Atherosclerosis 262 (2017) 51–54

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The Omega-3 Index and relative risk for coronary heart disease mortality: Estimation from 10 cohort studies

William S. Harris [a, *], Liana Del Gobbo [b], Nathan L. Tintle [c]

[a] OmegaQuant Analytics, LLC and Sanford School of Medicine, University of South Dakota, Sioux Falls, SD, USA
[b] Stanford University School of Medicine, Palo Alto, CA, USA
[c] Department of Mathematics & Statistics, Dordt College, Sioux Center, IA, USA

ARTICLE INFO

Article history:
Received 4 March 2017
Received in revised form
23 April 2017
Accepted 5 May 2017
Available online 6 May 2017

Keywords:
Fish oil
Omega-3
Eicosapentaenoic acid
Docosahexaenoic acid
Omega-3 Index
Coronary heart disease
Biomarker
Prospective cohort
Meta-analysis

ABSTRACT

Background and aims: A recent 19-cohort meta-analysis examined the relationships between biomarkers of omega-3 fatty acids and risk for coronary heart disease (CHD). That study did not, however, report hazard ratios (HRs) specifically as a function of erythrocyte eicosapentaenoic (EPA) plus docosahexaenoic (DHA) levels, a metric called the Omega-3 Index in which EPA + DHA content is expressed as a percent of total fatty acids. The Omega-3 Index has been used in several recent studies and is a validated biomarker of omega-3 fatty acid tissue levels, but additional data are needed to confirm (or refute) the originally-proposed clinical cut-points of <4% (higher risk) and 8%–12% (lower risk).
Methods: The present study was therefore undertaken using published data from this meta-analysis to estimate HRs per 1-SD increase in the Omega-3 Index and median quintile values for this metric across 10 of the cohorts for which the needed data were available.
Results: The overall mean (SD) for the Omega-3 Index in these 10 cohort studies was 6.1% (2.1%), and the HR for a 1-SD increase was 0.85 (95% confidence interval, 0.80–0.91). Median quintile 1 and 5 levels were 4.2% *vs.* 8.3%, respectively. Based on these values, we estimate that risk for fatal CHD would have been reduced by about 30% moving from an Omega-3 Index of 4%–8%.
Conclusions: These findings support the use of <4% and >8% as reasonable therapeutic targets for the Omega-3 Index.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

The relationship between circulating long chain omega-3 fatty acid (LC n-3 FA) levels and risk for future coronary heart disease (CHD) has been challenging to decipher, in part due to the different lipid pools in which LC n-3 FA levels have been measured. Some authors have used red blood cell (RBC) levels of eicosapentaenoic acid and docosahexaenoic acid (EPA plus DHA; the Omega-3 Index) to describe *in vivo* LC n-3 FA status, whereas others have used whole blood, whole plasma/serum, or lipid classes from the latter, i.e., phospholipids (PLs), cholesteryl esters (CEs), triglycerides (TGs) and/or non-esterified FAs. Still others have estimated LC n-3 FA status from adipose tissue biopsies. While the LC n-3 FA content of all of these pools intercorrelate [1], the absolute levels in each depot differ, making it difficult to compare results based on different metrics.

It has been proposed that, much like hemoglobin A1c is a better long-term marker of glycemic status than is plasma glucose, RBC membranes may also be the preferred matrix for assessing LC n-3 FA status [2]. RBC EPA + DHA (i.e., the Omega-3 Index) levels have one-fourth the within-person variability over time compared to plasma measures [3], and they are less sensitive to perturbation by acute intakes of LC n-3 FA [4]. The Omega-3 Index is highly correlated with levels of EPA + DHA in human cardiac tissue [5,6] and with those in multiple organs in animal models [7–9]. EPA and DHA are carried in the membranes of RBCs, which is where they are primarily found in all other tissues (except adipose tissue), and most of the biochemical/physiological effects of these FAs are believed to flow from their presence in cell membranes [10,11] Based in part on these considerations, Stark et al. [12] recently summarized the current knowledge on LC n-3 FA status worldwide by converting published LC n-3 FA data from nearly 400 data sets including about 24,000 individuals into Omega-3 Index

* Corresponding author. OmegaQuant Analytics, LLC, 5009 W. 12th St, Ste 8, Sioux Falls, SD 57106, USA.
E-mail address: bill@omegaquant.com (W.S. Harris).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.05.007
0021-9150/© 2017 Elsevier B.V. All rights reserved.

equivalents. This was accomplished by creating equations relating the LC n-3 FA content of each depot to that of RBCs and then calculating the estimated Omega-3 Index for each study [13]. This exercise revealed widely divergent Omega-3 Index scores around the world (e.g., North America <4% *vs.* Japan/Korea >8%). Health Canada chose the Omega-3 Index for use in its most recent national health survey [14], and the largest dataset yet published on circulating FA status in humans (~160,000 individuals in the USA) utilized the Omega-3 Index [15].

In 2016, Del Gobbo et al. [16] pooled coronary heart disease (CHD) outcomes across 19 cohorts with over 45,000 patients in which biomarkers of LC n-3 status were measured. Since many different lipid pools were used to determine LC n-3 FA status (as noted above), CHD incidence in quintile (Q) 1 was compared to that of Q5 across all studies regardless of which pool they were measured in. Risk for CHD between these extremes was calculated, as was the change in risk per 1-SD increase in LC n-3 FAs. The purpose of this report is to determine what the mean Omega-3 Index equivalents for Q1 and Q5 would have been had RBC FAs been measured in all these studies. Using this information and the estimated change in CHD risk across quintiles, we hoped to gain further insight into what levels of the Omega-3 Index might be linked with higher *vs.* lower risk for CHD. These cut-points could then be used in the clinic, in concert with other CHD risk factors, to help identify those patients at highest risk for fatal CHD.

2. Materials and methods

2.1. Data extraction

We used published data from 10 cohorts in Del Gobbo et al. that reported risk for fatal CHD and had data on EPA + docosapentaenoic acid (DPA) + DHA levels in plasma or plasma PL. The following cohorts were included: Health Professionals Follow-up study (HPFU) [17], Kupio Ischemic Heart Disease study (KIHD) [18], Cardiovascular Health Study (CHS) [19], Nurses' Health Study (NHS) [20], Physician's Health Study (PHS) [21], European Prospective Investigation into Cancer – Norfolk (EPIC) [22], Melbourne Collaborative Cohort Study (MCCS) [23], The Multi-Ethnic Study of Atherosclerosis (MESA) [24], the Northern Sweden Health and Disease Study-II (NSHDS) [25], and the Singapore Chinese Health Study (SCHS) [26]. The details for each were provided in Del Gobbo et al. (Table 1 and eMethods). Median values for EPA + DPA + DHA in quintiles 1 and 5 from each lipid depot were taken from eTable 3, and for the mean and SD for each fatty acid separately from eTable 2 [16].

2.2. Data manipulation

In order to convert plasma and plasma PL LC n3 FA values into the equivalent Omega-3 Index, we generated conversion equations based on the reported EPA + DPA + DHA content of the sample. For plasma PL, we used data from 50 random samples tested in the laboratory. For conversion of whole plasma EPA + DPA + DHA to the Omega-3 Index, we used data from 2312 subjects from an ongoing research study in which both RBC and whole plasma are being analyzed. (We did not do the same for plasma CE or for adipose tissue since there was only one trial using the former metric, and since we have no data from which to create a conversion equation for the latter). The two equations thus generated and subsequently used in this analysis were: Omega-3 Index = 0.0452*ln (plasma EPA + DPA + DHA)+0.2214 (r = 0.88), and Omega-3 Index = 0.851*(plasma PL EPA + DPA + DHA)+0.0047 (r = 0.92). When both RBC and plasma PL data were available from the same data set (i.e., in the Nurses' Health Study-I), the plasma data were used as the primary exposure measure [because those were the data used to calculate hazard ratios (HRs) for eFig. 1 [16]]. When only RBC data were available (i.e., in the Physicians' Health Study), they were used and pooled with phospholipid-based studies. In one study [26], plasma EPA and DHA were reported, but not DPA. In this case, DPA's contribution to the EPA + DPA + DHA metric was calculated from the other 9 studies, and using that, a DPA value was imputed for the SCHS study. The EPA + DPA + DHA data for the first and fifth Qs in each of the 10 cohorts (eTable 3) were used to calculate an estimated Omega-3 Index for these Qs. We also calculated the weighted (by n) mean and standard deviation (SD) for the EPA + DPA + DHA value from these 10 studies and then converted them to the mean (SD) Omega-3 Index using the equations above. Lipid-pool specific, pair-wise correlations among EPA, DPA and DHA (needed for the SD calculations) were derived from the same extracted data described above. The primary endpoint in this study was fatal CHD (eFig. 1) where the HR per 1SD was calculated as described previously [16].

Table 1
First and fifth quintile median values for EPA + DPA + DHA (percent of total fatty acids) by sample type, and the estimated Omega-3 Index weighted by study sample size.

	n	EPA + DPA + DHA	Estimated Omega-3 Index[a]
CHS	3941	**3.10%**	**3.11%**
EPIC	7384	**5.24%**	**4.93%**
MCCS	5279	**4.66%**	**4.44%**
MESA	2856	**3.91%**	**3.80%**
NSHDS	759	**5.61%**	**5.24%**
HPFU	1291	1.76%	3.88%
KIHD	1837	3.11%	6.45%
SCHS	1555	1.40%	3.72%
NHS	603	1.51%	3.19%
PHS	2000	-	*2.34%*
Quintile 1 weighted mean			4.20%
CHS		**6.46%**	**5.97%**
EPIC		**10.97%**	**9.81%**
MCCS		**8.42%**	**7.64%**
MESA		**9.27%**	**8.36%**
NSHDS		**9.41%**	**8.48%**
HPFU		4.35%	7.97%
KIHD		6.49%	9.78%
SCHS		4.87%	9.22%
NHS		6.14%	9.53%
PHS		-	*6.79%*
Quintile 5 weighted mean			8.30%[b]

Plasma PL (**bold**); plasma (normal type); RBC, *italics*. Study abbreviations as in Materials and methods.
[a] The equation applied in plasma samples was: Omega-3 Index = 0.0452*ln (plasma EPA + DPA + DHA)+0.2214 (r = 0.88), and that applied in plasma phospholipid samples was: Omega-3 Index = 0.851*(plasma PL EPA + DPA + DHA)+0.0047 (r = 0.92).
[b] $p < 0.0001$.

3. Results

The overall, weighted mean (SD) of the Omega-3 Index calculated from mean EPA + DPA + DHA values in these 10 studies was 6.1% (2.1%). Q1 and Q5 values for EPA + DPA + DHA and the Omega-3 Index derived from it are shown in Table 1. The overall weighted median Omega-3 Index for these two quintiles was 4.2% *vs.* 8.3% ($p < 0.0001$ by *t*-test), respectively. The overall HR for fatal CHD per a 1-SD increase in EPA + DPA + DHA (or the Omega-3 Index) was 0.85 (0.80–0.91) (from eFig. 1 in [16]).

4. Discussion

This analysis was undertaken to estimate how risk for fatal CHD

varied by Omega-3 Index values using data from the meta-analysis by Del Gobbo et al. [16]. In that study, the relative risk was evaluated using data from five sample types (erythrocyte, plasma, plasma CE, plasma PL and adipose tissue) both by quintile and linear analysis for the 4 individual n-3 FAs (ALA, EPA, DPA and DHA). The only combined metric reported there was EPA + DPA + DHA, and for this metric, only the HR for fatal CHD per 1SD increase was calculated. For the present analysis, only studies that reported data on fatal CHD and that used erythrocytes, whole plasma or plasma PL analysis were used (n = 10). As there is considerable prior literature using the Omega-3 Index (erythrocyte EPA + DHA) as a marker of n-3 FA status (see below), it was of interest to re-analyze the Del Gobbo data with respect to this metric. We found that risk for fatal CHD was significantly reduced by 15% for each 1-SD increase in the Omega-3 Index. We also found that the corresponding Omega-3 Index median values for Q1 and Q5 were 4.2% and 8.3%, respectively. These are similar to the 4% and 8% cut-points that were originally-proposed for the Omega-3 Index in 2004 based on estimations from published studies then available [27].

The estimated mean Omega-3 Index in these cohorts was 6.1%, and from the linear analysis, a 1 SD (2.1%) increase (i.e., a level of 8.2%) was associated with a 15% risk reduction for fatal CHD relative to the mean level. Conversely, an Omega-3 Index 2.1% lower than the mean (i.e., 4%) would be associated with a 15% increase in risk. Therefore, the relative risk for fatal CHD at an Omega-3 Index of about 8% was reduced by about 30% compared with 4%.

Although we cannot infer causal relationships from these observational data, it is nevertheless interesting to consider how much more EPA + DHA an individual with an Omega-3 Index of 4% (a level common in most Western countries [12]) would need to consume to effect a 4% point increase in the Omega-3 Index. Based on a recent dose-response study [28], a change of this magnitude in the Omega-3 Index would require an increased consumption of about 1.5 g/day of EPA + DHA. This would equate to a daily intake of 100 g of farmed Atlantic salmon [29], 5 standard fish oil capsules, or 2 capsules of the most highly concentrated products.

To the extent that the Omega-3 Index provides additional, independent prognostic value for risk for CHD, its use in clinical medicine will likely grow. Indeed, several clinical laboratories in the US and EU already offer omega-3 testing to healthcare providers, but there is no uniformity in testing metrics among labs. This inconsistency will need to be addressed before widespread testing becomes a reality. In this regard, the Omega-3 Index has much to recommend it, since no other single marker of omega-3 status has been associated with lower risk for coronary disease [30] sudden cardiac death [31,32], acute coronary syndromes [33], all-cause mortality [34–36] and other health conditions such as impaired cognitive function [37–41], depression [42–46], aggressive behaviors [47] and bipolar disease [48]. As noted earlier, the relations between age and sex and the Omega-3 Index have been reported in over 160,000 patients [15], in a Canadian national survey [14], and worldwide levels of this metric were recently reported in over 24,000 subjects from 54 countries [12]. Hence, studies to more clearly define the clinically-relevant cut-points or target ranges are needed.

Using only the published data from Del Gobbo et al. and not undertaking new analyses from their original data sources, we could only develop estimates for fatal (not non-fatal or total) CHD. This is because HRs were published for only this endpoint (per 1 SD of EPA + DPA + DHA, which we then converted to Omega-3 Index equivalents). Moreover, without access to the original data, we were not able to perform a formal dose-response analysis. Another limitation was the use of correlational equations derived in one laboratory to convert the n-3 PUFA content of various lipid compartments which were measured in other labs. Although this approach has been used in the past [13,27,49,50], it assumes that all labs are generating plasma (or erythrocyte or plasma PL) data in a standardized and comparable manner. There are several methods for determining FA composition, and there is no uniformity in units. Even when conventionally expressed as a percent of total FAs, exactly which FAs constitute the denominator is not often stated and not standardized. Hence, using (as we have here) correlational data from our lab (where the FA of RBCs and other circulating lipid pools are measured using identical methods) to generate conversion equations, which are then applied to FA data generated in another lab, must be considered somewhat tentative. Nevertheless, such an approach is the only possible way to bring some degree of harmony to FA metrics reported in a wide variety of lipid pools. Finally, although overall population mean levels of the Omega-3 Index were relatively easily calculated from the cohort-specific mean levels of EPA + DPA + DHA, from each given separately in Supplemental data from Del Gobbo et al. in order to calculate the cohort-specific SDs for this combined metric, we needed to assume that pairwise correlations between EPA, DPA and DHA were stable across studies (but within lipid pool). We also had to assume that the pooled covariance was equivalent to the weighted average of individual cohort covariances in order to compute the pooled SD. These are reasonable assumptions which have limited impact on the conclusions.

In conclusion, the originally proposed cut-points of <4% and >8% for 'high risk' and 'low risk' Omega-3 Index values, respectively, are generally supported by findings for fatal CHD from Del Gobbo et al. Further research to define the incremental predictive value of these cut-points over and above classical CHD risk markers is needed.

Conflict of interest

WSH is the co-developer of the Omega-3 Index test and the President of OmegaQuant, LLC, a laboratory that offers the test commercially.

Financial support

This analysis was internally funded at OmegaQuant Analytics, LLC.

Author contributions

WSH conceived of this project and wrote the first draft. LDG was the lead author on the original meta-analysis from which data for this analysis was based. NLT provided biostatistical support. All authors contributed to and approved the final manuscript.

References

[1] L.M. Browning, C.G. Walker, A.P. Mander, A.L. West, J. Madden, J.M. Gambell, S. Young, L. Wang, S.A. Jebb, P.C. Calder, Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish, Am. J. Clin. Nutr. 96 (2012) 748–758.
[2] W.S. Harris, The omega-3 index as a risk factor for coronary heart disease, Am. J. Clin. Nutr. 87 (2008) 1997S–2002S.
[3] W.S. Harris, R.M. Thomas, Biological variability of blood omega-3 biomarkers, Clin. Biochem. 43 (2010) 338–340.
[4] W.S. Harris, S.A. Varvel, J.V. Pottala, G.R. Warnick, J.P. McConnell, Comparative effects of an acute dose of fish oil on omega-3 fatty acid levels in red blood cells versus plasma: implications for clinical utility, J. Clin. Lipidol. 7 (2013) 433–440.
[5] R.G. Metcalf, L.G. Cleland, R.A. Gibson, K.C. Roberts-Thomson, J.R. Edwards, P. Sanders, R. Stuklis, M.J. James, G.D. Young, Relation between blood and atrial fatty acids in patients undergoing cardiac bypass surgery, Am. J. Clin. Nutr. 91 (2010) 528–534.

[6] W.S. Harris, S.A. Sands, S.L. Windsor, H.A. Ali, T.L. Stevens, A. Magalski, C.B. Porter, A.M. Borkon, Omega-3 fatty acids in cardiac biopsies from heart transplant patients: correlation with erythrocytes and response to supplementation, Circulation 110 (2004) 1645–1649.
[7] C. Arnold, M. Markovic, K. Blossey, G. Wallukat, R. Fischer, R. Dechend, A. Konkel, S.C. von, F.C. Luft, D.N. Muller, M. Rothe, W.H. Schunck, Arachidonic acid-metabolizing cytochrome p450 enzymes are targets of {omega}-3 fatty acids, J. Biol.Chem. 285 (2010) 32720–32733.
[8] J.I. Fenton, E.A. Gurzell, E.A. Davidson, W.S. Harris, Red blood cell pufas reflect the phospholipid pufa composition of major organs, Prostagl. Leukot. Essent. Fat. Acids 112 (2016) 12–23.
[9] W.C. Tu, B.S. Muhlhausler, L.N. Yelland, R.A. Gibson, Correlations between blood and tissue omega-3 lcpufa status following dietary ala intervention in rats, Prostagl. Leukot. Essent. Fat. Acids 88 (2013) 53–60.
[10] S.R. Shaikh, J.J. Kinnun, X. Leng, J.A. Williams, S.R. Wassall, How polyunsaturated fatty acids modify molecular organization in membranes: insight from nmr studies of model systems, Biochim. Biophys. Acta 1848 (2015) 211–219.
[11] H.F. Turk, R.S. Chapkin, Membrane lipid raft organization is uniquely modified by n-3 polyunsaturated fatty acids, Prostagl. Leukot. Essent. Fat. Acids 88 (2013) 43–47.
[12] K.D. Stark, M.E. Van Elswyk, M.R. Higgins, C.A. Weatherford, N. Salem Jr., Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults, Prog. Lipid Res. 63 (2016) 132–152.
[13] K.D. Stark, J.J. Aristizabal Henao, A.H. Metherel, L. Pilote, Translating plasma and whole blood fatty acid compositional data into the sum of eicosapentaenoic and docosahexaenoic acid in erythrocytes, Prostagl. Leukot. Essent. Fat. Acids 104 (2016) 1–10.
[14] K. Langlois, W.M. Ratnayake, Omega-3 index of canadian adults, Health Rep. 26 (2015) 3–11.
[15] W.S. Harris, J.V. Pottala, S.A. Varvel, J.J. Borowski, J.N. Ward, J.P. McConnell, Erythrocyte omega-3 fatty acids increase and linoleic acid decreases with age: observations from 160,000 patients, Prostagl. Leukot. Essent. Fat. Acids 88 (2013) 257–263.
[16] L.C. Del Gobbo, F. Imamura, S. Aslibekyan, M. Marklund, J.K. Virtanen, M. Wennberg, M.Y. Yakoob, S.E. Chiuve, L. Dela Cruz, A.C. Frazier-Wood, A.M. Fretts, E. Guallar, C. Matsumoto, K. Prem, T. Tanaka, J.H. Wu, X. Zhou, C. Helmer, E. Ingelsson, J.M. Yuan, P. Barberger-Gateau, H. Campos, P.H. Chaves, L. Djousse, G.G. Giles, J. Gomez-Aracena, A.M. Hodge, F.B. Hu, J.H. Jansson, I. Johansson, K.T. Khaw, W.P. Koh, R.N. Lemaitre, L. Lind, R.N. Luben, E.B. Rimm, U. Riserus, C. Samieri, P.W. Franks, D.S. Siscovick, M. Stampfer, L.M. Steffen, B.T. Steffen, M.Y. Tsai, R.M. van Dam, S. Voutilainen, W.C. Willett, M. Woodward, D. Mozaffarian, Omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies, JAMA Intern. Med. 176 (2016) 1155–1166.
[17] E.B. Rimm, E.L. Giovannucci, W.C. Willett, G.A. Colditz, A. Ascherio, B. Rosner, M.J. Stampfer, Prospective study of alcohol consumption and risk of coronary disease in men, Lancet 338 (1991) 464–468.
[18] M. Vanharanta, S. Voutilainen, T.A. Lakka, M. van der Lee, H. Adlercreutz, J.T. Salonen, Risk of acute coronary events according to serum concentrations of enterolactone: a prospective population-based case-control study, Lancet 354 (1999) 2112–2115.
[19] L.P. Fried, N.O. Borhani, P. Enright, C.D. Furberg, J.M. Gardin, R.A. Kronmal, L.H. Kuller, T.A. Manolio, M.B. Mittelmark, A. Newman, et al., The cardiovascular health study: design and rationale, Ann. Epidemiol. 1 (1991) 263–276.
[20] W.C. Willett, M.J. Stampfer, G.A. Colditz, B.A. Rosner, C.H. Hennekens, F.E. Speizer, Dietary fat and the risk of breast cancer, N. Engl. J. Med. 316 (1987) 22–28.
[21] W.G. Christen, J.M. Gaziano, C.H. Hennekens, Design of physicians' health study ii–a randomized trial of beta-carotene, vitamins e and c, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials, Ann. Epidemiol. 10 (2000) 125–134.
[22] N. Day, S. Oakes, R. Luben, K.T. Khaw, S. Bingham, A. Welch, N. Wareham, Epic-norfolk: study design and characteristics of the cohort. European prospective investigation of cancer, Br. J. Cancer 80 (Suppl 1) (1999) 95–103.
[23] G.G. Giles, D.R. English, The melbourne collaborative cohort study, IARC Sci. Publ. 156 (2002) 69–70.
[24] D.E. Bild, D.A. Bluemke, G.L. Burke, R. Detrano, A.V. Diez Roux, A.R. Folsom, P. Greenland, D.R. Jacob Jr., R. Kronmal, K. Liu, J.C. Nelson, D. O'Leary, M.F. Saad, S. Shea, M. Szklo, R.P. Tracy, Multi-ethnic study of atherosclerosis: objectives and design, Am. J. Epidemiol. 156 (2002) 871–881.
[25] H. Lowel, A. Doring, A. Schneider, M. Heier, B. Thorand, C. Meisinger, The monica augsburg surveys–basis for prospective cohort studies, Gesundheitswes. Bundesverb. Arzte Offentlichen Gesundheitsd. Ger. 67 (Suppl 1) (2005) S13–S18.
[26] J.H. Hankin, D.O. Stram, K. Arakawa, S. Park, S.H. Low, H.P. Lee, M.C. Yu, Singapore chinese health study: development, validation, and calibration of the quantitative food frequency questionnaire, Nutr. Cancer 39 (2001) 187–195.
[27] W.S. Harris, C. von Schacky, The omega-3 index: a new risk factor for death from coronary heart disease? Prev. Med. 39 (2004) 212–220.
[28] M.R. Flock, A.C. Skulas-Ray, W.S. Harris, T.D. Etherton, J.A. Fleming, P.M. Kris-Etherton, Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial, J. Am. Heart Assoc. 2 (2013) e000513.
[29] M. Sprague, J.R. Dick, D.R. Tocher, Impact of sustainable feeds on omega-3 long-chain fatty acid levels in farmed atlantic salmon, 2006-2015, Sci. Rep. 6 (2016) 21892.
[30] R. Chowdhury, S. Warnakula, S. Kunutsor, F. Crowe, H.A. Ward, L. Johnson, O.H. Franco, A.S. Butterworth, N.G. Forouhi, S.G. Thompson, K.T. Khaw, D. Mozaffarian, J. Danesh, E. Di Angelantonio, Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis, Ann. Intern. Med. 160 (2014) 398–406.
[31] C.M. Albert, H. Campos, M.J. Stampfer, P.M. Ridker, J.E. Manson, W.C. Willett, J. Ma, Blood levels of long-chain n-3 fatty acids and the risk of sudden death, N. Engl. J. Med. 346 (2002) 1113–1118.
[32] D.S. Siscovick, T.E. Raghunathan, I. King, S. Weinmann, K.G. Wicklund, J. Albright, V. Bovbjerg, P. Arbogast, H. Smith, L.H. Kushi, et al., Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest, JAMA 274 (1995) 1363–1367.
[33] R.C. Block, W.S. Harris, K.J. Reid, S.A. Sands, J.A. Spertus, Epa and dha in blood cell membranes from acute coronary syndrome patients and controls, Atherosclerosis 197 (2007) 821–828.
[34] M.E. Kleber, G.E. Delgado, S. Lorkowski, W. Marz, C. von Schacky, Omega-3 fatty acids and mortality in patients referred for coronary angiography. The ludwigshafen risk and cardiovascular health study, Atherosclerosis 252 (2016) 175–181.
[35] J.V. Pottala, S. Garg, B.E. Cohen, M.A. Whooley, W.S. Harris, 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. 3 (2010) 406–412.
[36] W.S. Harris, J.V. Pottala, M.E. Espeland, K.E. Margolis, J.E. Manson, L. Wang, T.M. Brasky, J.G. Robinson, Red blood cell polyunsaturated fatty acids and mortality in the women's health initiative memory study, J. Clin. Lipidol. 11 (2017) 250–259.
[37] Z.S. Tan, W.S. Harris, A.S. Beiser, R. Au, J.J. Himali, S. Debette, A. Pikula, C. Decarli, P.A. Wolf, R.S. Vasan, S.J. Robins, S. Seshadri, Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging, Neurology 78 (2012) 658–664.
[38] D.T. Johnston, P.A. Deuster, W.S. Harris, H. Macrae, M.N. Dretsch, Red blood cell omega-3 fatty acid levels and neurocognitive performance in deployed u.S. Service members, Nutr. Neurosci. 16 (2013) 30–38.
[39] I.S. van der Wurff, C. von Schacky, K. Berge, M.P. Zeegers, P.A. Kirschner, R.H. de Groot, Association between blood omega-3 index and cognition in typically developing Dutch adolescents, Nutrients 108 (2016) 22–29.
[40] K. Lukaschek, C. von Schacky, J. Kruse, K.H. Ladwig, Cognitive impairment is associated with a low omega-3 index in the elderly: results from the kora-age study, Dementia Geriatric Cognitive Disord. 42 (2016) 236–245.
[41] J.V. Pottala, K. Yaffe, J.G. Robinson, M.A. Espeland, R. Wallace, W.S. Harris, Higher rbc epa + dha corresponds with larger total brain and hippocampal volumes: whims-mri study, Neurology 82 (2014) 435–442.
[42] S.J. Bigornia, W.S. Harris, L.M. Falcon, J.M. Ordovas, C.Q. Lai, K.L. Tucker, The omega-3 index is inversely associated with depressive symptoms among individuals with elevated oxidative stress biomarkers, J. Nutr. 146 (2016) 758–766.
[43] D. Baek, Y. Park, Association between erythrocyte n-3 polyunsaturated fatty acids and biomarkers of inflammation and oxidative stress in patients with and without depression, Prostagl. Leukot. Essent. Fat. acids 89 (2013) 291–296.
[44] Y. Park, M. Kim, D. Baek, S.H. Kim, Erythrocyte n-3 polyunsaturated fatty acid and seafood intake decrease the risk of depression: case-control study in korea, Ann. Nutr. Metab. 61 (2012) 25–31.
[45] T.C. Baghai, G. Varallo-Bedarida, C. Born, S. Hafner, C. Schule, D. Eser, R. Rupprecht, B. Bondy, C. von Schacky, Major depressive disorder is associated with cardiovascular risk factors and low omega-3 index, J. Clin. Psychiatry 72 (2010) 1242–1247.
[46] A.A. Amin, R.A. Menon, K.J. Reid, W.S. Harris, J.A. Spertus, Acute coronary syndrome patients with depression have low blood cell membrane omega-3 fatty acid levels, Psychosom. Med. 70 (2008) 856–862.
[47] B.J. Meyer, M.K. Byrne, C. Collier, N. Parletta, D. Crawford, P.C. Winberg, D. Webster, K. Chapman, G. Thomas, J. Dally, M. Batterham, I. Farquhar, A.M. Martin, L. Grant, Baseline omega-3 index correlates with aggressive and attention deficit disorder behaviours in adult prisoners, PLoS One 10 (2015) e0120220.
[48] R.K. McNamara, J.A. Welge, Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder, Bipolar Disord. 18 (2016) 300–306.
[49] F.L. Crowe, P.N. Appleby, R.C. Travis, M. Barnett, T.M. Brasky, H.B. Bueno-de-Mesquita, V. Chajes, J.E. Chavarro, M.D. Chirlaque, D.R. English, R.A. Gibson, G.G. Giles, G.E. Goodman, S.M. Henning, R. Kaaks, I.B. King, L.N. Kolonel, A.R. Kristal, M.L. Neuhouser, S.Y. Park, G. Severi, A. Siddiq, M.J. Stampfer, P. Stattin, C.M. Tangen, A. Tjonneland, D. Trichopoulos, R. Tumino, L.R. Wilkens, T.J. Key, N.E. Allen, Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies, J. Natl. Cancer Inst. 106 (2014).
[50] R.A. Murphy, E.A. Yu, E.D. Ciappio, S. Mehta, M.I. McBurney, Suboptimal plasma long chain n-3 concentrations are common among adults in the United States, nhanes 2003-2004, Nutrients 7 (2015) 10282–10289.