta$ , Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: A REDUCE-IT Biomarker Substudy. *Circulation* **146**, 372–379 (2022).

Rimm, E. B. et al. Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation* **138**, e35–e47 (2018).

Shen, S. et al. Omega-3 Fatty Acid Supplementation and Coronary Heart Disease Risks: A Meta-Analysis of Randomized Controlled Clinical Trials. *Front. Nutr.* **9**, 809311 (2022).

Sheppard, J. P. et al. EPA Versus Mixed EPA/DHA Plus Statin for Coronary Atherosclerosis Meta-Analysis of Prospective Imaging Trials. *JACC: Cardiovasc. Imaging* **15**, 1825–1828 (2022).

Sheppard, K. W. & Cheatham, C. L. Executive functions and the  $\omega$ -6-to- $\omega$ -3 fatty acid ratio: a cross-sectional study 1 , 2. *Am. J. Clin. Nutr.* **105**, 32–41 (2017).

Shetty, S. S., N., S. K. & Shetty, P. K.  $\omega$ -6/ $\omega$ -3 fatty acid ratio as an essential predictive biomarker in the management of type 2 diabetes mellitus. *Nutrition* **79**, 110968 (2020).

Sivakumar, R., Sachin, S., Priyadarshini, R. & Ghosh, S. Sustainable production of eicosapentaenoic acid-rich oil from microalgae: Towards an algal biorefinery. *J. Appl. Microbiol.* **132**, 4170–4185 (2022).

Skulas-Ray, A. C. et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. *Circulation* **140**, e673–e691 (2019).

Stark, K. D., Elswyk, M. E. V., Higgins, M. R., Weatherford, C. A. & Salem, N. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. *Prog. Lipid Res.* **63**, 132–152 (2016).

Sun, Y. et al. Association of Seafood Consumption and Mercury Exposure With Cardiovascular and All-Cause Mortality Among US Adults. *JAMA Netw. Open* **4**, e2136367 (2021).

Sutariya, B. et al. Emphasis on Icosapent Ethyl for Cardiovascular Risk Reduction: A Systematic Review. *Cureus* **14**, e32346 (2022).

Vanschoonbeek, K. et al. Variable Hypocoagulant Effect of Fish Oil Intake in Humans. *Arter.*

*Thromb., Vasc. Biol.* **24**, 1734–1740 (2004).

Villani, A. M. et al. Fish oil administration in older adults with cardiovascular disease or cardiovascular risk factors: Is there potential for adverse events? A systematic review of the literature. *Int. J. Cardiol.* **168**, 4371–4375 (2013).

Wachira, J. K., Larson, M. K. & Harris, W. S. n-3 Fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. *Br. J. Nutr.* **111**, 1652–1662 (2014).

Wang, I. E., Yi, S., Block, R. C. & Mousa, S. A. Aspirin and omega-3 polyunsaturated fatty acid use and their interaction in cardiovascular diseases and colorectal adenomas. *Nutr. Res. Rev.* **35**, 295–307 (2022).

Wang, J. et al. Does Omega-3 Fatty Acid Supplementation Have Favorable Effects on the Lipid Profile in Postmenopausal Women? A Systematic Review and Dose–response Meta-analysis of Randomized Controlled Trials. *Clin. Ther.* **45**, e74–e87 (2023).

Watson, P. D., Joy, P. S., Nkonde, C., Hessen, S. E. & Karalis, D. G. Comparison of Bleeding Complications With Omega-3 Fatty Acids + Aspirin + Clopidogrel—Versus—Aspirin + Clopidogrel in Patients With Cardiovascular Disease. *Am. J. Cardiol.* **104**, 1052–1054 (2009).

Weinberg, R. L., Brook, R. D., Rubenfire, M. & Eagle, K. A. Cardiovascular Impact of Nutritional Supplementation With Omega-3 Fatty Acids JACC Focus Seminar. *J. Am. Coll. Cardiol.* **77**, 593–608 (2021).

Welty, F. K. et al. Regression of Coronary Fatty Plaque and Risk of Cardiac Events According to Blood Pressure Status: Data From a Randomized Trial of Eicosapentaenoic Acid and Docosahexaenoic Acid in Patients With Coronary Artery Disease. *J. Am. Hear. Assoc.: Cardiovasc. Cerebrovasc. Dis.* **12**, e030071 (2023).

Yang, B. et al. Comparative efficacy of omega-3 polyunsaturated fatty acids on major cardiovascular events: A network meta-analysis of randomized controlled trials. *Prog. Lipid Res.* **88**, 101196 (2022).

Yokoyama, M. et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* **369**, 1090–1098 (2007).

Yu, F. et al. Effects of omega-3 fatty acid on major cardiovascular outcomes: A systematic review and meta-analysis. *Medicine* **101**, e29556 (2022).

Zelniker, T. A. et al. Plasma Omega-3 Fatty Acids and the Risk of Cardiovascular Events in Patients After an Acute Coronary Syndrome in MERLIN-TIMI 36. *J. Am. Hear. Assoc.* **10**,

e017401 (2020).

Zhang, X., Ritonja, J. A., Zhou, N., Chen, B. E. & Li, X. Omega-3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis* 11, e025071 (2022).

Zhou, J. et al. Association of oily fish and nonoily fish intakes with all-cause mortality and cause-specific mortality: a large population-based prospective study. *J. Transl. Med.* **21**, 280 (2023).

Zhuang, P., Wang, W., Wang, J., Zhang, Y. & Jiao, J. Polyunsaturated fatty acids intake, omega-6/omega-3 ratio and mortality: Findings from two independent nationwide cohorts. *Clin. Nutr.* 38, 848–855 (2019).

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet (Lond., Engl.)* **354**, 447–55 (1999).