4 Optimal Omega-3 Levels for Different Age Groups

Clemens von Schacky

Key Points

- The status of an individual in EPA and DHA is represented by the Omega-3 Index (i.e., the percentage of EPA and DHA in red cell fatty acids), as determined with a highly standardized methodology. A highly standardized methodology makes it possible for scientists to directly compare results of different scientific studies, and for clinicians to apply the results in clinical medicine.
- For the human brain to grow in utero, proteins transport arachidonate and DHA across the placenta, trying to adjust the fetus to an Omega-3 Index of approximately 8–11%. As in all other populations studied, the distribution of the Omega-3 Index values in pregnant women is a bell-shaped curve, which makes it almost impossible that any one dose of omega-3 fatty acids can be optimal for all pregnant women (or any other population), including the recommended dose of 200 mg DHA/day. A low Omega-3 Index or low levels of EPA and DHA have been demonstrated to be associated with risk for suboptimal outcomes of pregnancy, in childhood, and adolescence.
- Also, persons with a low Omega-3 Index (<4%) are less physically fit, and are at greater risk for depression than persons with a high Omega-3 Index.
- An Omega-3 Index >8% is associated with evidence for increased longevity, decreased mortality, and absence of cardiovascular events.
- Because the relation between the Omega-3 Index and risk tends to level off at values >11%, and because of safety considerations, 11% has been suggested as upper limit for the target Omega-3 Index.
- Preliminary and circumstantial evidence supports the concept of the Omega-3 Index also for prevention and treatment of other diseases.

Key words: Eicosapentaenoic acid, Docosahexaenoic acid, Omega-3 Index

INTRODUCTION

Some sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have disappeared from our diet, like brain, because of fears of bovine spongiform encephalitis. Other sources are declining in content, like farmed fish, because fish oil prices rise, and EPA- and DHA-rich fish oil is replaced by other oils, containing little or no EPA and DHA (1). For similar reasons, few eggs contain appreciable amounts of EPA and/or DHA (2). Under current Western dietary conditions, one-third of humans cannot convert alpha-linolenic acid (ALA) to EPA, about one-third convert some, and about one-third can convert up to 5% of ALA ingested to EPA (3). In humans, conversion of EPA to DHA is negligible, while retroconversion of DHA to EPA seems more efficient (3, 4). Taken together, ingestion of EPA and DHA has been and is continuing to be declining, and plant-derived ALA is not a viable alternative. Alternative sources, like algae-derived DHA, currently cannot provide sufficient quantities of EPA and DHA to compensate for the declining availability and intake of EPA and DHA.

To complicate matters, correlations between ingestion of EPA and DHA and suboptimal outcome or disease are much looser than correlations between levels and suboptimal outcome or disease (5). This seems to be largely due to inter-individual differences in absorption and translation of intake into levels of omega-3 fatty acids, differences in bioavailability between different chemical forms of omega-3 fatty acids, and matrix effects (5). Therefore, this review focuses on levels of EPA and DHA, as they relate to outcomes and diseases throughout a humans' lifespan.

HOW TO ASSESS LEVELS AND WHAT FACTORS INFLUENCE THEM

Fatty acid compositions can be assessed in a host of compartments—from plasma free fatty acids (FFA) to tissue (e.g., adipose tissue biopsies). It is beyond the scope of this review to discuss and weigh thoroughly the merits of all possible compartments. Plasma free fatty acids appear as a compartment with a rapid turnover, with EPA appearing within 4 h of ingestion, peaking after 8 h, and levels close to baseline levels after 24 h (6). In plasma phospholipids, EPA increases after 4 h of ingestion, with a further increase after 24 h, and levels increase further with further ingestion (6). In platelet fatty acids, EPA does not change within 24 h of ingestion, but only after several days (6). In red cells, EPA and DHA do not change within 24 h of ingestion, but only after several weeks to months, depending on the dose given (7, 8). Thus, short-term changes of EPA and DHA are reflected in plasma free or phospholipid fatty acid compositions, while cellular compartments, like platelet or red cell fatty acid compositions, reflect longer term changes. These differences impact on the design of studies, with short-term kinetic studies using, for example, plasma phospholipids, and epidemiologic and other studies interested in long-term effects of EPA and DHA using, for example, red cell phospholipids.

For decades, fatty acid compositions were and are being analyzed with a large variety of methods, one method usually specific to a single laboratory. Quality assurance usually was restricted to an internal standard. While this approach led to some degree of internal validity, this approach precluded external validity (necessary to compare results from laboratory to laboratory), and the generation of large databases (necessary to

establish reference values, target values, asf). Thus, research results could never be directly compared, and results could never be applied to clinical medicine.

In 2004 Harris and von Schacky defined red cell EPA plus DHA as the Omega-3 Index, and suggested the Omega-3 Index as a risk factor for sudden cardiac death (9). This suggestion was based on previous work just mentioned (6–8), and on a steep relationship between red cell or whole blood EPA plus DHA and sudden cardiac death (10, 11). In persons with high levels of EPA and DHA, risk for sudden cardiac death was one-tenth of the risk in persons with low levels (10, 11). Because Harris and von Schacky saw a potential of the Omega-3 Index to become a clinically useful parameter, a standardized analytical method was part of the definition of the Omega-3 Index (9). The standardization of the method had to comprise a surprisingly large number of parameters, including, for example, shaking vigor and time. However, as is, the method has an analytical variability similar to other clinical routine parameters, and served to clearly demonstrate the low biological variability of red cell EPA and DHA (12). In keeping with clinical chemistry, quality assurance includes constancy checks, plausibility testing, regular proficiency testing, and other methods (5). The standardized analytical method for red cell fatty acid composition led to a large number of collaborations and research projects, which are one basis of the present review. An initial result was that the Omega-3 Index reflects human heart tissue levels of EPA and DHA and, in the experimental animal, other tissue levels as well (5). Therefore, the Omega-3 Index can be considered to reflect a person's status in EPA and DHA.

Of note, important pre-analytical factors or acute clinical events do not influence the Omega-3 Index (Table 4.1) (5). Intuitively, one would think that the most important factor for the Omega-3 Index would be intake of EPA and DHA. However, reported dietary omega-3 fatty acid intake explained <16% of the total variation of the Omega-3 Index in one study (13), and 12% in another (14). Thus, it is impossible to predict an individual's level of the Omega-3 Index from assessing the dietary intake of this individual. In keeping, although the mean Omega-3 Index in a population reliably increases after an increase in intake of EPA and DHA, individual responses differ vastly (e.g., (15)).

IMPACT ON STUDY RESULTS AND STUDY DESIGN

Inter-individual differences in response partly explain conflicting results of previous intervention studies with EPA and DHA. Another part of the explanation is the statistically normal distribution of the Omega-3 Index in every population studied so far (5). Previously, study participants were recruited irrespective of their baseline Omega-3 Index. Previously, the effect of a fixed dose of EPA and/or DHA was compared to the effect of placebo (or to a control population). The previous approach led to a large overlap of the Omega-3 Index levels in the total study population (i.e., a portion of study participants had similar or identical Omega-3 Index levels), irrespective of being randomized to EPA and/or DHA or placebo/control (5). Therefore, previous studies had a bias towards neutral results. By use of the Omega-3 Index, this bias can be minimized—on the one hand, by recruiting study participants with a low Omega-3 Index (e.g., <4%), and on the other, by using a variable dose to achieve a

Table 4.1
Factors impacting/correlating or not impacting/correlating the Omega-3 Index (5, 69)

Not impacting/correlating:	
Fasting/fed	
Recent intake of omega-3s	No change
Myocardial infarction	No change
Sudden cardiac death	No change
Other acute events	No change
Transport at ambient temperature:	No change
up to 5 days in EDTA-blood tubes	
up to 7 days on filter paper	
Freeze at −80 °C: >10 years	No change
Impacting/correlating:	
Intake	+0.24%/4 g/month
Age	+0.50%/decade (in Japan, not in United States)
Diabetes	−1.13% in cases
BMI	−0.3%/3 units
Genes	Higher in converters of alpha-linolenic acid
Gender	+0.5% in women
Regular alcohol intake	Higher in consumers
Social status	Correlates with status
Hormone replacement therapy	Higher in users
Others	To be defined

predefined target level (e.g., 8–11%). This kind of study design increases the efficiency of intervention studies with EPA and/or DHA, and may lead to clearer results.

PREGNANCY AND LACTATION

The normal human brain contains large amounts of arachidonate and of DHA. It is formed in the last trimester of pregnancy, but takes up DHA also in later years (16). In placenta, fatty acid binding and transport proteins actively transport arachidonate and DHA (17, 18). Enzyme kinetics indicate a saturation point for DHA at a red cell DHA of 8.87% (not measured with the Omega-3 Index method (19)). This means that placenta tries to adjust the fetus to this red cell DHA level, irrespective of the mother's levels.

Numerous, but not all, intervention trials have demonstrated a positive effect of a supplementation with EPA and/or DHA in pregnant women in terms of less premature birth, and, in the child, in terms of complex brain performance, like visual acuity, attention spans, intelligence and others (20, 21) (see Chap. 8, Impact of Long-Chain Polyunsaturated Fatty Acids on Cognitive and Mental Development). Epidemiologic studies indicate that EPA and/or DHA might reduce preeclampsia and postpartum depression. This evidence is discussed in more detail elsewhere (21, 22). The evidence just mentioned formed the basis of a recommendation to pregnant women to supplement

daily with 200 mg DHA (22). In this recommendation, it is stated that doses up to 2.7 g EPA plus DHA/day were well tolerated by pregnant women in intervention studies (22), indicating an uncertainty of the correct dose. The Omega-3 Index has a statistically normal (i.e., bell-shaped) distribution also in pregnant women, and was found to range from 2.6 to 14.9% (21). This makes it quite unlikely that any given dose of EPA and/or DHA will serve the needs of all pregnant women, and makes it more likely that supplementation with omega-3 fatty acids needs to be tailored to an individual baseline Omega-3 Index, preferably determined before or early in pregnancy (21). Although direct evidence remains to be provided, a target range for the Omega-3 Index in pregnancy of 8–11% has been suggested (21). Based on the kinetics of the placenta enzymes just mentioned, a similar range might also be valid for babies.

CHILDHOOD AND ADOLESCENCE

The human brain growth spurt starts in week 28 of pregnancy and lasts until the end of the first year of life (20). An increased need for arachidonate and DHA persists in the second year of life (20). Although the evidence for improving complex brain functions by supplementing EPA and/or DHA during the first 2 years of life is less convincing (20, 22), supplementation reduced respiratory infections in toddlers (23). In adolescents, low levels of EPA and DHA are associated with a higher likelihood for bipolar depression, and supplementation with EPA and DHA improves bipolar depression in adolescents (24). Unpublished evidence extends these findings to the Omega-3 Index in major depression in adolescents (Pottala JV et al., submitted). An optimal range for the Omega-3 Index in childhood and adolescence remains to be defined.

PHYSICAL FITNESS

EPA plus DHA supplementation increased stroke volume and cardiac output and reduced heart rate (peak and submaximal) and whole body and myocardial oxygen consumption in trained persons (25, 26). In one study, the red cell content of EPA and DHA increased by 37%, but this was not measured in the other study (25, 26). It is unclear how this translates into the Omega-3 Index. In patients who had had a myocardial infarction, exercise capacity, exercise time, and heart rate recovery were positively associated with the Omega-3 Index (27). In a randomized cross-over study in patients with reduced left ventricular systolic function due to myocardial infarction, EPA and DHA lowered resting heart rate, and improved heart rate recovery and parameters of heart rate variability (28). Taken together, supplementation with EPA plus DHA improves parameters of cardiac function in healthy persons and in cardiac patients, but a target Omega-3 Index remains to be defined.

PSYCHIATRIC DISEASES

A low Omega-3 Index (3.9%) predisposes to major depression (29). This is supported by a meta-analysis of 14 other studies, demonstrating that low levels of EPA and DHA in any blood compartment to predispose to depression (30). In a meta-analysis of randomized

intervention trials in major depression, supplements containing EPA≥60% of total EPA and DHA, in a dose range of 200–2,200 mg/day of EPA in excess of DHA, were effective against primary depression (31). Thus, current evidence argues for trials recruiting patients with major depression and a low Omega-3 Index (e.g., <4%) and treating them to a target Omega-3 Index—for example, a range between 8 and 11% with a combination of EPA plus DHA, with EPA≥60% of total EPA and DHA. Current evidence supports the statement that persons with a high Omega-3 Index are less prone to fall ill with major depression than persons with a low Omega-3 Index. What level precisely is "high" in this context, however, remains to be defined.

In bipolar depression, a meta-analysis of randomized intervention trials (five pooled datasets, $n=291$) found strong evidence that depressive symptoms may be improved by EPA and DHA, but no effect on mania was found (32). We are currently conducting a trial on bipolar patients with a low Omega-3 Index (NCT00891826).

Other psychiatric diseases currently under investigation are schizophrenia (e.g., NCT00585390), attention-deficit hyperactivity disorder (ADHD) (e.g., NCT01340690), posttraumatic stress disorder (e.g., (33), NCT00644423), and many more.

PREVENTION OF CARDIOVASCULAR EVENTS

In the "Heart and Soul Study," in patients after a myocardial infarction an Omega-3 Index above average was associated with improved survival by 27%, as compared to an Omega-3 Index below average (median: hazard ratio (HR] 0.73; 95% confidence interval [CI] 0.56–0.94) (34). Of note, within the 5.9-year observation period, the difference in survival was 1.2 years (34). Adjustment for traditional risk factors or inflammatory markers did not alter this result (34). In the framework of a similar study (TRIUMPH), the predictive power of the Omega-3 Index was compared to traditional risk factors, and was found to be more predictive than age, smoking, gender, diabetes, and others, but not congestive heart failure (35). A similar study in Norway did not confirm these results, and the authors speculated that an average Omega-3 Index of 6.42% precluded events from occurring in the study's 2-year timeframe (36). A case–control study compared 768 patients with nonfatal acute coronary syndrome to 768 matched healthy controls, and found the multivariable-adjusted odds for case status to be 0.77 (95% CI 0.70–0.85, $p<0.001$) for a 1-unit increase in the Omega-3 Index (37). When compared to the group with the lowest Omega-3 Index (<4%), the odds ratio for an acute coronary syndrome event was 0.58 (95% CI 0.42–0.80) in the group with an intermediate Omega-3 Index (4.1–7.9%); the odds ratio was 0.31 (95% CI 0.14–0.67; p for trend <0.0001) in the group with the highest Omega-3 Index (≥8%). This means that persons with an Omega-3 Index <4% had a threefold risk for the acute coronary syndrome, as compared to persons with an Omega-3 Index >8%. Taken together, a low Omega-3 Index (<4%) was associated with the greatest risk, while an Omega-3 Index >8% was found to offer greatest protection from cardiovascular events, while an intermediate Omega-3 Index (>4, <8%) was associated with intermediate risk, as initially suggested (9, 37). In a Western country, no association between the Omega-3 Index and bleeding in patients with an acute myocardial infarction was found (38). Data from Korea demonstrated little additional benefit for Omega-3 Index values >11% (39). For these and other reasons, an upper limit for the Omega-3 Index of 11% was suggested (40).

Several lines of evidence support a causal relation between increased longevity and absence of adverse cardiovascular events and a high Omega-3 Index. Epidemiologic studies demonstrated a low incidence of cardiovascular disease in populations with high intake or high levels of EPA and DHA (5, 40). Mechanistically, EPA and DHA have anti-arrhythmic effects, and they mitigated the course of coronary atherosclerosis (40, 41). A high Omega-3 Index is associated with slow telomere shortening, which is supposed to reflect slow biological aging (42). In most, but not all, large-scale randomized cardiovascular intervention studies with clinical endpoint investigating EPA, or EPA and DHA, reductions in total mortality and in cardiovascular mortality and morbidity were found (40, 41). In current meta-analyses, this translated into a reduction of cardiovascular mortality of some 12% (43). As mentioned previously, in a population increased intake of EPA and/or DHA reliably increases the mean Omega-3 Index. Taken together, current evidence supports a causal relation for a high Omega-3 Index (8–11%) and protection from cardiovascular disease.

CONGESTIVE HEART FAILURE

Congestive heart failure is a frequent disease of the elderly, with a large proportion of the patients in the second half of their sixth decade (44). In a large, placebo-controlled intervention trial in patients with congestive heart failure, 1 g EPA plus DHA reduced the primary endpoint, a combination of total mortality, sudden cardiac death, and rehospitalizations, largely by reducing mortality from worsening heart failure and sudden cardiac death (44). Mechanistically, EPA plus DHA not only have anti-arrhythmic effects, but they also improve parameters of left ventricular function in patients with congestive heart failure, like small improvements in left ventricular function and functional capacity (45–48), which may partly be mediated by decreased inflammation and prevention of pressure overload-induced cardiac dysfunction (49). As mentioned, other parameters are also beneficially affected (27, 28). The author's own unpublished observations indicate that the Omega-3 Index is low ($3.47 \pm 1.20\%$) in patients with congestive heart failure. A target level remains to be defined.

CERTAIN CANCERS

Some, but not all, epidemiologic and preclinical studies support a protective role for marine omega-3 fatty acids in breast cancer (50). The data for prostate cancer are even less convincing (51, 52). Other cancers currently studied are lung and colon cancers (53, 54). The author's own unpublished evidence indicates that the Omega-3 Index might provide a new and productive perspective for these lines of research.

ALZHEIMER'S DISEASE AND COGNITIVE DECLINE

While omega-3 fatty acids have not been demonstrated to hold promise as a cure for Alzheimer's disease, they do hold promise as a means to prevent the cognitive decline that frequently precedes Alzheimer's disease (55, 56). High plasma levels of DHA were found to be associated with a reduced risk for dementia (57, 58). Randomized controlled

trials in persons at risk for or with mild cognitive decline (but not Alzheimer's) have not had entirely consistent results (59–62), which might be partly due to the trial design issues discussed previously.

OTHER DISEASES

Children between ages 4 and 6 with a low Omega-3 Index are more likely to have atopy than children with a high Omega-3 Index (63). A low Omega-3 Index appears to be a risk factor for hemorrhagic and ischemic stroke in Korea (64). A low Omega-3 Index predisposes to sleep apnea (65).

COMORBIDITY

Depression and sleep apnea are frequently detected in patients with heart failure (66, 67). A low Omega-3 Index has been found in all three diseases (unpublished; (29, 65)). This observation might open up new avenues to better understanding these and other comorbidities.

FUTURE DIRECTIONS

Currently, a number of studies have been concluded and are awaiting publication, and many more studies are being conducted. Among other developments, the data from these studies will add further precision to the strengths and limitations of the Omega-3 Index as a cardiovascular risk factor. Introduction of the Omega-3 Index into clinical routine is likely to start in the cardiovascular field. The data will also weigh new uses for the Omega-3 Index (e.g., in ADHD). Another area that is being actively investigated is bioavailability of omega-3 fatty acids. Since the analytical method of the Omega-3 Index is a standardized fatty acid analysis of 26 fatty acids in the red cell membrane, more data will become available on the respective correlations and specific contributions of other fatty acids, like individual omega-6 or trans fatty acids, to health and specific disease processes, as already published for the acute coronary syndrome (68). As already mentioned, use of the Omega-3 Index in inclusion/exclusion criteria and/or as a treatment target will make intervention studies more efficient. Ultimately, randomized controlled intervention trials, comparing a non-Omega-3 Index-based approach to an Omega-3 Index-based approach (e.g., treating to a target of 8–11%), will need to be conducted in the various scientific fields mentioned.

CONCLUSION

Consistently, throughout all publications so far, a lower Omega-3 Index was found to be associated with a poorer outcome than was a higher Omega-3 Index. Clearly, adverse clinical events, like death, myocardial infarction, depression, and others, are more likely to occur in persons with a low Omega-3 Index (<4%) than in persons with a higher Omega-3 Index. The same is true for outcomes of pregnancy. An optimal Omega-3

Table 4.2
Currently suggested optimal Omega-3 Index levels for different age groups and conditions[a]

Pregnancy and lactation	8–11%
Babies and toddlers	8–11%
Childhood	tbd
Adolescence	tbd
Physical fitness	tbd
Prevention and treatment of some psychiatric diseases	tbd
Longevity	8–11%
Prevention and treatment of cardiovascular disease	8–11%
Congestive heart failure	tbd
Cognitive decline	tbd

tbd to be determined

[a]Some suggestions are based on preliminary evidence. For groups and conditions mentioned, a low Omega-3 Index (e.g., <4%) has been demonstrated to be associated with suboptimal outcome, and/or benefits of omega-3 supplementation have been demonstrated. See text for more detailed discussion. Please note that more precision will be added with results from ongoing and future research

Index is more difficult to define. For pregnancy and lactation, a target between 8 and 11% was suggested based on kinetic data on the handling of DHA in placenta, and population data in Korea. For prevention and treatment of cardiovascular disease, a target above 8% was initially suggested, based on circumstantial evidence, and now is directly supported by epidemiologic data generated in the meantime. The relation between the Omega-3 Index and cardiovascular risk appeared to flatten out at levels >11%, which, together with safety concerns, led to definition of a target range of 8–11%. Whether this range is also true for other areas, like psychiatric diseases, remains to be defined (Table 4.2). However, since the target ranges for pregnancy and lactation and cardiovascular disease turned out to be identical, it is tempting to speculate that this target range might also be true for other areas and age groups.

REFERENCES

1. Naylor RL, Hardy RW, Bureau DP, Chiu A, Elliott M, Farrell AP, et al. Feeding aquaculture in an era of finite resources. Proc Natl Acad Sci U S A. 2009;106:15103–10.
2. Bourre JM. Effect of increasing the omega-3 fatty acid in the diets of animals on the animal products consumed by humans. Med Sci (Paris). 2005;21:773–9 [Article in French].
3. Brenna JT, Salem Jr N, Sinclair AJ, Cunnane SC, International Society for the Study of Fatty Acids and Lipids, ISSFAL. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. Prostaglandins Leukot Essent Fatty Acids. 2009;80:85–9.
4. Plourde M, Chouinard-Watkins R, Vandal M, Zhang Y, Lawrence P, Brenna JT, et al. Plasma incorporation, apparent retroconversion and β-oxidation of 13C-docosahexaenoic acid in the elderly. Nutr Metab (Lond). 2011;8:5.
5. von Schacky C. The omega-3 index as a risk factor for cardiovascular diseases. Prostaglandins Other Lipid Mediat. 2011;96:94–8. doi:10.1016/j.prostaglandins.2011.06.008.
6. von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. J Clin Invest. 1985;76:2446–50.

7. von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest. 1985;76:1626–31.

8. von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1999;130:554–62.

9. Harris WS, von Schacky C. The omega-3 index: a new risk factor for death from CHD? Prev Med. 2004; 39:212–20.

10. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. J Am Med Assoc. 1995;275:836–7.

11. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med. 2002;346:1113–8.

12. Harris WS, Thomas RM. Biological variability of blood omega-3 biomarkers. Clin Biochem. 2010; 43:338–40.

13. Ebbesson SO, Devereux RB, Cole S, Ebbesson LO, Fabsitz RR, Haack K, et al. Heart rate is associated with red blood cell fatty acid concentration: the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. Am Heart J. 2010;159:1020–5.

14. Sala-Vila A, Harris WS, Cofán M, Pérez-Heras AM, Pintó X, Lamuela-Raventós RM, et al. Determinants of the omega-3 index in a Mediterranean population at increased risk for CHD. Br J Nutr. 2011;106:425–31.

15. Köhler A, Bittner D, Löw A, von Schacky C. Effects of a convenience drink fortified with n-3 fatty acids on the n-3 index. Br J Nutr. 2010;104:729–36.

16. Carver JD, Benford VJ, Han B, Cantor AB. The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. Brain Res Bull. 2001;56:79–85.

17. Cunningham P, McDermott L. Long chain PUFA transport in human term placenta. J Nutr. 2009;139: 636–9.

18. Larqué E, Demmelmair H, Gil-Sánchez A, Prieto-Sánchez MT, Blanco JE, Pagán A, et al. Placental transfer of fatty acids and fetal implications. Am J Clin Nutr. 2011;94(6 Suppl):1908S–13.

19. Dunstan JA, Mori TA, Barden A, Beilin LJ, Holt PG, Calder PC, et al. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty acid composition. Eur J Clin Nutr. 2004;58:429–37.

20. Brenna JT, Lapillonne A. Background paper on fat and fatty acid requirements during pregnancy and lactation. Ann Nutr Metab. 2009;55:97–122.

21. von Schacky C. Schwangerschaft, kindliche entwicklung, omega-3-fettsäuren und HS-omega-3 index. J Frauengesundheit. 2010;3:10–21.

22. Koletzko B, Cetin I, Brenna JT, Perinatal Lipid Intake Working Group, Child Health Foundation, Diabetic Pregnancy Study Group, European Association of Perinatal Medicine, European Association of Perinatal Medicine, European Society for Clinical Nutrition and Metabolism, European Society for Paediatric Gastroenterology, Hepatology and Nutrition, Committee on Nutrition, International Federation of Placenta Associations, International Society for the Study of Fatty Acids and Lipids. Dietary fat intakes for pregnant and lactating women. Br J Nutr. 2007;98:873–7.

23. Minns LM, Kerling EH, Neely MR, Sullivan DK, Wampler JL, Harris CL, et al. Toddler formula supplemented with docosahexaenoic acid (DHA) improves DHA status and respiratory health in a randomized, double-blind, controlled trial of US children less than 3 years of age. Prostaglandins Leukot Essent Fatty Acids. 2010;82:287–93.

24. Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Long-chain omega-3 polyunsaturated fatty acids in the blood of children and adolescents with juvenile bipolar disorder. Lipids. 2008;43:1031–8.

25. Walser B, Stebbins CL. Omega-3 fatty acid supplementation enhances stroke volume and cardiac output during dynamic exercise. Eur J Appl Physiol. 2008;104:455–61.

26. Peoples GE, McLennan PL, Howe PR, Groeller H. Fish oil reduces heart rate and oxygen consumption during exercise. J Cardiovasc Pharmacol. 2008;52:540–7.

27. Moyers B, Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. Relation of whole blood n-3 fatty acid levels to exercise parameters in patients with stable coronary artery disease (from the Heart and Soul Study). Am J Cardiol. 2011;107:1149–54.

28. O'Keefe Jr JH, Abuissa H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. Am J Cardiol. 2006;97:1127–30.

29. Baghai TC, Varallo-Bedarida G, Born C, Häfner S, Schüle C, Eser D, et al. Major depressive disorder is associated with cardiovascular risk factors and low omega-3 index. J Clin Psychiatry. 2011;72:1242–7.

30. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry. 2010;68:140–7.

31. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011;72:1577–84.

32. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73:81–6.

33. Matsuoka Y, Nishi D, Nakaya N, Sone T, Hamazaki K, Hamazaki T, et al. Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake: the APOP randomized controlled trial. BMC Psychiatry. 2011;11:132.

34. Pottala JV, Garg S, Cohen BE, Whooley MA, Harris WS. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul Study. Circ Cardiovasc Qual Outcomes. 2010;3:406–12.

35. Abuannadi M, O'Keefe JH, Spertus JA, Kennedy KF, Harris WS, et al. Omega-3 index: an independent predictor of 1 year all cause mortality in myocardial infarction (MI) patients. Poster 174, AHA QCOR Meeting, 19–21 May 2010. Accessible at http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_319392.pdf

36. Aarsetoey H, Pönitz V, Grundt H, Staines H, Harris WS, Nilsen DW. (n-3) fatty acid content of red blood cells does not predict risk of future cardiovascular events following an acute coronary syndrome. J Nutr. 2009;139:507–13.

37. Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis. 2008;197:821–8.

38. Salisbury AC, Harris WS, Amin AP, Reid KJ, O'Keefe Jr JH, Spertus JA. Relation between red blood cell omega-3 fatty acid index and bleeding during acute myocardial infarction. Am J Cardiol. 2012;109:13–8.

39. Park Y, Lim J, Lee J, Kim SG. Erythrocyte fatty acid profiles can predict acute non-fatal myocardial infarction. Br J Nutr. 2009;102:1355–6.

40. von Schacky C. Omega-3 Index and cardiovascular disease prevention: principle and rationale. Lipid Technol. 2010;22:151–4.

41. von Schacky C. Omega-3 fatty acids vs. cardiac disease: the contribution of the omega-3 index. Cell Mol Biol. 2010;56:90–8.

42. Farzneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. JAMA. 2010;303:250–7.

43. Filion KB, El Khoury F, Bielinski M, Schiller I, Dendukuri N, Brophy JM. Omega-3 fatty acids in high-risk cardiovascular patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2010;10:24.

44. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1223–30.

45. von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. Cardiovasc Res. 2007;73:310–5.

46. Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, et al.; GISSI-HF investigators. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. Eur J Heart Fail. 2010;12:1345–53

47. Moertl D, Hammer A, Steiner S, Hutuleac R, Vonbank K, Berger R. Dose-dependent effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of nonischemic origin: a double-blind, placebo-controlled, 3-arm study. Am Heart J. 2011;161:915.e1–9.

48. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2011;57:870–9.

49. Duda MK, O'Shea KM, Tintinu A, Xu W, Khairallah RJ, Barrows BR, et al. Fish oil but not flaxseed oil decreases inflammation and prevents pressure-overload induced cardiac dysfunction. Cardiovasc Res. 2009;81:319–27.

50. Signori C, El-Bayoumy K, Russo J, Thompson HJ, Richie JP, Hartman TJ, et al. Chemoprevention of breast cancer by fish oil in preclinical models: trials and tribulations. Cancer Res. 2011;71:6091–6.

51. Hori S, Butler E, McLoughlin J. Prostate cancer and diet: food for thought? BJU Int. 2011;107:1348–59.

52. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr. 2010;92:1223–33.

53. Fasano E, Serini S, Piccioni E, Innocenti I, Calviello G. Chemoprevention of lung pathologies by dietary n-3 polyunsaturated fatty acids. Curr Med Chem. 2010;17:3358–76.

54. Dupertuis YM, Meguid MM, Pichard C. Colon cancer therapy: new perspectives of nutritional manipulations using polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care. 2007;10:427–32.

55. Huang TL. Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. J Alzheimers Dis. 2010;21:673–90.

56. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010;304:1903–11.

57. Lopez LB, Kritz-Silverstein D, Barrett Connor E. High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo study. J Nutr Health Aging. 2011;15:25–31.

58. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol. 2006;63:1545–50.

59. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al.; MIDAS Investigators. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6:456–64

60. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010;91:1725–32.

61. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL. OM3 randomized trial. Am J Clin Nutr. 2011;94:278–86.

62. van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008;71:430–8.

63. Hwang I, Cha A, Lee H, Yoon H, Yoon T, Cho B, et al. n-3 Polyunsaturated fatty acids and atopy in Korean preschoolers. Lipids. 2007;42(4):345–9.

64. Park Y, Park S, Yi H, Kim HY, Kang SJ, Kim J, et al. Low level of n-3 polyunsaturated fatty acids in erythrocytes is a risk factor for both acute ischemic and hemorrhagic stroke in Koreans. Nutr Res. 2009;29:825–30.

65. Ladesich JB, Pottala JV, Romaker A, Harris WS. Membrane levels of omega-3 docosahexaenoic acid is associated with obstructive sleep apnea. J Clin Sleep Med. 2011;7:391–6.

66. Gnanasekaran G. Epidemiology of depression in heart failure. Heart Fail Clin. 2011;7:1–10.

67. McKelvie RS, Moe GW, Cheung A, Costigan J, Ducharme A, Estrella-Holder E, et al. The 2011 Canadian Cardiovascular Society heart failure management guidelines update: focus on sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care. Can J Cardiol. 2011;27:319–38.

68. Block RC, Harris WS, Reid KJ, Spertus JA. Omega-6 and trans fatty acids in blood cell membranes: a risk factor for acute coronary syndromes? Am Heart J. 2008;156:1117–23.

69. Aarsetoey H, Aarsetoey R, Lindner T, Staines H, Harris WS, Nilsen DW. Low levels of the omega-3 index are associated with sudden cardiac arrest and remain stable in survivors in the subacute phase. Lipids. 2011;46:151–6.